Asymmetric Catalysis

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Enantioselective Allylic C–H Oxidation of Terminal Olefins to Isochromans by Palladium(II)/Chiral Sulfoxide Catalysis

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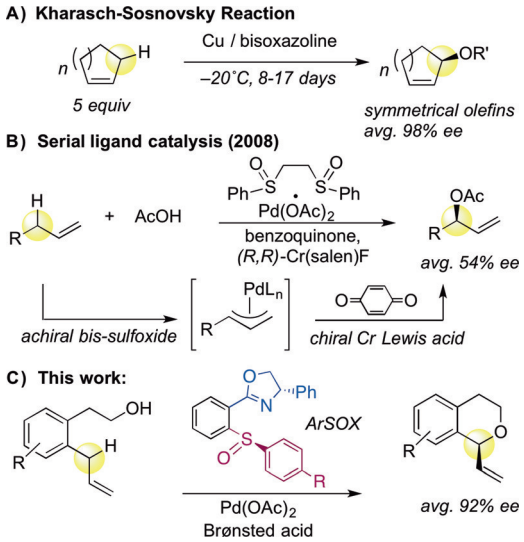
Abstract: *The enantioselective synthesis of isochroman motifs has been accomplished by palladium(II)-catalyzed allylic C–H oxidation from terminal olefin precursors. Critical to the success of this goal was the development and utilization of a novel chiral aryl sulfoxide-oxazoline (ArSOX) ligand. The allylic C–H oxidation reaction proceeds with the broadest scope and highest levels of asymmetric induction reported to date (avg. 92 % ee, 13 examples with greater than 90 % ee).*

The enantioselective functionalization of prochiral C–H bonds represents a highly efficient transformation by installing both valuable oxidized functionality and absolute stereochemistry in a single step. Asymmetric allylic C–H oxidations have been pursued over the last five decades; copper-catalyzed Kharasch–Sosnovsky reactions have achieved satisfactory enantiomeric excesses, however only with symmetrical, cyclic olefins under synthetically undesirable conditions (excess equivalents of olefin, days at cryogenic temperatures; Scheme 1 A).[1] Palladium has shown a broad scope in enantioselective C–H desymmetrizations and kinetic resolutions,[2] however palladium-catalyzed asymmetric allylic C–H functionalizations have been achieved hereto with only modest levels of asymmetric induction.[3–6] Additionally, palladium-catalyzed asymmetric C–H to C–O bond-forming reactions in both areas are rare.[2d,3,5]



Scheme 1. Enantioselective allylic C–H oxidation.

Palladium(II)/bis(sulfoxide) catalysis has proven to be a uniquely general platform for effecting allylic C–H oxidation, amination, fluorination, and alkylation of terminal olefins with broad scope, preparative yields, and excellent regio- and *E*/*Z*-selectivity.[7] Many of these reactions proceed by a serial ligand catalysis mechanism where the bis(sulfoxide) ligand promotes C–H cleavage, and *p*-benzoquinone (BQ), acting as a π-acidic ligand, promotes functionalization. However, limited success has been achieved in adapting this catalytic platform for asymmetric catalysis.[3] Mechanistic studies have illuminated two significant challenges. The bis(sulfoxide) ligand, while effective for C–H cleavage and oxidatively stable, is transiently associated with the palladium metal and does not exert influence during functionalization. BQ acts as a ligand at high concentrations to promote functionalization.[7a] Second, rapid π–σ–π isomerization precedes the C–O bond-forming step and scrambles any chiral information that may be imparted during C–H cleavage by a chiral bis(sulfoxide) ligand. Working within the constraints of these challenges, a chiral chromium Lewis-acid cocatalyst was identified and works with BQ to promote enantioinduction during functionalization, albeit with modest enantiomeric excess (Scheme 1 B).[3] Alternatively, chiral palladium/phosphoramidite catalysts for allylic C–H functionalizations have demonstrated modest enantioselectivity (avg. 75 % *ee*, 1 example ≥ 90 % *ee*,[4] avg. 83 % *ee*, 2 examples at 90 % *ee*[5]), limited olefin scope (generally doubly activated C–H bonds), and high sensitivity to O_2.[4,5] We hypothesized the ideal catalytic platform would utilize an oxidatively stable, chiral ligand capable of promoting both C–H cleavage and functionalization, thus circumventing the challenges of serial ligand catalysis.

Chiral isochromans are well-represented in natural products and pharmaceuticals, and are classically furnished by diastereoselective cyclizations or chiral resolution of racemates.[8] Enantioselective organocatalytic and metal-catalyzed methods are emerging to furnish this motif, however, generally starting from preoxidized precursors.[9] We recently reported the synthesis of racemic cyclic ethers by palladium(II)/bis(sulfoxide)-catalyzed, BQ-promoted allylic C–H oxidation.[10] Given that pre-coordination of the alcohol to palladium was found to be important for functionalization, we hypothesized that such a system might enable high levels of asymmetric induction in the C–O bond-forming step, and provide a valuable means to furnish chiral isochromans.

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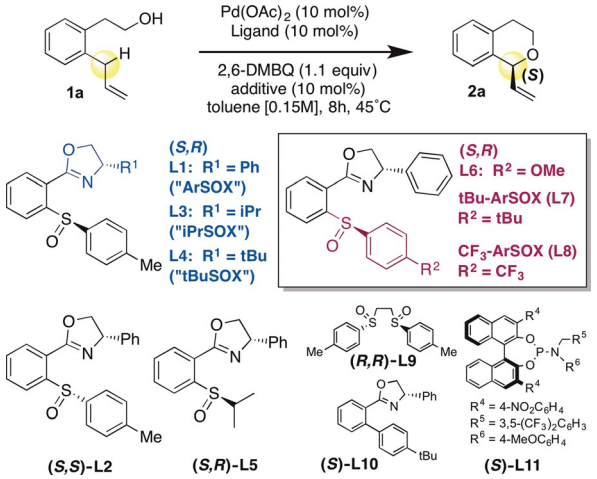
Drawing inspiration from the success of mixed P,N-donor ligands in asymmetric catalysis,[11] we hypothesized that combining a sulfoxide (promotes C–H cleavage) with the π-acidic/σ-donor properties of an oxazoline (may promote functionalization and effect a static chiral environment at the metal) would enable an efficient asymmetric reaction. Mixed S,N ligands are known to effect asymmetric induction in palladium(0)-catalyzed allylic substitutions, however with a very limited scope (1,3-diphenylpropenyl acetate).[12] Alkyl-substituted sulfoxide-oxazoline ligands were recently shown to promote palladium-catalyzed branched allylic C–H acetoxylations, however with no asymmetric induction.[13] Herein we report the development of a chiral diarylated sulfoxide-oxazoline (ArSOX) ligand/palladium(II)-catalyzed asymmetric allylic C–H oxidation system which proceeds with broad scope and high asymmetric induction (avg. 92% *ee*, 13 examples with ≥90% *ee*).

We identified ArSOX [(*S*,*R*)-**L1**; Table 1, entry 1) as effective for asymmetric palladium(II)-catalyzed[14] formation of the isochroman **2a**, though in low yield. Based on our recent studies showing that Brønsted acids enhance the reactivity of palladium(II) sulfoxide catalyzed allylic C–H oxidations,[7g] we surveyed Brønsted acid additives (entries 2–5) for the reaction. Whereas the Brønsted acid did not significantly impact asymmetric induction, a significant enhancement in yield was observed. Utilizing the diastereomer (*S*,*S*)-**L2** resulted in dramatically lowered yield and enantioinduction (entry 6), thus suggesting that the relative stereochemistry of the sulfoxide and the oxazoline is important. Examining the previously reported alkyl-substituted sulfoxide-oxazoline ligands[13] resulted in significantly diminished yields and enantioselectivity (entries 7 and 8). We next turned to modifications at the sulfoxide: utilizing an isopropyl group was beneficial for enantioselectivity, but significantly diminished reactivity (entry 9).[15] Further examination of aryl sulfoxides revealed that a *para*-methoxy-substituent was not beneficial (entry 10), however both *para*-tert-butyl- and *para*-trifluoromethyl-benzene moieties resulted in enantioselectivities above 90% *ee* (entries 11 and 12).[16] We selected *t*Bu-ArSOX [(*S*,*R*)-**L7**] for further study because of its combination of high enantioinduction and reactivity, and its relative ease of synthesis. However, CF_3-ArSOX [(*S*,*R*)-**L8**] is optimal in cases where enantiomeric excesses fall below 90% *ee*, and product yields may be improved by extending reaction times. Utilizing either the chiral bis(sulfoxide) (*R*,*R*)-**L9** (entry 13) or chiral oxazoline (*S*)-**L10** (entry 14) ligands resulted in minimal enantioinduction. Notably, examination of the phosphoramidite (*S*)-**L11** under both our standard conditions and O_2-free conditions previously reported[5] resulted in trace formation of **2a** (entry 15). Replacing the sterically-bulky 2,6-dimethylbenzoquinone (2,6-DMBQ) with BQ as the stoichiometric oxidant diminished enantioselectivity (entry 16), possibly because of an undesirable competition between BQ and (*S*,*R*)-**tBu-ArSOX L7** as a ligand for palladium(II).[7f]

We next examined the scope of the reaction for furnishing the vinylisochroman motif (Figure 1). Gratifyingly, broad aromatic substitution is tolerated, with both electron-rich substrates (**2b–d**) and electron-deficient substrates (**2e–i**) furnishing the desired products in good yields and high enantioselectivities. Broad tolerance for electronic substitution on aryls has not been previously shown for other asymmetric allylic C–H methods, which show either decreased enantioselectivity for electron-rich aryl moieties,[4] or inconsistent trends for aryl tolerance.[5] Bromide and chloride substitution is well tolerated, and these groups serve as handles for further manipulation (**2e**,**h**). The *ee* values of the products **2d** and **2i** were improved to greater than 90% by utilizing (*S*,*R*)-**CF_3-ArSOX L8** in place of (*S*,*R*)-**tBu-ArSOX L7**.

Stereochemically defined substitutions in isochromans at both the 3- and 4-positions are well represented in biologically active compounds. In the case of the 1,3-disubstituted **4** (see Table 2), a motif found in such compounds as the antibiotic elutherin and D1 agonist A77636, syntheses are generally achieved by Pictet–Spengler reaction under diastereoselective substrate control, and catalyst-controlled diastereoselectivity has not been demonstrated.[17] Notably, allylic C–H oxidation in the presence of the achiral palladium(II)/**L12**

Table 1: Reaction development.



Entry	Ligand	Additive	Yield [%][a]	*ee* [%][a]
1	(*S*,*R*)-**L1**	none	8	83
2	(*S*,*R*)-**L1**	benzoic acid	13	84
3	(*S*,*R*)-**L1**	$(nBuO)_2PO_2H$	54	87
4	(*S*,*R*)-**L1**	$(PhO)_2PO_2H$	47	82
5	(*S*,*R*)-**L1**	Ph_2PO_2H	63	87
6	(*S*,*S*)-**L2**	Ph_2PO_2H	32	19
7	(*S*,*R*)-**L3**	Ph_2PO_2H	31	76
8	(*S*,*R*)-**L4**	Ph_2PO_2H	8	25
9	(*S*,*R*)-**L5**	Ph_2PO_2H	24	88
10	(*S*,*R*)-**L6**	Ph_2PO_2H	60	86
11	(*S*,*R*)-**tBu-ArSOX (L7)**	Ph_2PO_2H	70	92
12	(*S*,*R*)-**CF_3-ArSOX (L8)**	Ph_2PO_2H	49	93
13[b]	(*R*,*R*)-**L9**	Ph_2PO_2H	31	−6
14[b]	(*S*)-**L10**	Ph_2PO_2H	13	12
15[c]	(*S*)-**L11**	Ph_2PO_2H	<5	n.d.
16[d]	(*S*,*R*)-**L7**	Ph_2PO_2H	59	77

[a] Reactions run open to air. Yield is that of the isolated product and an average of two runs. The *ee* value was determined by GC using a chiral column. [b] Reaction run for 72 hours at [0.5 M]. [c] Reaction run under argon using reaction conditions reported in Ref. [5] also resulted in trace amounts of product (see S.I.). [d] *p*-Benzoquinone used in place of 2,6-DMBQ. 2,6-DMBQ = 2,6-dimethylbenzoquinone. n.d. = not determined.

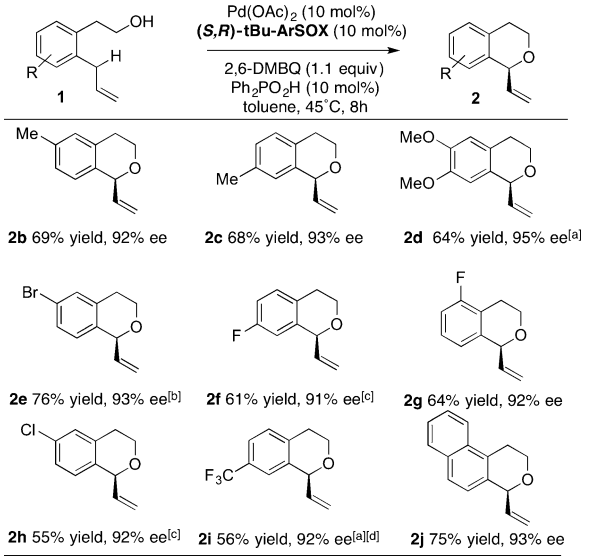
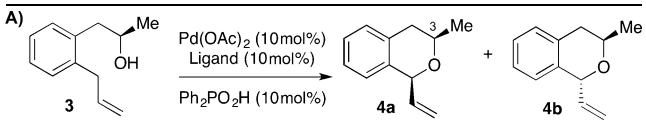


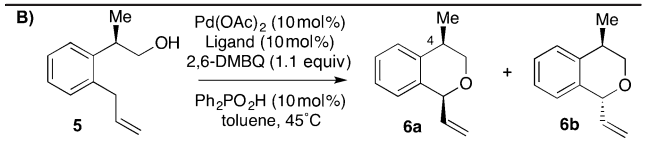
Figure 1. Enantioselective formation of isochromans. Reaction conditions: alcohol **1** (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), (*S*,*R*)-**L7** (0.1 equiv), Ph_2PO_2H (0.1 equiv), 2,6-DMBQ (1.1 equiv), toluene (0.15 M), 45 °C. Yields reported are those of the isolated product and are an average of three runs. The *ee* values were determined by chiral GC and chiral high performance liquid chromatography (HPLC). [a] (*S*,*R*)-**L8** used in place of (*S*,*R*)-**L7**. [b] Reaction run for 9 h. [c] Reaction run for 10 h. [d] Reaction run for 48 h.

furnishes **4** with a modest 1.5:1 d.r. value favoring the *cis*-diastereomer **4a** (Table 2 A). When the reaction is run with palladium(II)/(*S*,*R*)-**tBu-ArSOX L7**, the d.r. value is increased to greater than 20:1 favoring **4a**. Significantly, when the reaction is run with the mismatched palladium-(II)/(*R*,*S*)-**tBu-ArSOX L7**, the d.r. value is overturned to 1:2.8, thus favoring the *trans*-diastereomer **4b**. The ability to influence diastereoselectivity with this palladium(II)/**tBu-ArSOX L7**-catalyzed asymmetric C–H oxidation method is similarly observed in the formation of the structurally distinct 1,4-disubstituted **6**. Allylic C–H oxidation in the presence of achiral palladium(II)/**L12** furnishes the *cis*-diastereomer in 3.6:1 d.r. The use of matched palladium(II)/(*S*,*R*)-**tBu-ArSOX L7** once again increased the d.r. value to greater than 20:1 in favor of **6a**, and mismatched palladium(II)/(*R*,*S*)-**tBu-ArSOX L7** d.r. led to a d.r. value of 1:1.4 in favor of **6b** (Table 2 B).

Table 2: Catalyst influence on diastereoselective C–H cyclization.



Entry	Ligand	Yield [%][a]	d.r.[b] (**4a**/**4b**)
1	*meso*-1,2-bis(phenylsulfinyl)ethane **(L12)**	16	1.5:1
2	(*S*,*R*)-**tBu-ArSOX L7**	62	>20:1
3	(*R*,*S*)-**tBu-ArSOX L7**	49	1:2.8



Entry	Ligand	Yield [%]	d.r. (**6a**/**6b**)
1	*meso*-1,2-bis(phenylsulfinyl)ethane **(L12)**	60	3.6:1
2	(*S*,*R*)-**tBu-ArSOX L7**	67	>20:1
3	(*R*,*S*)-**tBu-ArSOX L7**	68	1:1.4

[a] Yield is that of the isolated product, average of three runs. [b] Determined by ^1H NMR analysis.

PNU-109291 (**8**) is a pharmaceutical compound that functions as a selective $5HT_{1D}$ agonist.[18] Previous asymmetric syntheses of this target suffered from the need for chiral resolution of racemates. We evaluated our enantioselective method in the context of a more efficient synthesis (Figure 2 A). Starting from the aryl amide **1k** (see the Supporting Information for preparation), the vinylisochroman **2k** is formed by C–H oxidation in good yield and enantioselectivity, thus demonstrating this reaction's tolerance of N-Boc protected amides which may chelate palladium.[19] Subsequent hydroboration/oxidation of **2k** furnished the alcohol **7** in 80 % yield. Nucleophilic displacement of **7** with aryl

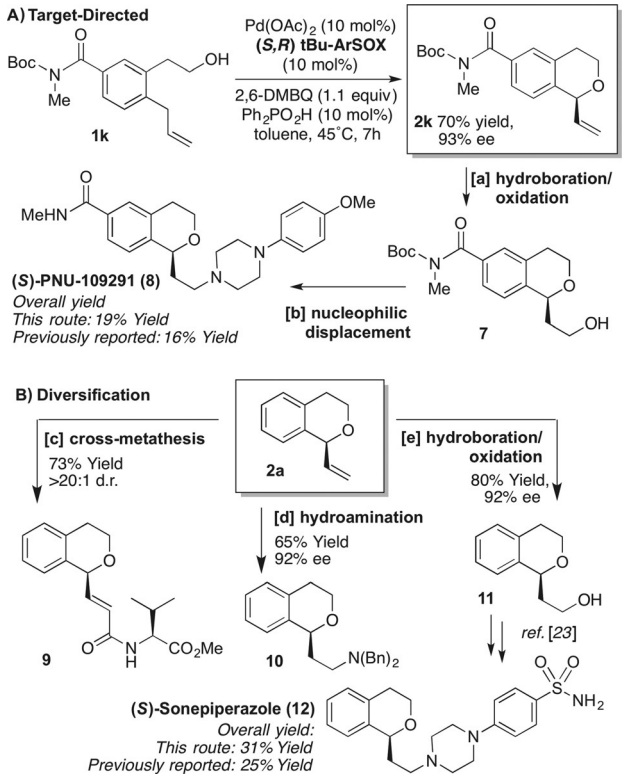


Figure 2. Vinylisochromans as versatile chiral intermediates. Reaction conditions: a) 9-BBN (1.5 equiv), THF, 0 °C, then $NaBO_3$ (5 equiv), 80 % yield. b) MsCl (1.05 equiv), DMAP (5 mol %), DIPEA (2.5 equiv), THF; then aryl piperazine (1.5 equiv), 50 % yield, 93 % *ee*. c) Hoveyda–Grubbs II (7 mol %), olefin (2 equiv), CH_2Cl_2. d) $Cu(OAc)_2$ (4 mol %), DTBM-SEGPHOS (4.4 mol %), amine (1.2 equiv), DEMS (2 equiv), THF. e) 9-BBN (1.5 equiv), THF; then $NaBO_3$ (5 equiv). 9-BBN = 9-borabicyclo[3.3.1]nonane, DEMS = diethoxymethylsilane, DTBM-SEGPHOS = (*R*)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, DIPEA = diisopropylethylamine, Ms = methanesulfonyl, THF = tetrahydrofuran.

piperazine furnished the piperazine **8**. Overall, starting from commercial materials, the asymmetric C–H oxidation route resulted in a higher overall yield.[20] Additionally, we sought to exploit the latent reactivity of the allylic-substituted terminal olefin, thus demonstrating orthogonality to past efforts which have focused on late-stage modifications to the aryl moiety.[18] The isochroman **2a** may be diversified into the α,ß-unsaturated amide **9** by ruthenium-catalyzed cross-metathesis,[21] into the aliphatic amine **10** by copper-catalyzed hydroamination,[22] and also into terminal the alcohol **11** via hydroboration oxidation (Figure 2B). Importantly, all of these manipulations proceeded without racemization of the stereocenter. The compound **11** is a precursor to (*S*)-Sonepiprazole (**12**), whose synthesis by asymmetric C–H oxidation proceeds with a higher overall yield than the reported synthesis by kinetic resolution.[23]

As a preliminary mechanistic investigation, we sought to distinguish between an oxypalladation or C–H cleavage/π-allyl palladium pathway. To evaluate an olefin isomerization/oxypalladation mechanism, we subjected the internal olefin **13** to the reaction conditions, and observed no formation of **2a** (Figure 3A), thus indicating an oxypalladation pathway is not operative. We probed the capacity of this catalyst system to effect allylic C–H cleavage with unactivated C–H bonds, which has been demonstrated previously under palladium/bis(sulfoxide) catalysis.[10] With chiral catalyst palladium/(*R*,*S*)-**tBu-ArSOX L7**, the alcohol **14** furnishes pyran **15** in good yield and enhanced diastereoselectivity relative to the achiral palladium(II)/**L12** (19:1 d.r. versus 8:1 d.r., Figure 3B). We next sought to elucidate which step of the reaction is responsible for asymmetric induction. Evaluation of the reaction with substrate [D]-**1a** furnished [D]-**2a** with complete scrambling of the deuterium at the terminal alkene (Figure 3C). This scrambling signifies π–σ–π isomerization of the π-allyl palladium intermediate and indicates that C–H cleavage cannot be the enantiodetermining step.[3] Additionally, we evaluated another scenario where the isochromans might undergo a subsequent resolution to enhance the product's enantioenrichment. However, exposure of *rac*-**2a** to the reaction conditions does not result in enantioenriched **2a**, and no change in isochroman enantioenrichment was observed over time (see the Supporting Information). Thus, from these experiments we infer that the catalyst imparts asymmetric induction during functionalization.

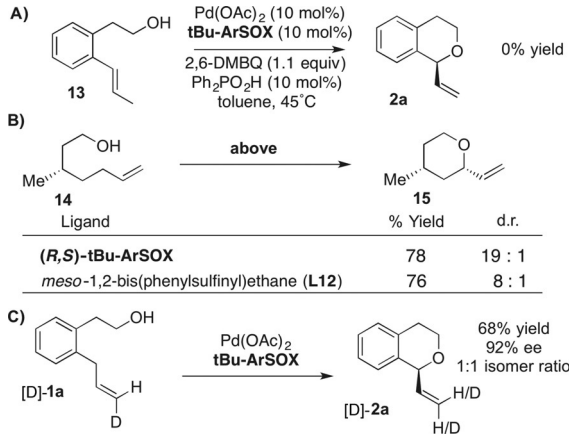


Figure 3. Mechanistic investigation.

In conclusion, we have reported a catalytic system for enantioselective palladium(II)-catalyzed allylic C–H oxidations, with an ArSOX ligand which enables both C–H cleavage and a stable chiral environment for asymmetric induction during functionalization. We have demonstrated the utility of this operationally simple method (open to air and moisture) to furnish isochromans with broad scope, in good yields and high enantioselectivities. Further investigations are underway to evaluate Pd^{II}/ArSOX in other allylic C–H functionalizations.

Experimental Section

To a ½ dram vial was added the ligand (*S*,*R*)-**tBu-ArSOX L7** (8.1 mg, 0.02 mmol) and $Pd(OAc)_2$ (4.4 mg, 0.02 mmol). Toluene (0.4 mL) was added, and the vial was capped and heated to 45 °C until all solids had dissolved. Separately, to a 1 dram vial with stir bar was added **1a** (32.4 mg, 0.20 mmol), 2,6-dimethylbenzoquinone (30 mg, 0.22 mmol), and diphenylphosphinic acid (4.4 mg, 0.02 mmol), with no precautions to exclude air or moisture. The catalyst solution was subsequently added to the reaction flask, and toluene (0.9 mL) was used to rinse (total volume toluene = 1.3 mL). The 1 dram vial was sealed with a Teflon cap, and allowed to stir for 8 hours at 45 °C, until complete conversion of the starting material was observed by TLC. Afterward, the vial was cooled to room temperature. The majority of the toluene was removed under reduced pressure, and the remaining mixture was directly subjected to flash column chromatography (10 % EtOAc in hexanes) to provide the vinylisochroman as a clear oil.[24]

Acknowledgments

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Keywords: asymmetric catalysis · C–H activation · oxidation · palladium · S ligands

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