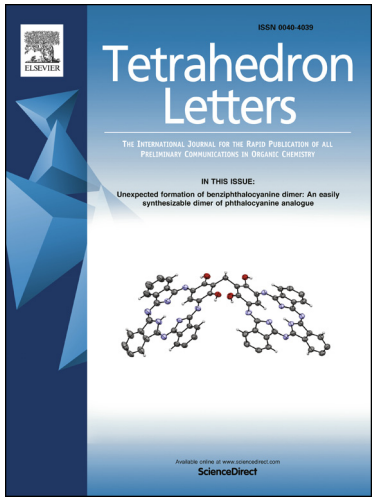

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Pd(II)-Catalyzed Enantioselective Intramolecular Oxidative Amination Utilizing (+)-Camphorsulfonic acid

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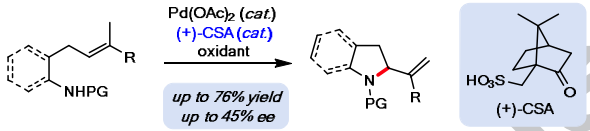

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Pd(II)-catalyzed enantioselective intramolecular oxidative amination utilizing (+)-camphorsulfonic acid

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ABSTRACT

An enantioselective Pd(II)-catalyzed intramolecular oxidative amination reaction was developed utilizing the commercially available chiral X-type ligand (1*S*)-(+)-camphorsulfonic acid. The Wacker-type cyclization produced chiral indoline products with enantioselectivies up to 45% ee. Electronic structure calculations employing density functional theory support a *trans*-aminopalladation mechanism.

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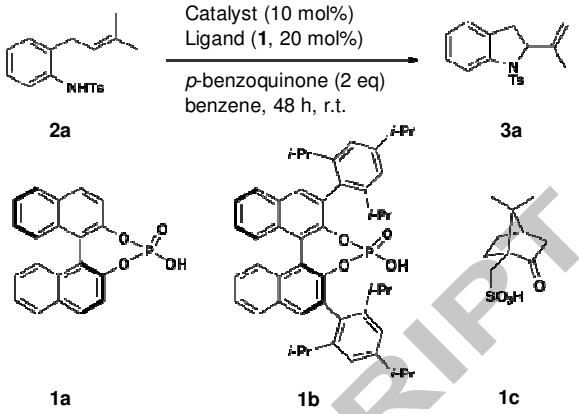
Introduction

The Pd-catalyzed Wacker-type oxidative functionalization of unactivated alkenes and alkynes has garnered significant attention over the past three decades.[1] Although progress has been made regarding mechanistic elucidation,[2] efficiency, and catalyst re-oxidation (including the use of aerobic conditions),[3] the number of enantioselective examples, specifically with the formation of chiral centers with C–N bonds, remains low.[4] To date, enantioselective oxidative amination has almost exclusively utilized bidentate nitrogenous ligands to impart asymmetric induction.[5] Despite the utility of this scaffold, these electron-donating L-type ligands can dramatically attenuate the electrophilicity of the Pd-alkene complex. In contrast, we sought to explore the use of chiral X-type ligands for the synthesis of indoline derivatives through intramolecular oxidative amination.

Surprisingly, the use of chiral X-type ligands in palladium catalysis has received very little attention. Beginning in 1990, Alper utilized a BINOL-derived chiral phosphoric acid ((*S*)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate—**1a**) for the enantioselective palladium-catalyzed hydrocarboxylation of vinyl arenes.[6] More recently, in the development of asymmetric counteranion-directed catalysis (ACDC),[7] List applied similar chiral phosphoric acid ligands towards an enantioselective Overman rearrangement and enantioselective allylations of aldehydes.[8] Ooi found success in pairing chiral binaphtholate[9] and phosphate ions[10] with achiral ammonium-phosphine ligands in asymmetric allylation of α-nitro esters and benzofurans. Similarly, Gong combined a chiral phosphoramidite and a chiral phosphoric acid to elicit facial-selective nucleophilic attack on a π-allyl-Pd complex in the asymmetric allylic alkylation of pyroazol-5-ones.[11] Hu developed a three-component reaction for the synthesis of pyrrole derivatives through a chiral phosphoric acid-ligated palladium-carbenoid-mediated transformation with good enantio- and diastereoselectivity.[12] Yao applied the chiral phosphoric acid (*S*)-TRIP (**1b**) in combination with Pd(II) in an enantioselective oxa-Diels-Alder reaction.[13] Lastly, our group has synthesized spiroketones through an asymmetric Pd(II)/chiral phosphoric acid-catalyzed semipinacol rearrangement.[14,15]

Results and discussion

With the established success of chiral phosphoric acid ligands by our group and others, initial attempts to convert **2a** to the desired product **3a** began with BINOL-derived phosphoric acids **1a** and **1b**. Unfortunately, only moderate conversion and poor enantioselectivity were observed with this class of ligands (Table 1, entries 1 and 2).[16] At this time we decided to examine the use of chiral sulfonic acid ligands and were pleased to discover that commercially available (1*S*)-(+)-10-camphorsulfonic acid ((+)-CSA—**1c**) greatly improved the enantioselectivity (Table 1, entry 3). We hypothesized that acid-promoted ligand exchange was affording $Pd[(+)\text{-}CSA]_2$ as the active catalyst; indeed, stepwise synthesis and application of $Pd[(+)\text{-}CSA]_2$ in this transformation afforded nearly identical results to those obtained using the standard conditions (Table 1, entry 4). No appreciable reaction occurred upon omission of the palladium source (Table 1, entry 5); likewise, addition of the sulfonic acid proved essential for reactivity (Table 1, entry 6). After selecting (+)-CSA as the optimal ligand for the enantioselective transformation, further reaction optimization was conducted (Table 2).



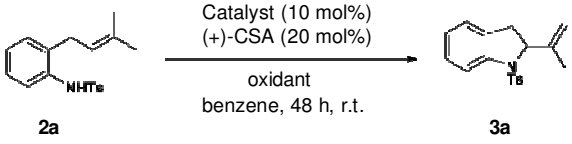
2a 3a 1a 1b 1c

Table 1. Ligand selection[a]

Entry	Catalyst	Ligand	Yield **3a** (%)[b]	% ee[c]
1	$Pd(OAc)_2$	**1a**	29	17
2	$Pd(OAc)_2$	**1b**	6[d]	14
3	$Pd(OAc)_2$	**1c**	55	40
4	$Pd[(+)\text{-}CSA]_2$	no ligand	56	41
5	no catalyst	**1c**	<5[d]	n.d.
6	$Pd(OAc)_2$	no ligand	8[d]	n.d.

[a]Reagents and conditions: **2a** (0.05 mmol), $Pd(OAc)_2$ (0.005 mmol), ligand (0.01 mmol), 1,4-benzoquinone (0.2 mmol), benzene (0.5 mL).
[b]Isolated yield.
[c]Determined by chiral HPLC.
[d]Conversion determined by crude ^{1}H-NMR

Table 2. Reaction optimization[a]



2a 3a

Entry	Catalyst	Oxidant	Yield **3a** (%)[b]	% ee[c]
1	$Pd(CH_3CN)_2Cl_2$	BQ (2 eq)	73	11
2	$Pd_2(dba)_3$	BQ (2 eq)	40	38
3	$Pd(TFA)_2$	BQ (2 eq)	53	24
4	$Pd(OAc)_2$	BQ (2 eq)	55	40
5[d]	$Pd(OAc)_2$	BQ (2 eq)	85[e]	19
6[f]	$Pd(OAc)_2$	BQ (2 eq)	74	44
7[g]	$Pd(OAc)_2$	BQ (2 eq)	38	41
8[f,h]	$Pd(OAc)_2$	BQ (2 eq)	8[e]	n.d.
9[f]	$Pd(OAc)_2$	O_2	34	44
10[f]	$Pd(OAc)_2$	MnO_2	12	10
11[f]	$Pd(OAc)_2$	O_2/BQ (20 mol%)	32	n.d.
12[f,i]	$Pd(OAc)_2$	BQ (2 eq)	54	44
13[f,j]	$Pd(OAc)_2$	BQ (2 eq)	40	44

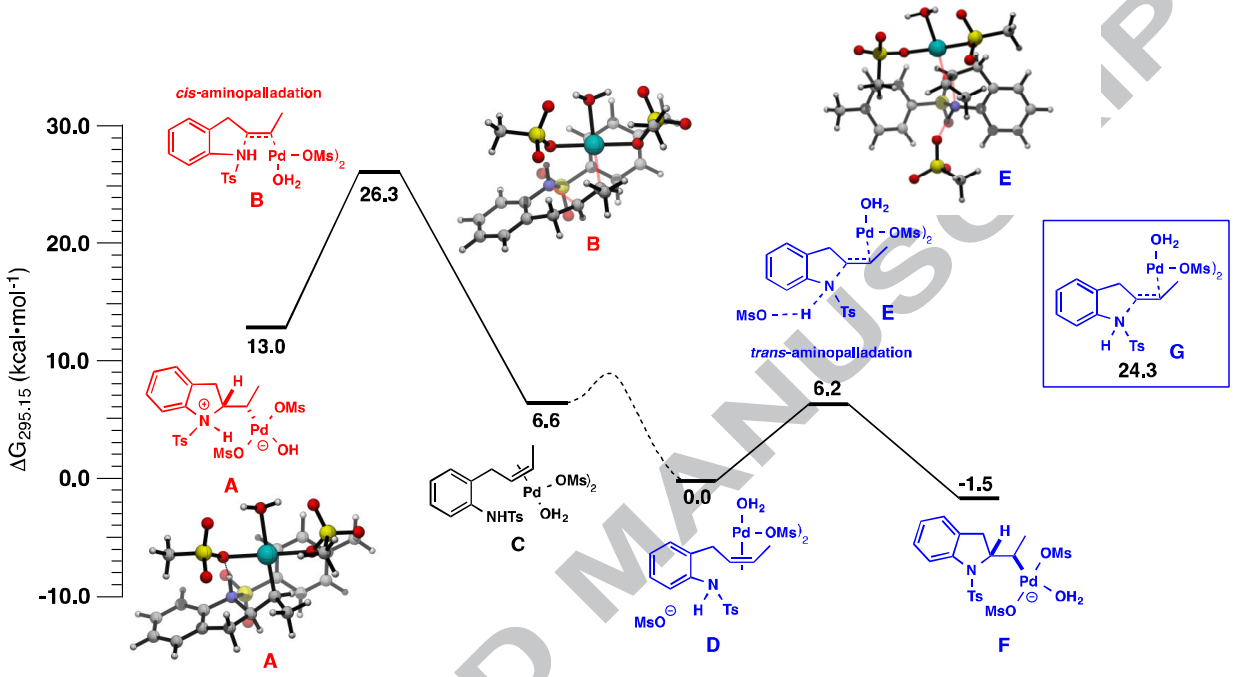
[a]Reaction conditions: substrate (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), **1c** (0.02 mmol), 1,4-benzoquinone (0.2 mmol), benzene (1.0 mL), 48 h, 22 °C.
[b]Isolated yield.
[c]Determined by chiral HPLC.
[d]60 °C
[e]Conversion determined by crude ^{1}H-NMR
[f](+)-NaCSA (10 mol%) added.
[g](+)-NaCSA (1 equiv) added.
[h]No (+)-CSA
[i]Reaction performed in toluene.
[j]Reaction performed in dichloromethane.

Table 3. Pd(II)-catalyzed oxidative amination[a]

Entry	Substrate	Product	Yield (%)[b]	% ee[c]
1	**2a**	**3a**	74	44
2	**2b**	**3b**	55	38
3	**2c**	**3c**	76	43
4	**2d**	**3d**	70	42
5	**2e**	**3e**	67	45
6	**2f**	**3f**	66	13
7[d]	**2g**	**3g**	53	0
8[e]	**2h**	**3h**	54	29
9[e]	**2i**	**3i**	55	27
10[e]	**2j**	**3j**	62	27
11[e]	**2k**	**3k**	68	27
12[f]	**2l**	**3l**	66	0
13[g]	**2m**	**3m**	46	0
14[g]	**2n**	**3n**	52	44
15[h]	**2o**	**3o**	44	0

[a]Reaction conditions: substrate (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), **1c** (0.02 mmol), (+)-NaCSA (0.01 mmol), 1,4-benzoquinone (0.2 mmol), benzene (1.0 mL), 60 h, 22 °C.
[b]Isolated yield.
[c]Determined by chiral HPLC
[d]60 h, 50 °C
[e]5 h, 22 °C
[f]18 h, 22 °C
[g]24 h, 50 °C
[h]72 h, 50 °C

Scheme 1. Proposed Mechanism



$Pd(OAc)_2$ proved to be the best palladium source and an elevated reaction temperature resulted in decreased enantioselectivity (Table 2, entry 5). The addition of the sodium salt of (+)-camphorsulfonic acid [(+)-NaCSA] was found to improve the yield without affecting the enantioselectivity. However, the addition of (+)-NaCSA alone did not generate the active catalyst (Table 2, entry 8). While molecular oxygen was a competent oxidant for the reaction, *p*-benzoquinone (BQ) provided higher overall yields. Lastly, benzene was determined to be the ideal, non-coordinating solvent for the reaction.[17]

With the optimized conditions in hand we sought to explore the limitations and scope of the catalyst system. A variety of substrates cyclized to produce indolines with varying levels of enantioselectivity (Table 3). The tosyl-protecting group proved to be superior in reactivity and enantioselectivity in comparison to the mesylate.

Tri-substituted substrates, while requiring longer reaction times, gave higher yields and increased enantioselectivity. Para-substituted derivatives proceeded smoothly to give good yields and moderate enantioselectivity. However, upon subjecting ortho-substituted substituents to the reaction conditions, a marked decrease in enantioselectivity was observed. These findings are consistent with the literature.[18] The formation of tosylcarbamate **5** occurred with similar enantioselectivity to indoline derivatives **3**, while morpholine derivative **6** could also be formed, albeit with no enantioselectivity. The modest enantioselectivity attained in these transformations is unsurprising given that the source of chirality in the ligand is distant from the Pd-alkene complex.

To shed light on the mechanism of these transformations, we evaluated key intermediates and transition states relevant to both *trans*- and *cis*-aminopalladation mechanisms using computational methods for model substrate **4a**; for computational expediency methanesulfonic acid was substituted for (+)-CSA. (Scheme 1).

Previous work from our group has highlighted the imporance of low levels of adventitious water on Brønsted acid/Pd(II)-catalyzed reactions.[14] A similar observation was made for the current transformation; this was further borne out in the mechanistic calculations which evaluated water and benzoquinone as neutral ligands during the key C–N forming event. Under the reaction conditions, $Pd(OAc)_2$ undergoes acid-promoted ligand exchange to yield a $Pd(OMs)_2(H_2O)_2$ complex. Coordination to the substrate with loss of a water ligand gives complex **C**. From this common intermediate, facile general base-catalyzed *trans*-aminopalladation takes place via transition state **E** ($\Delta G^{\ddagger}$ 6.2 kcal/mol) to give intermediate **F**; for comparison, the non-base-catalyzed reaction has a markedly higher activation energy of 26.3 kcal/mol, relative to intermediate **D**. Ultimately, ligand dissociation followed by β-hydride elimination furnishes the observed product. Alternatively, *cis*-aminopalladation was found to proceed via the unusual activated complex **B**, in which the sulfonamide group is unligated to the Pd center. This yields the hydrogen bond-stabilized intermediate **A**; ligand loss, proton transfer, and β-hydride elimination furnishes the observed product. These results suggest that the *trans*-aminopalladation

pathway is favored over the *cis*- ($\Delta G^{\ddagger}$ 6.2 vs 26.3 kcal/mol). Additional calculation details are available in the Supporting Information.

Conclusion

In summary, to our knowledge, we have developed the first enantioselective Pd-catalyzed transformation utilizing a chiral sulfonic acid ligand. Novel chiral indoline products were synthesized with up to 45% ee. Computation studies suggest that a *trans*-aminopalladation pathway is operative.

Experimental

General procedure for the enantioselective oxidative amination

To a flame-dried 2-dram vial was added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and (+)-CSA (4.6 mg, 0.02 mmol). Benzene (0.4 mL) was charged and the mixture was then stirred under an argon atmosphere at 20 °C for 20 min. To the vial was then added a solution of the substrate (0.1 mmol), benzoquinone (21.8 mg, 0.2 mmol) and (+)-CSA$^-$Na$^+$ (2.5 mg, 0.01 mmol) in benzene (0.6 mL). The vial was capped then stirred for the indicated time with heating, as indicated in Table 2. Upon reaction completion, the reaction mixture was diluted with EtOAc (3 mL) then stirred vigorously with sat. $Na_2S_2O_3$ (4 mL). The organic layer was then washed sequentially with sat. $Na_2S_2O_3$ (2 x 5 mL), sat. K_2CO_3 (2 x 5 mL), and water (5 mL) then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica column chromatography (4:1 hexanes/Et_2O or 10–20% EtOAc/Hex).

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Supplementary Material

Supplementary data (synthetic procedures, spectral data, chiral HPLC traces and details of the electronic structure calculations, including Cartesian coordinates) can be found at…

Highlights

- Catalytic enantioselective construction of nitrogen-containing heterocycles
- Use of a ***chiral sulfonic acid ligand*** to impart asymmetric induction
- High-level electronic structure calculations were carried out
- A *trans*-aminopalladation mechanism is proposed