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# Hydrogen-Bonding-Assisted Cationic Aqua Palladium(II) Complex Enables Highly Efficient Asymmetric Reactions in Water

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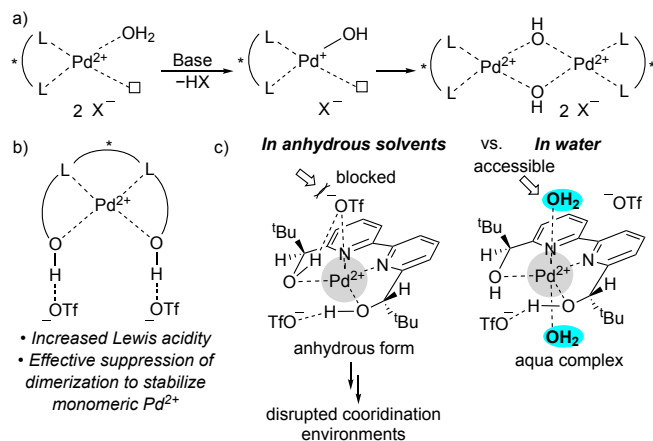
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**Abstract:** Metal-bound water molecules have recently been recognized as a new facet of soft Lewis acid catalysis. Herein, a chiral palladium aqua complex was constructed that enables carbon–hydrogen bonds of indoles to be functionalized efficiently. We embraced a chiral 2,2'-bipyridine as both ligand and hydrogen-bond donor to configure a robust, yet highly Lewis acidic, chiral aqua complex in water. Whereas the enantioselectivity could not be controlled in organic solvents or under solvent-free conditions, the use of aqueous environments allowed the  $\sigma$ -indolylpalladium intermediates to react efficiently in a highly enantioselective manner. This work thus describes a potentially powerful new approach to the transformation of organometallic intermediates in a highly enantioselective manner under mild reaction conditions.

Chiral aqua or hydroxo complexes of transition metals have received increasing attention due to their immense potential for application in catalytic processes involving carbon–carbon bond formation, compared with the corresponding anhydrous complexes.<sup>[1],[2]</sup> Coordinating water molecules in aqua complexes form much stronger hydrogen bonds than free water molecules,<sup>[3]</sup> thus participating in intramolecular hydrogen bonds within the first hydration shell,<sup>[4]</sup> and sometimes conferring a pronounced Brønsted acidity.<sup>[10]</sup> Metal-bound water molecules and hydroxides can act, *inter alia*, as a nucleophile to promote transmetalation or  $\sigma$ -metathesis.<sup>[1m],[2b],[5]</sup> That is, precious-metal aqua complexes offer orthogonal catalysis capable of functionalizing carbon–hydrogen bonds through the formation of organometallic intermediates, which are not feasible with 3d metals.<sup>[1]</sup> Because of their unique stereoelectronic properties, these 16-electron catalysts could impart unprecedented reactivity and selectivity to conventional Lewis acid-catalyzed reactions. While a conceivable drawback of these aqua complexes is their precarious activity under anhydrous conditions caused by the liberation of a water molecule from their primary coordination sphere, aqueous environments would offer them improved durability. Furthermore, asymmetric environments in water often carry transcendent performance that cannot be exerted in organic solvents.<sup>[6]</sup> Chiral precious-metal complexes have, however, rarely been used in aqueous media,<sup>[1b,k],[6]-[10]</sup> in spite of an increasing awareness that performing organic reactions in water meets the worldwide need for green sustainable chemistry. The problem may lie with the insolubility and inherent ease of hydrolysis of these complexes in water because soft acids are reluctant to coordinate with the hard base H<sub>2</sub>O and furthermore they exhibit low hydrolysis constants (e.g. 2.3 for Pd<sup>2+</sup>),<sup>[11]</sup> irreversibly leading to the less soluble  $\mu$ -hydroxo-bridged dimer or oligomer<sup>[1c,h-m],[2e]</sup> (Scheme

1a). Lured by the pluripotency of chiral aqua precious metal complexes for functionalizing carbon–hydrogen bonds in water, we herein describe the development of a chiral palladium complex that is highly stable and active in water.

Applications of chiral palladium complexes to reactions in aqueous media include examples of complexes embedding into a protein scaffold,<sup>[6a],[8]</sup> a robust PEPPSI complex,<sup>[9]</sup> a complex supported on an amphiphilic resin,<sup>[10]</sup> and a micellar system.<sup>[11]</sup> We envisaged a complementary approach wherein a chiral hydrogen-bond donor associated with trifluoromethanesulfonate (triflate) anion would furnish a charge-separated palladium aqua complex with enhanced Lewis acidity (Scheme 1b).<sup>[13]</sup> The high Lewis acidity and the vacant coordination site of such a complex make it more electrophilic than the corresponding neutral complex in coordination with carbon–carbon or carbon–heteroatom multiple bonds.<sup>[14]</sup> The pseudo-square-planar coordination of a chiral hydrogen-bond donor bound to the palladium core would preclude the presence of equatorially bound water molecules that invoke hydrolysis, resulting in enhanced longevity in water. We sought to apply this design to chiral 2,2'-bipyridine ligand **L** bearing two OH groups, which is often found to play a sophisticated role in catalysis exerted in water.<sup>[15]</sup> The structure of the hydrated palladium ion in an aqueous solution adopts a pseudo-Jahn–Teller distorted octahedron, wherein two weakly bound water molecules occupy axial positions with a bond length of 0.7 Å longer than equatorially bound water molecules.<sup>[16]</sup> Given that these properties are clearly distinct from equatorial water molecules in the first hydration shell (Pd–O<sub>water</sub> ca. 2.0 Å) and the second shell (Pd–O<sub>water</sub> >4.0 Å), the axial hydration shell is termed the meso-shell (Pd–O<sub>water</sub> ca. 2.8 Å).<sup>[17]</sup> Aqueous environments thus allow facile access of electron-rich molecules, for example, indole, to the apical position in place of readily exchangeable water molecules. In contrast, under anhydrous conditions, the apical occupancy of one counteranion with another occupying the equatorial region<sup>[18]</sup> would mask the meso-shell and impose the trajectory of indole or solvent molecules on the equatorial plane due to the electrostatic repulsion, disrupting a coordination geometry around palladium(II) to form dangling alcohol units. That is, preferred palladation of indole within the meso-shell in water would enable a highly enantioselective transformation of indole (Scheme 1c).

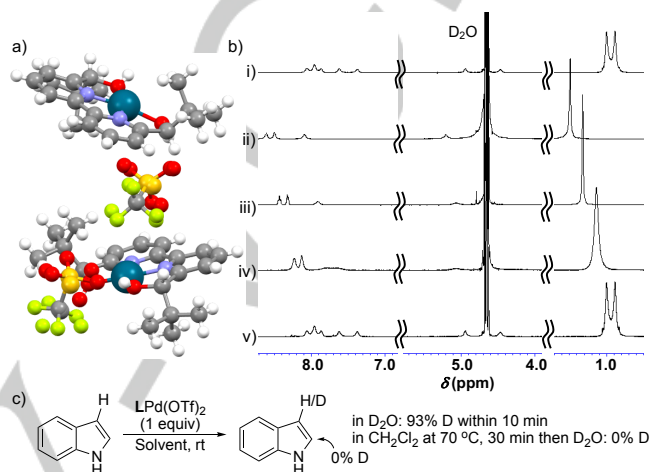


**Scheme 1.** a) Potential problems of palladium aqua complexes under basic conditions. b) The concept of the hydrogen-bond-assisted cationic palladium complex in this study. c) The design of the chiral 2,2'-bipyridine palladium aqua complex that is effective for indole palladation and subsequent asymmetric reaction. The apical triflate anion is labile to exchange with meso-shell water molecules in aqueous environments, further exchanging with reactants. The preferred equatorial intrusion of indole or solvent molecules under anhydrous conditions would weaken the Pd–O<sub>L</sub> bonds, disrupting the coordination environments surrounding Pd<sup>2+</sup>.

We were encouraged by the identification of conditions that enabled isolation of the bench-stable, anhydrous LPd(OTf)<sub>2</sub> complex. The X-ray packing structure of the complex revealed a herringbone packing arrangement within which the palladium ion adopts a pseudo-square-planar structure in a tetradentate manner with ca. 2.0 Å Pd–O<sub>L</sub> bonds (Figure 1a; see the Supporting Information for full details of X-ray crystallography data).<sup>[19]</sup> In the single crystal, two triflate anions occupy the apical position and the equatorial position, with the Pd–O<sub>OTf</sub> bond length (ca. 4.0 Å) being twofold longer than the Pd–O<sub>L</sub> bond, and approximately equivalent to the distance to the second hydration sphere, and forms hydrogen bonding with OH group of **L** (ca. 1.8 Å). As anticipated, the occupancy of the triflate anions within the second shell of the anhydrous LPd(OTf)<sub>2</sub> complex provides only an outer-sphere site for the approaching indole, which may impede the formation of the σ-indolylpalladium complex considering that a C–Pd bond with a bond length of 2.2 Å or shorter is required unless coordination bonds around Pd<sup>2+</sup> are broken.<sup>[14]</sup> The complex in solution was characterized based on UV-vis and <sup>1</sup>H NMR spectroscopic studies. The NMR spectrum of the LPd(OTf)<sub>2</sub> complex in D<sub>2</sub>O exhibited dissymmetric configuration, with one OH group of **L** unexchanged, indicating the preferential hydrogen-bond formation with the equatorial triflate anion, as expected. Variable-temperature <sup>1</sup>H NMR studies revealed that the palladium aqua complex underwent a reversible conformational change in the range from 20 to 80 °C in D<sub>2</sub>O (Figure 1b). The desymmetrized peaks recorded at room temperature were superimposed to form a C<sub>2</sub>-symmetric complex as the temperature was raised, and the spectrum remained unaltered upon cooling to room temperature, denoting the conformational reversibility of the complex.

Noticeable color change was visualized upon mixing LPd(OTf)<sub>2</sub> complex and indole in water (Figure S2). As widely espoused, the palladium(II) would perform an electrophilic palladation of the indole to give an indolylpalladium intermediate

as a trigger of the indole substitution.<sup>[20]</sup> To corroborate the formation of the σ-indolylpalladium intermediate, LPd(OTf)<sub>2</sub> complex was incubated with indole at room temperature in D<sub>2</sub>O. The indole was found to forthwith undergo H/D exchange exclusively at C3 position, despite its immiscibility in D<sub>2</sub>O (Figure 1c and Table S2). In contrast, incubating under anhydrous conditions attributed to no D incorporation. As presumed, the occupancy of triflate anion within the second shell of the anhydrous complex would impede the formation of the σ-indolylpalladium intermediate.

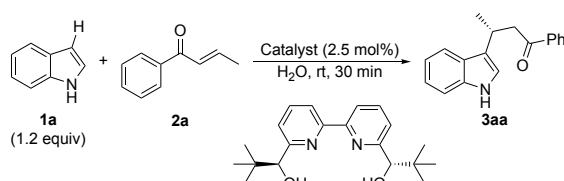


**Figure 1.** a) Crystal structure of anhydrous LPd(OTf)<sub>2</sub>. The site-occupancy disorder of triflate anions is shown. b) Variable-temperature <sup>1</sup>H NMR studies of LPd(OTf)<sub>2</sub> complex in D<sub>2</sub>O recorded at i) 20 °C, ii) 40 °C, iii) 60 °C, iv) 80 °C, and v) 20 °C after cooling from 80 °C. c) Deuterium quenching experiments of a putative σ-indolylpalladium intermediate.

The complex was then amenable to a model asymmetric reaction that involves C–H functionalization of the privileged indole pharmacophore (Table 1). Although there have been several reports delineating catalytic asymmetric Friedel–Crafts alkylation of indole **1a**, β-substituents are known to have a profound influence on enantioselection; *trans*-1-phenylbut-2-en-1-one **2a** has been recognized as one of the most difficult substrates on which to impose stereoselectivity without the need for high catalyst loadings.<sup>[21]</sup> Under the optimized reaction conditions, the C–H bond of **1a** could be functionalized with **2a** in a highly enantioselective fashion within 30 min (entry 1). According to our definition,<sup>[6a]</sup> this reaction is classified as Type IIIa (Figure S2). The distinguished catalytic activity of LPd(OTf)<sub>2</sub> was apparent by comparing it with the micellar system previously reported as Type IIb reaction,<sup>[11]</sup> with the latter showing significantly retarded kinetics and erosion of enantioselectivity (entry 2). Likewise, the reaction was sluggish and less selective in the presence of the polyoxyethanyl-α-tocopheryl succinate-based amphiphile designed by Lipshutz and Ghorai,<sup>[22]</sup> although the field of transition-metal-catalyzed chemistry has flourished in water with the aid of this surfactant (entry 3). The activity was highly contingent on the ligands coordinating to palladium, with a tetra-coordination fashion being superior to bidentate coordination (entries 4–6). Because the μ-hydroxo-bridged dimer is more stable than monomeric [Pd(2,2'-bpy)(OH<sub>2</sub>)<sub>2</sub>]<sup>2+</sup>,<sup>[23]</sup> the results underpin the importance of hydrogen bonds between the alcohol unit of **L** and the triflate

anion. A loss of cationicity impeded the progress of the reaction (entry 7). Similarly, the activity of methanesulfonate deteriorated due to the reduced cationic nature compared with triflate, with a comparable level of enantioselectivity (entry 8). The use of lipophilic anions which allowed the reaction to be Type IIIb, did not alter their catalytic activities, with a poorer nucleophile being more enantioselective (entries 9–13). The water-immiscible perfluorooctanesulfonate, albeit with its electron-withdrawing property, resulted in decreased enantioselectivity (entry 14).

**Table 1.** Effect of ligands surrounding palladium cation.



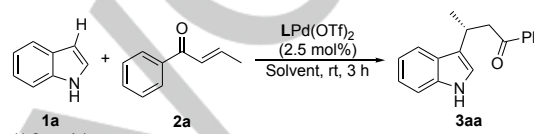
Entry	Catalyst	Yield (%) <sup>[a]</sup>	Ee (%) <sup>[c]</sup>
1	LPd(OTf) <sub>2</sub>	55	89
2 <sup>[d]</sup>	PdCl <sub>2</sub> , SDS, L, PhNMe <sub>2</sub>	5	56
3 <sup>[e]</sup>	LPd(OTf) <sub>2</sub>	22	70
4	Pd(MeCN) <sub>4</sub> (OTf) <sub>2</sub>	15 <sup>[b]</sup>	–
5	Pd(2,2'-bpy)(OTf) <sub>2</sub>	3 <sup>[b]</sup>	–
6	Pd(phen)(OTf) <sub>2</sub>	0 <sup>[b]</sup>	–
7	LPdCl <sub>2</sub>	<1	0
8	LPd(OSO <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	7	84
9	LPd[OSO <sub>2</sub> (4-MeC <sub>6</sub> H <sub>4</sub> )] <sub>2</sub>	57	53
10	LPd[OSO <sub>2</sub> (4-FC <sub>6</sub> H <sub>4</sub> )] <sub>2</sub>	40	65
11	LPd[OSO <sub>2</sub> (4-MeOC <sub>6</sub> H <sub>4</sub> )] <sub>2</sub>	62	37
12	LPd[OSO <sub>2</sub> (2-naph)] <sub>2</sub>	56	19
13	LPd[OSO <sub>2</sub> (1-pyrene)] <sub>2</sub>	86	4
14	LPd(OSO <sub>2</sub> C <sub>8</sub> F <sub>17</sub> ) <sub>2</sub>	69	35

[a] Isolated yield. [b] Determined by <sup>1</sup>H NMR analysis. [c] Determined by HPLC analysis. [d] PdCl<sub>2</sub> (2.5 mol%), SDS (5 mol%), L (3 mol%), PhNMe<sub>2</sub> (5 mol%). Conditions are adopted from Ref. [11] with reduced catalyst loading. [e] Run in the presence of 2 wt% aqueous TPGS-750-M.

Consistent with our hypothesis and the NMR studies of the LPd(OTf)<sub>2</sub> complex, enantioselection deteriorated when the reaction was run in organic solvents (entries 1–10 in Table 2). The palladium complex LPd(OTf)<sub>2</sub> was capable of promoting the reaction in an anhydrous form in nonpolar solvents albeit with reduced selectivity (entries 1–3), whereas it catalyzed the reaction in a nonselective fashion in polar solvents (entries 4–6). The feasible electrophilic activation of carbonyl or soft  $\pi$ -bond<sup>[24]</sup> would provoke the C3-alkylation of indole in aprotic solvents without forming a  $\sigma$ -indolylpalladium intermediate. The use of dimethylsulfoxide as a solvent disabled its catalytic activity (entry 7). In a solution of coordinating solvent, the Pd–L binding was vulnerable to the superior enthalpy of solvent coordination, inducing aggregation and formation of Pd black during the progress of the reaction (entries 8–10). Moreover, the catalyst

displayed reduced levels of enantioselection under neat conditions (entry 11). In contrast, the putative aqua complex that would form in water enabled high enantioselection to be realized with quantitative product formation (entry 12). The catalyst induced decreased enantioselectivity when it was not incubated with water but with substrates even though the reaction was performed in water (entry 13), highlighting the conspicuous effect of an aqua complex on the formation of a  $\sigma$ -indolylpalladium intermediate and a subsequent enantioselective control. Equally, the most effective chiral environments are assembled at the substrate-water interface, while enantioselectivity plunged in homogeneous reactions.

**Table 2.** Influence of solvents.



Entry	Solvent	Yield (%) <sup>[a]</sup>	Ee (%) <sup>[b]</sup>
1	n-hexane	95	31
2	CH <sub>2</sub> Cl <sub>2</sub>	80	34
3	toluene	94	16
4	THF	92	1
5	Et <sub>2</sub> O	72	0
6	EtOAc	77	1
7	DMSO	0	–
8	acetone	44	1
9	MeCN	90	1
10	MeOH	91	2
11	– (neat)	95	12
12	H <sub>2</sub> O	97	90
13 <sup>[c]</sup>	H <sub>2</sub> O	94	61

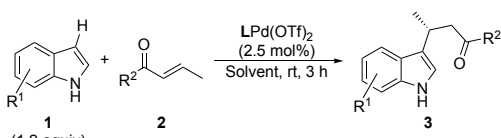
[a] Isolated yield. [b] Determined by HPLC analysis. [c] During the procedure, water was added at the end.

With optimized conditions in hand, the substituent effects with respect to both indole **1** and  $\alpha,\beta$ -unsaturated ketone **2** were appraised (Table 3). The products **3** formed in a highly enantioselective manner, irrespective of the electronic features of the substituents on the phenyl group of **2** (entries 1–7). The heteroaromatic enone **2h** and **2i** could serve as a substrate, giving the corresponding product **3ah** and **3ai** in excellent yield with high enantioselectivity (entry 8 and 9). The reaction was applicable to a new candidate of optically active ferrocene/cymantrene-indole hybrids, without Pd black formation even in the presence of metal carbonyls (entry 10, 11). Ferrocene and cymantrene serve as a potent organometallic species that can endow compounds with enhanced biological activity in areas such as antimalaria and anticancer drugs.<sup>[25]</sup> The cyclohexyl group also provided the desired product **3ak** with good enantioselectivity (entry 12). Eroded enantioselectivity



might be associated with the formation of palladium black in the course of the reaction. The addition of even small amounts of organic solvents proved fruitless because the aqua complex preferably undergoes water exchange reactions with these organic solvents and loses the intended performance (Table S1). These results underscore the essential use of water as a reaction medium. The palladium complex was also applicable to the enantioenriched formation of a fluorinated tertiary carbon stereocenter despite a solid-solid reaction (entry 13). The reaction with indoles substituted with electron-donating or electron-withdrawing groups proceeded smoothly with high enantioselectivities (entries 15–21). Noteworthy is the tolerance of bromo groups on indole under our catalysis (entry 21). In addition, our catalysis was applicable to challenging, enantioselective C2-alkylation of a putative pyrrolylpalladium species (Scheme S2).

**Table 3.** Substituent effects.



Entry	R <sup>1</sup>	1	R <sup>2</sup>	R <sup>3</sup>	2	3	Yield (%) <sup>[a]</sup>	Ee (%) <sup>[b]</sup>
1	–	<b>1a</b>	Ph	Me	<b>2a</b>	<b>3aa</b>	97	90
2 <sup>[f]</sup>	–	<b>1a</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Me	<b>2b</b>	<b>3ab</b>	99	92
3	–	<b>1a</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>2c</b>	<b>3ac</b>	95	88
4 <sup>[c]</sup>	–	<b>1a</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Me	<b>2d</b>	<b>3ad</b>	90	90
5 <sup>[c]</sup>	–	<b>1a</b>	4-FC <sub>6</sub> H <sub>4</sub>	Me	<b>2e</b>	<b>3ae</b>	86	90
6 <sup>[c]</sup>	–	<b>1a</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Me	<b>2f</b>	<b>3af</b>	82	89
7 <sup>[e,f]</sup>	–	<b>1a</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Me	<b>2g</b>	<b>3ag</b>	93	82
8 <sup>[c]</sup>	–	<b>1a</b>	2-thienyl	Me	<b>2h</b>	<b>3ah</b>	94	93
9 <sup>[e,f]</sup>	–	<b>1a</b>	2-furyl	Me	<b>2i</b>	<b>3ai</b>	92	84
10 <sup>[c]</sup>	–	<b>1a</b>	2-ferrocenyl	Me	<b>2j</b>	<b>3aj</b>	37	85
11 <sup>[e,f]</sup>	–	<b>1a</b>	CpMn(CO) <sub>3</sub>	Me	<b>2k</b>	<b>3ak</b>	40	87
12 <sup>[e,f]</sup>	–	<b>1a</b>	Cy	Me	<b>2l</b>	<b>3al</b>	86	78
13 <sup>[c,f]</sup>	–	<b>1a</b>	Ph	CF <sub>3</sub>	<b>2m</b>	<b>3am</b>	>99	78
14 <sup>[e,f]</sup>	–	<b>1a</b>	Ph	Et	<b>2n</b>	<b>3an</b>	>99	84
15 <sup>[e]</sup>	5-Me	<b>1b</b>	Ph	Me	<b>2a</b>	<b>3ba</b>	97	89
16	6-Me	<b>1c</b>	Ph	Me	<b>2a</b>	<b>3ca</b>	94	84
17	5-MeO	<b>1d</b>	Ph	Me	<b>2a</b>	<b>3da</b>	97	87
18	5-BnO	<b>1e</b>	Ph	Me	<b>2a</b>	<b>3ea</b>	94	80
19 <sup>[e,f]</sup>	5-F	<b>1f</b>	Ph	Me	<b>2a</b>	<b>3fa</b>	>99	87
20 <sup>[e,f]</sup>	5-Cl	<b>1g</b>	Ph	Me	<b>2a</b>	<b>3ga</b>	86	81
21 <sup>[e,f,g]</sup>	5-Br	<b>1h</b>	Ph	Me	<b>2a</b>	<b>3ha</b>	95	81

[a] Isolated yield. [b] Determined by HPLC analysis. [c] For 6 h. [d] For 12 h. [e] For 24 h. [f] At 5 mol% catalyst loading. [g] 2.5 mol% of **L** was added.

In conclusion, we have demonstrated that a chiral palladium aqua complex, wherein a chiral ligand interacts with trifluoromethanesulfonate anion as hydrogen-bond donor,

displays high durability, high Lewis acidity, and high levels of enantioselection through electrophilic palladation. The power of the designed complex **LPd(OTf)<sub>2</sub>** was shown to manifest exclusively in water through the robust and enantiocontrolled functionalization of indole C–H bond, via an efficient and operationally simple protocol. Noteworthy, substrates are reacted in a highly enantioselective manner although immiscible with water (Type IIIa reaction). The design represents a potentially powerful method to transform highly active organometallic intermediates in a highly enantioselective manner under mild reaction conditions.

## Acknowledgements

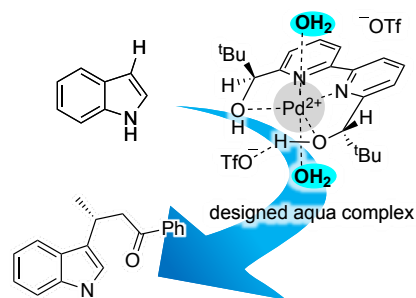
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**Keywords:** asymmetric catalysis • Lewis acids • reaction in water • cationic palladium • aqua complex

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## Entry for the Table of Contents



- Reduced catalyst loading
- Water-promoted indole C–H functionalization
- "In water"-driven stereoselectivity

Metal-bound water molecules have recently been recognized as a new facet of soft Lewis acid catalysis. Herein, a chiral palladium aqua complex was constructed and used to functionalize carbon–hydrogen bonds of indoles robustly and efficiently in a highly enantioselective manner. The power of the designed complex was displayed exclusively in water. The inclusion of organic solvents deteriorated the designed catalysis.