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Communication

Efficient Synthesis of Sulfur-Stereogenic Sulfoximines via Ru(II)-Catalyzed Enantioselective C−H Functionalization Enabled by Chiral Carboxylic Acid

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Cite This: J. Am. Chem. Soc. 2021, 143, 6810−6816
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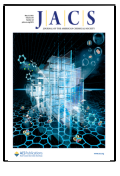
ABSTRACT: Ru(II)-catalyzed enantioselective C−H functionalization involving an enantiodetermining C−H cleavage step remains undeveloped. Here we describe a Ru(II)-catalyzed enantioselective C−H activation/annulation of sulfoximines with α-carbonyl sulfoxonium ylides using a novel class of chiral binaphthyl monocarboxylic acids as chiral ligands, which can be easily and modularly prepared from 1,1′-binaphthyl-2,2′-dicarboxylic acid. A broad range of sulfur-stereogenic sulfoximines were prepared in high yields with excellent enantioselectivities (up to 99% yield and 99% ee) via desymmetrization, kinetic resolution, and parallel kinetic resolution. Furthermore, the resolution products can be easily transformed to chiral sulfoxides and key intermediates for kinase inhibitors.

Ruthenium(II) catalysts have attracted much attention in high-valent metal-catalyzed C−H activation because of their robustness, versatile reactivity, and unique selectivity, as exemplified by Oi and Inoue, Ackermann, Bruneau and Dixneuf, and many others during the past decade.[1−6] Although significant advances have been made, the enantioselective version of Ru(II)-catalyzed C−H activation remains undeveloped.[7−12] On the basis of the structure of the Ru(II)−arene complexes, three possible strategies might be feasible to enable Ru(II)-catalyzed asymmetric C−H activation (Scheme 1a). The first one is to develop Ru(II) catalysts with precisely designed chiral arene ligands (Strategy I). Although such a strategy has been successfully applied to asymmetric C−H functionalization catalyzed by group 9 Cp^xM^{III}(M = Co, Rh, Ir) catalysts with tailor-made chiral Cp^x ligands,[13] unfortunately, CpRu(II) complexes are inactive in C−H activation, and the design of chiral arene ligands to replace *p*-cymene in the most commonly used (*p*-cymene)Ru(II) is extremely difficult and has never been achieved.[1−6,14] The second possible strategy (Strategy II) is the use of a chiral transient directing group (*c*TDG),[15−17] which was first developed by Yu in Pd(II)-catalyzed asymmetric C−H activation[17] and elegantly applied to Ru(II)-catalyzed enantioselective intramolecular C−H activation/hydroarylation by Cui[18] and Wang[19] in 2019. However, this strategy has been applied only in Ru(II)-catalyzed C−H activation followed by an enantiodetermining insertion (Scheme 1b). The last and most appealing strategy would be the use of easily available external chiral ligands. It is well-established that Ru(II)-catalyzed C−H activation can be accelerated by carboxylate assistance.[20] Therefore, one can argue that the use of chiral carboxylic acids (CCAs) as external ligands may be able to induce an enantiodetermining C−H bond cleavage. This concept was first proved by Yu and co-workers in Pd(II)-catalyzed enantioselective C−H activation using monoprotected amino acids (MPAAs) as bidentate chiral ligands.[21−23] Recently, asymmetric C−H functionalization involving an enantiodetermining C−H cleavage step catalyzed by group 9 achiral Cp^xM^{III} (M = Co,[24−26] Rh,[27−31] Ir[32,33]) and CCA-type ligands have also been realized by Matsunaga, Yoshino, and us.[34−36] Very recently, Ru(II)-catalyzed asymmetric C−H activation reactions based on other approaches, such as enantioselective C−H amination via an outer-sphere nitrene insertion[37] or C−H alkylation through an enantiodetermining proto-demetalation,[38] have also been achieved. However, Ru(II)-catalyzed asymmetric C−H functionalization via an enantiodetermining C−H cleavage step has not been reported to date.

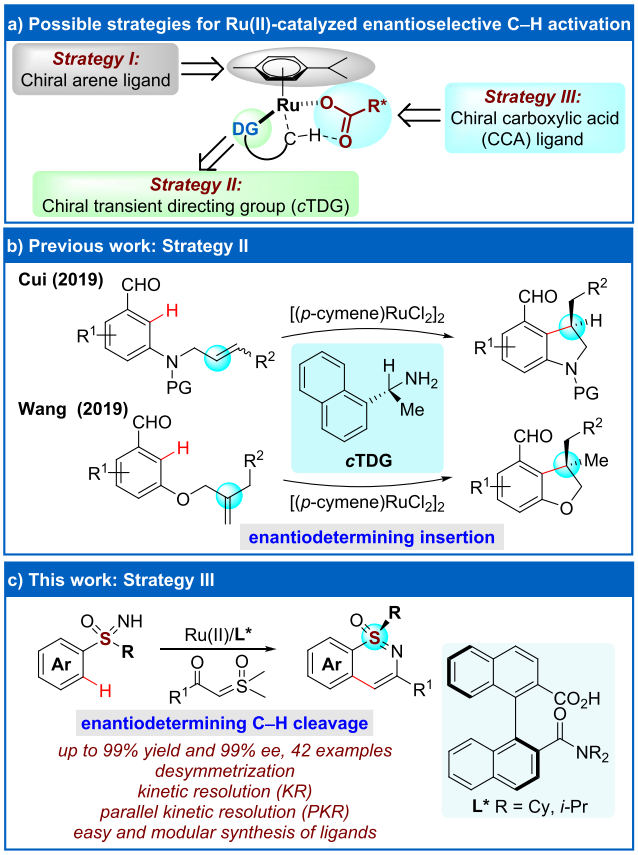
Sulfoximines are important motifs in pharmaceutical and agricultural chemicals[39−41] as well as effective directing groups for C−H functionalizations.[42−52] Compared with sulfones and sulfonamides, sulfoximines can provide strategic advantages related to improved solubility properties or higher metabolic stability. In particular, sulfoximines with stereogenic sulfur atoms often show significant bioactivity, offering high potential as active pharmaceutical ingredients.[39−41] However, catalytic asymmetric strategies for their efficient synthesis are rather scarce and remain to be developed. Bolm and co-workers developed several elegant methods, including the asymmetric imination and oxidation of sulfides and kinetic resolutions of sulfoximines, which have led to the reinforcement of this area.[53−56] More recently, the groups of Li and Cramer independently reported the synthesis of sulfur-stereogenic sulfoximines via a chiral Cp^xRh(III)-catalyzed asymmetric C−

Received: March 23, 2021
Published: April 28, 2021



https://doi.org/10.1021/jacs.1c03111
J. Am. Chem. Soc. 2021, 143, 6810−6816

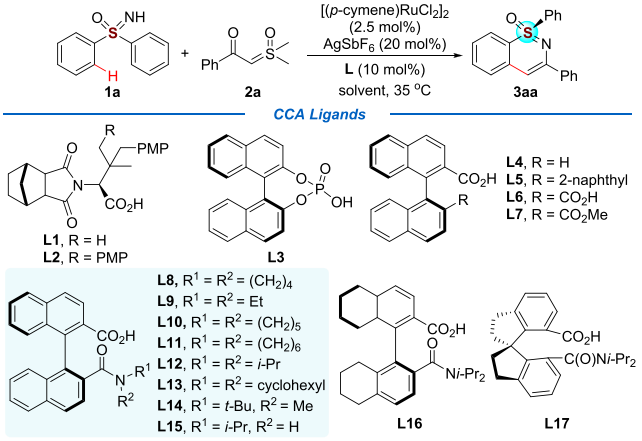
Scheme 1. Ru(II)-Catalyzed Enantioselective C−H Activation



H activation strategy.[35,57,58] Although these contributions elegantly demonstrated the power of asymmetric C−H activation, extra steps were needed to prepare the chiral Rh(III) cyclopentadienyl catalysts. In our continuous efforts to develop readily available chiral ligands for asymmetric C−H activation,[59−62] we wondered whether a properly designed CCA ligand would enable the Ru(II)-catalyzed asymmetric C−H activation through Strategy III. The results of the investigations are reported herein, and a novel class of chiral binaphthyl monocarboxylic acids were designed for the Ru(II)-catalyzed enantioselective C−H activation/annulation of sulfoximines with α-carbonyl sulfoxonium ylides. A range of chiral sulfoximines were prepared in high yields with excellent enantioselectivities (up to 99% yield and 99% ee) via desymmetrization, kinetic resolution (KR), and parallel kinetic resolution (PKR) (Scheme 1c).

We initiated our investigation by optimizing the desymmetrization coupling of sulfoximine **1a** and sulfoxonium ylide **2a** (Table 1). We realized that key to the success of this strategy is the judicious choice of a CCA ligand that can create a rigid chiral environment regardless of the monodentate nature due to the lack of vacant coordination site. Therefore, we first expected that a properly designed monodentate ligand with sterically bulky substitutions could exert high stereoinduction through steric repulsion. Two sterically bulky α-amino acids (**L1** and **L2**) were first examined (entries 1 and 2), and **3aa** was obtained in moderate yield and enantioselectivity, with the sterically bulkier ligand (**L2**) being better (69% yield, 72% ee). No product was observed when chiral phosphoric acid **L3** was evaluated (entry 3). We then investigated axially chiral CCAs

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	$CHCl_3$	36	63
2	**L2**	$CHCl_3$	69	72
3	**L3**	$CHCl_3$	n.r.	–
4	**L4**	$CHCl_3$	71	4
5	**L5**	$CHCl_3$	79	15
6	**L6**	$CHCl_3$	54	55
7	**L7**	$CHCl_3$	92	35
8	**L8**	$CHCl_3$	79	94
9	**L8**	DCE	82	94
10	**L8**	toluene	25	81
11	**L8**	THF	20	16
12	**L8**	MeOH	31	13
13	**L9**	DCE	84	96
14	**L10**	DCE	67	94
15	**L11**	DCE	81	97
16	**L12**	**DCE**	**96**[d]	**98**
17	**L13**	DCE	91	98
18	**L14**	DCE	69	95
19	**L15**	DCE	71	91
20	**L16**	DCE	31	91
21	**L17**	DCE	10	−95

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), and ligand (10 mol %) in 2.0 mL of solvent. [b]^{1}H NMR yields using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by chiral HPLC. [d]Isolated yield.

based on the binaphthyl backbone, a kind of privileged ligand skeleton. While binaphthyl 2-monocarboxylic acid (**L4**) led to almost racemic product (4% ee; entry 4), its 2′-naphthyl analogue **L5** with increased steric bulk gave slightly improved enantioselectivity (15% ee; entry 5). Intriguingly, the use of binaphthyl 2,2′-dicarboxylic acid (**L6**) and its monoester (**L7**) resulted in significantly improved enantioselectivity (55% ee with **L6** and 35% ee with **L7**; entries 6 and 7). These intriguing results suggested that the hydrogen-bonding interaction between the 2′-carboxylic acid (**L6**) or ester (**L7**) of the ligand and the NH group of sulfoximine **1a** might play an important role in the enantiodetermining step, rather than the traditional steric interactions.[63,64] We hypothesized that replacement of the ester with the N,N-disubstituted amide (a stronger hydrogen-bond acceptor than the ester) might led to better stereocontrol. To our delight, an ester-to-amide replacement (**L7** → **L8**) resulted in dramatically increased enantioselectivity (79% yield, 94% ee; entry 8). The yield

https://doi.org/10.1021/jacs.1c03111
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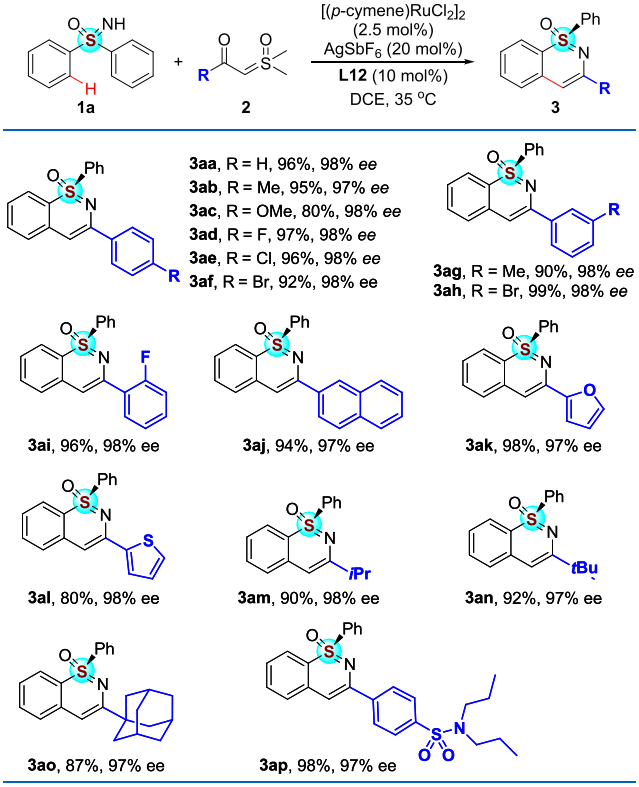
increased slightly when DCE was used as the solvent (entry 9). When THF or MeOH was used as the solvent, the enantioselectivity was dramatically decreased (16% ee with THF and 13% ee with MeOH; entries 11 and 12), which might be due to the destruction of hydrogen bonding between the ligand and the substrate. Although the detailed origin of the enantioselectivity is unclear at this stage, a postulated stereoinduction model involving a N−H···O hydrogen-bonding interaction between the sulfoximine and the ligand is proposed in Figure S1.

On the basis of the above rationalizations, various non-C_2-symmetric chiral monocarboxylic acids with N,N-disubstituted amides were then evaluated. We found that both the yield and enantioselectivity could be improved by increasing the bulkiness of the substituents on the amides (**L9**−**L15**; entries 13−19), and **3aa** was isolated in 96% yield with 98% ee when **L12** with a diisopropylcarbamoyl group was used (entry 16). **L16** and **L17** derived from (*S*)-H_8-BINOL and (*S*)-SPINOL also gave **3aa** with high enantioselectivity, albeit in significantly lower yields (entries 20 and 21). Notably, this novel class of chiral binaphthyl monocarboxylic acids could be easily and modularly prepared from 1,1′-binaphthyl-2,2′-dicarboxylic acid in a simple three-step sequence involving monoesterification/amidation/hydrolysis (see the Supporting Information (SI) for details).[65]

With the optimized conditions in hand, the scope of sulfoxonium ylides was first examined (Table 2). *α*-Substituted benzoyl sulfoxonium ylides bearing an electron-donating group

Table 2. Scope of Sulfoxonium Ylides[a]

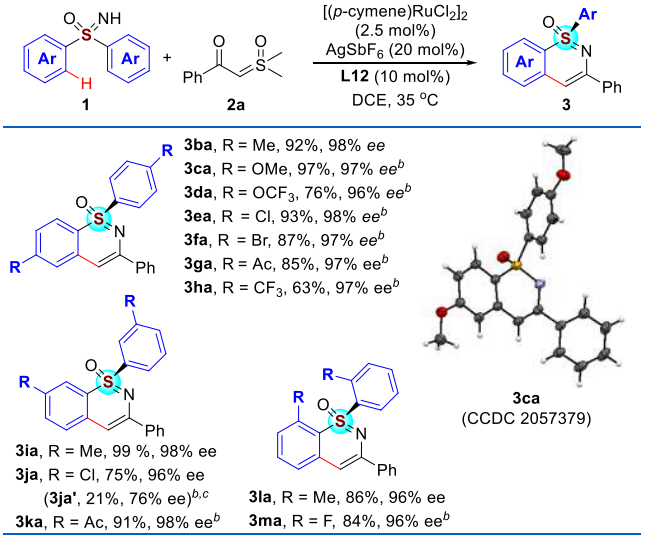


[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), and **L12** (10 mol %) in 2.0 mL of DCE at 35 °C for 12 h under N_2 in a sealed reaction tube.

(Me or OMe) or halide substituent (F, Cl, or Br) at the para position of the aryl ring were well-tolerated, affording the desired chiral cyclic sulfoximines in high yields with excellent enantioselectivities (**3ab**−**af**, 97−98% ee). Substrates with substituents at the meta or ortho position also reacted smoothly to give the corresponding products in high yields and ee values (**3ag**−**ai**). *α*-2-Naphthoyl, *α*-2-furanyl, and *α*-2-thienoyl sulfoxonium ylides also reacted well (**3aj**−**al**). Moreover, *α*-fatty acyl sulfoxonium ylides were also compatible with this transformation, giving the desired 3-alkyl-1,2-benzothiazines in good yields and enantioselectivities (**3an**, 92%, 97 ee; **3ao**, 87%, 97% ee).

We further evaluated the scope of sulfoximines (Table 3). A wide range of sulfoximines bearing various electron-donating

Table 3. Scope of Sulfoximines[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), and **L12** (10 mol %) in 2.0 mL of DCE at 35 °C for 12 h under N_2 in a sealed reaction tube. [b]The reaction was run at 45 °C. [c]**3ja**: react at the less hindered ortho position; **3ja'**: react at the sterically hindered ortho position.

groups (Me, OMe, or OCF_3) or electron-withdrawing groups (Cl, Br, Ac, or CF_3) were coupled with sulfoxonium ylide **2a** in good to excellent yields and enantioselectivities (**3ba**−**ha**, 63−97% yield, 96−98% ee). Sulfoximines with meta-Me and -Acsubstituents selectively reacted at the less sterically bulky ortho position (**3ia** and **3ka**) while meta-Cl-substituted **1j** gave a mixture of **3ja** and **3ja'**, with the reaction at the less hindered C−H bond occurring predominantly (**3ja**, 75%; **3ja'**, 21%). Interestingly, **3ja'** was obtained with obviously lower enantioselectivity than **3ja** (**3ja'**, 76% ee *vs***3ja**, 96% ee), probably due to the steric hindrance.Ortho-substituted sulfoximines were also tolerated, leading to high enantioselectivities (**3la** and **3ma**). The absolute configuration of **3ca** was determined by X-ray diffraction analysis and extrapolated to the other products.

Fortunately, Ru(II)-catalyzed kinetic resolution of racemic sulfoximines *rac*-**4** could also be achieved under slightly modified conditions using **L13** as a chiral ligand (Table 4). Both electron-donating and -withdrawing groups on the aryls were well-tolerated (**4a**−**h**), affording the cyclization products (*S*)-**5** and unreacted (*R*)-**4** with moderate to excellent

https://doi.org/10.1021/jacs.1c03111
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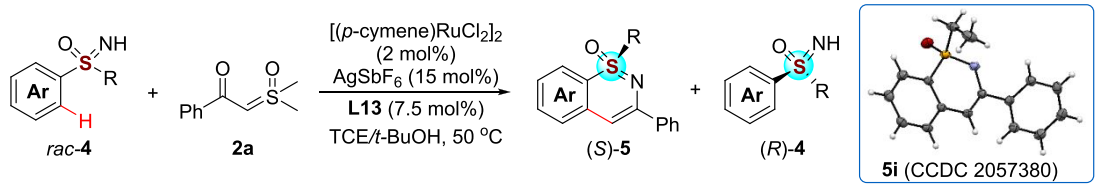
Table 4. Kinetic Resolution of Racemic Sulfoximines[a]



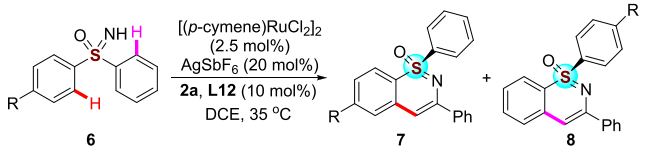
entry	*rac*-**4**	Ar	R	yield of (*S*)-**5** (%)[b]	ee of (*S*)-**5** (%)[c]	yield of (*R*)-**4** (%)[b]	ee of (*R*)-**4** (%)[c]	*s*[d]
1	**4a**	Ph	Me	50	91	41	96	83
2	**4b**	4-MeC_6H_4	Me	53	89	38	97	72
3	**4c**	4-MeOC_6H_4	Me	51	83	35	96	42
4	**4d**	4-BrC_6H_4	Me	50	78	41	98	36
5	**4e**	4-FC_6H_4	Me	49	89	40	96	67
6	**4f**	3-ClC_6H_4	Me	29 (**5f**), 18 (**5f′**)[e]	64 (**5f**), 65 (**5f′**)[e]	37	97	18
7	**4g**	3-AcC_6H_4	Me	46	82	35	86	28
8	**4h**	2-ClC_6H_4	Me	52	80	38	99	46
9	**4i**	Ph	Et	53	86	39	93	45
10	**4j**	Ph	cyclopropyl	50	83	41	95	40
11	**4k**	Ph	Bn	49	67	35	98	22

[a]Reaction conditions: **4** (0.2 mmol), **2a** (0.15 mmol), [(*p*-cymene)$RuCl_2$]$_2$ (2 mol %), $AgSbF_6$ (15 mol %), and **L13** (7.5 mol %) in TCE/*t*-BuOH = 0.5 mL/0.5 mL at 50 °C for 12 h under N_2 in a sealed reaction tube. [b]Isolated yields. [c]Determined by chiral HPLC. [d]Selectivity factor, given by $s = \ln[(1 - C)(1 - ee_4)]/\ln[(1 - C)(1 + ee_4)]$, where $C = (ee_4)/(ee_4 + ee_5)$. [e]**5f** was formed by reaction at the less sterically hindered ortho position and **5f′** by reaction at the more hindered ortho position.

enantioselectivities. Interestingly, when *m*-Cl-substituted **4f** was subjected to the reaction, a mixture of **5f** and **5f′** was obtained, with the reaction at the less hindered C−H bond occurring predominantly (29% for **5f** and 18% for **5f′**). Substituents such as ethyl, cyclopropyl, and benzyl on the sulfoximines were also compatible with this resolution (**4i**−**k**). The absolute configuration of (*S*)-**5i** was determined by X-ray diffraction analysis and extrapolated to the other products.

To our delight, the more challenging parallel kinetic resolution of sulfoximines bearing two different aromatic groups was also compatible with this protocol (Scheme 2).[66]

Scheme 2. Parallel Kinetic Resolution of Racemic Diaryl Sulfoximine *rac*-6

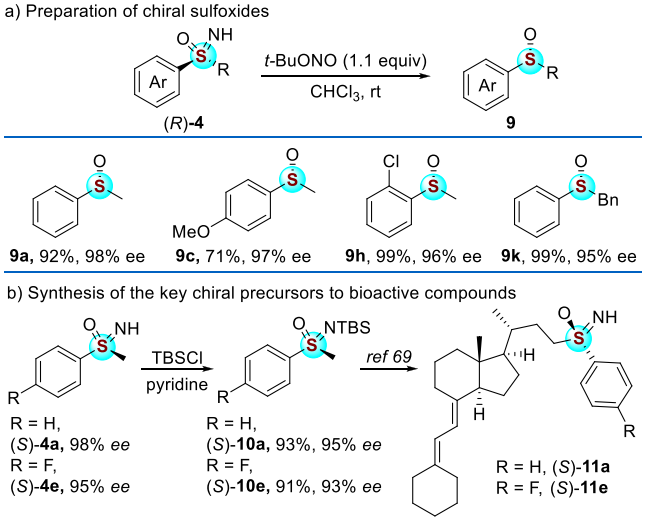


R = Me, **7a**, 49%, 97% ee; **8a**, 49%, 97% ee
R = CF_3, 91% (**7b** and **8b** mixture), 96% ee (for both **7b** and **8b**)
R = OMe, 82% (**7c** and **8c** mixture), 96% ee (for both **7c** and **8c**)

Sulfoximine **6a** with minimal electronic bias (R = Me) gave the products **7a** and **8a** in the same yield with excellent ee values. The yields of **7** and **8** were influenced when an electron-withdrawing group (R = CF_3, **6b**) or electron-donating group (R = OMe, **6c**) was used, but the excellent enantioselectivities were maintained.

The synthetic applications were then investigated to illustrate the significance of this protocol. Chiral sulfoximines (*R*)-**4** could be easily reduced to the corresponding chiral sulfoxides **9** in high yields without significant loss of enantiopurity (Scheme 3a).[67,68] Kinetic resolution of *rac*-**4** using (*R*)-**L13** as a chiral ligand led to the preparation of (*S*)-**4a** and (*S*)-**4e** with 98% and 95% ee, respectively (see SI section 2.6 for details). TBS protection gave **10a** and **10e**, which were key precursors for the synthesis of **11a** and **11e**,

Scheme 3. Synthetic Applications



which are inhibitors of human cytochrome P450C24 (CYP24) hydroxylase (Scheme 3b).[69]

Several experiments were conducted to gain mechanistic insights. H/D exchange studies in a mixture of D_2O and DCE were conducted. The reaction of sulfoximine **1b** in the absence of sulfoxonium ylide **2a** revealed 24% D incorporation into recovered **1b**. When the reaction was conducted in the presence of sulfoxonium ylide **2a**, no deuterium incorporation at the ortho position of the sulfoximine in either the recovered **1b** or the product **3ba** was observed. These results suggested that although the C−H activation step was reversible in the absence of ylide **2a**, the subsequent coupling with the ylide was significantly faster than the back reaction of C−H activation. The kinetic isotope effect was also investigated in a parallel experiment, giving a value of $k_H/k_D = 1.5$, indicating that C−H bond cleavage might be the rate-limiting step in this reaction. High-resolution mass spectrometry analysis suggested the

https://doi.org/10.1021/jacs.1c03111
J. Am. Chem. Soc. 2021, 143, 6810−6816

formation of a five-membered ruthenacycle species in the reaction of the Ru(II) catalyst and sulfoximine **1a** (see the SI for details).

In summary, we have reported the Ru(II)-catalyzed enantioselective C−H activation/annulation of sulfoximines with α-carbonyl sulfoxonium ylides enabled by a novel class of chiral binaphthyl monocarboxylic acids. A wide range of chiral sulfoximines were efficiently prepared in high yields with excellent stereocontrol (up to 99% yield and 99% ee) via desymmetrization, kinetic resolution, and parallel kinetic resolution. The resolution products can be easily transformed to chiral sulfoxides and key intermediates for kinase inhibitors. We expect that this novel class of CCAs might stimulate the development of other Ru(II)-catalyzed enantioselective C−H functionalizations in the future. Further studies of the mechanism and application of this new catalytic system are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03111.

Experimental procedures, spectral data for all new compounds, and X-ray crystal structure data for **3ca** (CCDC 2057379) and **5i** (CCDC 2057380) (PDF)

Accession Codes

CCDC 2057379 and 2057380 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21925109, 21772170, and 21801223) and Outstanding Young Talents of Zhejiang Province High-Level Personnel of Special Support (ZJWR0108) is gratefully acknowledged. This work is dedicated to the 100th anniversary of chemistry at Nankai University.

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