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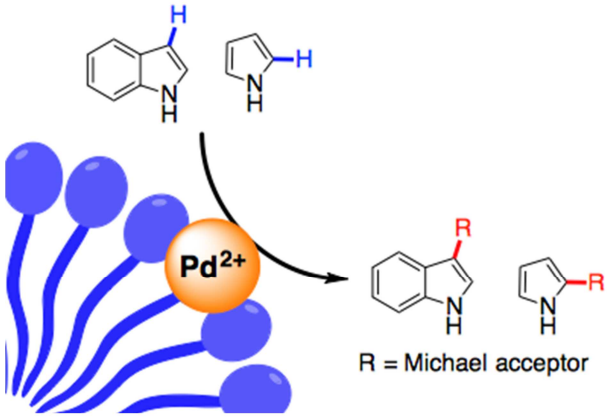

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The combined use of cationic palladium(II) with a surfactant for the C–H functionalization of indoles and pyrroles in water[#]

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[#]*Dedicated to Prof. Jiro Tsuji and Prof. Barry M. Trost on the occasion of receiving Tetrahedron Prize for Creativity in Organic Chemistry*

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ABSTRACT

The utility of electrophilic palladium(II) species was demonstrated for C–H bond functionalization of indoles and pyrroles in water. The system displayed attractive features that are reminiscent of both precious-metal catalysis and micellar catalysis.

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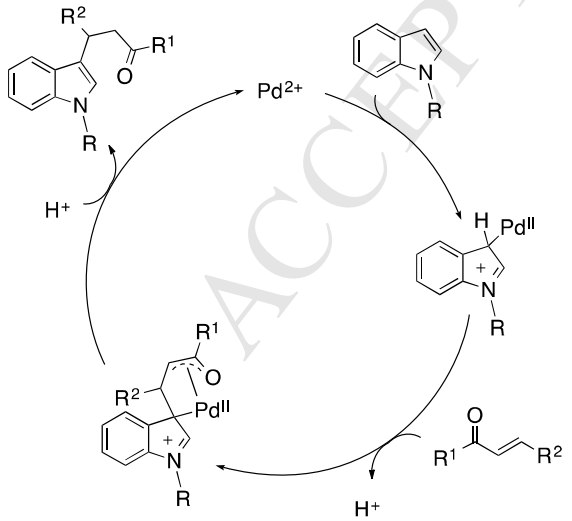
1. Introduction

In recent years, reactions involving transition-metal catalysts in aqueous media have attracted a great deal of attention from the chemical community. The benefits of such systems include the potential to achieve unique reactivity and selectivity in many chemical processes in an environmentally acceptable, practical manner, together with reduced cost. Although significant progress has been made through the use of traditional Lewis acid catalysts,[1] the application of precious-metal catalysts has been less explored.[2] Precious-metal catalysts have the unique ability to activate archetypal chemical bonds because of the mutual interaction between occupied metal d orbitals and empty σ* orbitals lying across a bond. Among these catalysts, palladium has occupied a pivotal position in organic chemistry because of its ability to form alkyl or aryl palladium(II) intermediates that can be used not only in numerous types of cross-coupling and Tsuji–Trost reactions but also for C–H bond functionalization; indeed, research on these reactions has flourished over the last two decades.[3] In contrast to the nucleophilic character of palladium(0) complexes, palladium(II) complexes are relatively electrophilic and tend to react with a wide range of electron-rich substrates.[4] Although the utility of other oxidation states (I, III, IV, V and VI) has been emerging,[5,6] the practical application of compounds that feature these oxidation states has been constrained by their relatively low stability.

We envisaged that the use of electrophilic palladium(II) species in water could expand the range of chemical transformations available (Scheme 1). This approach would involve electrophilic palladation with an electron-deficient palladium(II) catalyst to generate an indolyl-palladium(II) intermediate, and this intermediate is supported by a handful of reports including an X-ray crystallographic investigation.[7–9] The propensity of alkyl palladium(II) C-enolate intermediates, formed upon addition of α,β-unsaturated compounds, toward β-hydride elimination[10] is expected to be compensated for by instantaneous protonation subsequent to nucleophilic addition through a proton-shuttle mechanism, which is feasible in the Stern layer spreading on a micellar surface.



Scheme 1. Electrophilic C–H bond functionalization with cationic palladium(II), which retains its oxidation state.

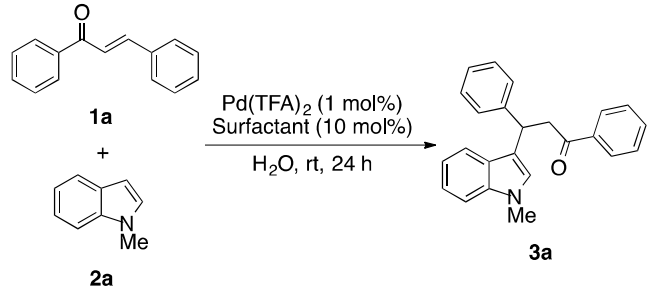
There are, however, serious challenges associated with exploiting electrophilic palladium(II) species in water. (1) Almost all palladium(II) salts have an inherently insoluble and unstable nature. (2) Palladium(II) can be readily reduced by reducing reagents such as alkenes, terminal alkynes, alcohols, amines, and phosphines to form Pd black, which frequently leads to rapid deactivation of the catalyst.[11] Great efforts have been made to overcome the intrinsic problem of Pd black formation from palladium(II) salts; these typically involve pyridine-based[12] and *N*-heterocyclic carbene-based[13] methods of stabilization. As an alternative approach, we have focused on the use of anionic surfactants to induce refined dispersibility and well-ordered electrostatic interaction to stabilize cationic palladium(II) species. It is well-defined and well-documented that Pd(0) nanoparticles and palladium(0) species generated in situ have been stabilized by ionic surfactants[14] and designed nonionic surfactants,[15] and that their formation has enabled palladacycles[16] in water; however, the remaining oxidation states have been less explored.

Among a myriad species that react with palladium(II), the C–H bond functionalization of indoles is one of the most alluring, in particular, the ability to transform a C–H bond into a new C–C bond.[17] The C3-functionalized products are valuable building blocks for the construction of indole architectures with potential biological activities, including a class of bioactive indole alkaloids known as hapalindoles and other 3-substituted indoles.[18] An example reported in 2005 of the application of palladium(II) catalysis for C3 functionalization of indole with α,β-unsaturated compounds in the absence of oxidants[10] involved the use of an ionic liquid and elevated temperature (100 °C).[19]

2. Results and discussion

We commenced our investigation by examining the behavior of an electrophilic indolyl-palladium(II) intermediate in the presence of surfactants. At the outset, the reaction of chalcone (**1a**) with *N*-methylindole (**2a**) was set as the model reaction (Table 1). In the absence of surfactant, no catalytic activity was found with 1 mol% palladium(II) trifluoroacetate, and the formation of Pd black was observed (entry 1). Nor did the inclusion of a cationic or nonionic surfactant assist the palladium(II) catalysis (entries 2–5); however, inclusion of the anionic surfactant sodium dodecyl sulfate (SDS) in the reaction led to the formation of the desired product **3a** in high yield under aerobic conditions (entry 7). Unfortunately, preliminary endeavors to isolate palladium bis(dodecyl sulfate) failed because of persistent agglomeration and precipitation of Pd black. Comparable activity was observed when the reaction was conducted in the presence of a sulfite-based surfactant with decreased isentropic compressibility (entry 8), which suggests that the reaction took place in the interior of micelles.[20] The use of surfactants with shorter chain length led to a reduction in catalyst performance, whereas the inclusion of a surfactant with extended chains afforded increased yield (entries 9 and 10). The use of palladium(II) catalyst combined with sodium dodecylbenzenesulfonate (SDBS) also exhibited superior performance (entry 11).

Table 1. Evaluation of surfactant effects on the reaction of **1a** with **2a**



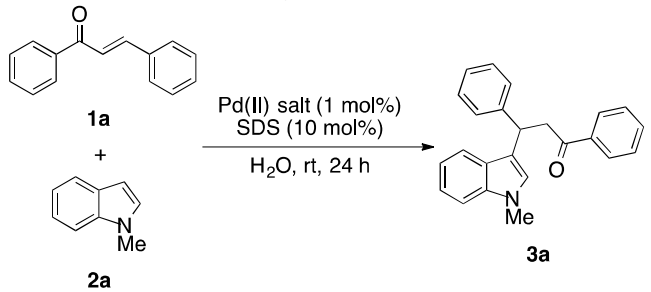
Entry	Surfactant	Yield (%)[a]
1	–	NR
2	CTAB	NR
3	Triton X114	NR
4	Triton Cf-10	NR
5	Triton N-101	NR
6	TPGS-750-M	NR
7	SDS	88
8	$NaOSO_2C_{11}H_{23}$	85
9	$NaOSO_3C_9H_{19}$	37
10	$NaOSO_3C_{16}H_{33}$	62
11	SDBS	94

[a] Yield based on NMR spectroscopic analysis.

The reaction described above catalyzed by 1 mol% palladium(II) trifluoroacetate in the presence of 10 mol% SDS delivered higher yield when it was conducted on a fivefold larger scale (Table 2, entry 1).

Other palladium(II) salts were then examined (Table 2). A significant decrease in the chemical yield was observed when palladium(II) acetate was used as catalyst instead of the corresponding trifluoroacetate (entry 2). The use of insoluble palladium(II) salts also provided a comparable yield of the product **3a** (entries 3 and 4). The inclusion of palladium(0) did not deliver any of the desired product (entry 5), suggesting that palladium(II) was stabilized in a micellar system. Although palladium(II) chloride and palladium(II) trifluoroacetate exerted almost the same level of catalysis, a significant reduction in the reaction yield was observed with the former in the reaction with indole **2b**, which contains a free NH moiety (39 vs. 67% yield after 20 h reaction).

Table 2. Evaluation of counteranion effects on the reaction

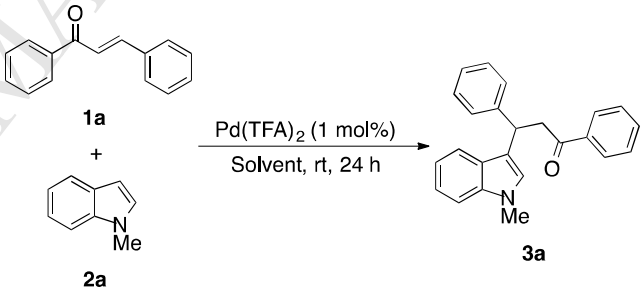


Entry	Palladium(II) salt	Yield (%)[a]
1	$Pd(TFA)_2$	88 (94)[b]
2	$Pd(OAc)_2$	11
3	$PdCl_2$	93 (87)[b]
4	$PdBr_2$	80
5	$Pd(PPh_3)_4$	NR

[a] Yield based on NMR spectroscopic analysis. [b] Reaction conducted on a fivefold larger scale (1.5 mmol).

The integral role of water was revealed by conducting the reaction in other protic and aprotic solvents (Table 3). Conducting the reaction of **1a** with **2a** in the presence of palladium(II) trifluoroacetate in methanol, without surfactant, led to a twofold reduction in the product yield (entry 2). The reaction proceeded even more sluggishly in ethanol (entry 3). Although palladium(II) salts are known to undergo electronic stabilization through back-donation of the antibonding π^* orbital of nitrile solvents, forming species such as readily available $PdX_2(PhCN)_2$ and $PdX_2(MeCN)_2$, coordination of acetonitrile to the palladium(II) core degraded its activity (entry 4). When dichloromethane was used as solvent, the reaction proceeded through intramolecular proton transfer after nucleophilic addition to deliver the desired product in 27% yield (entry 5). The reaction did not proceed in diethyl ether (entry 6).

Table 3. Effect of solvent on the reaction



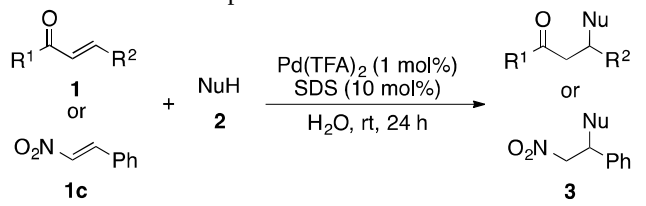
Entry	Solvent	Yield (%)[a]
1[b]	H_2O	88
2	MeOH	46
3	EtOH	8
4	MeCN	Trace
5	CH_2Cl_2	27
6	Et_2O	Trace

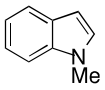
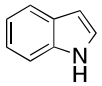
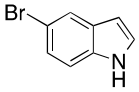
[a] Yield based on NMR spectroscopic analysis. [b] Reaction conducted in the presence of SDS.

With the optimized conditions in hand, a range of α,β-unsaturated compounds was reacted with indoles to afford the corresponding adducts in high yields (Table 4). Reaction of methylvinyl ketone (**1b**) with **2a** furnished the monosubstituted adduct **3b** exclusively in high yield (entry 2). No formation of polymeric materials was observed in the reaction. The same indole was also functionalized at the C3 position with β-nitrostyrene (**1c**; entry 3). The free NH of indole **2b** was found to be tolerant of the reaction conditions (entries 4 and 5). Notably, the bromo group of 5-bromoindole (**2c**) survived under these

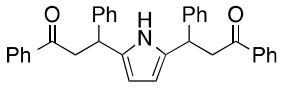
reaction conditions without dehalogenation (entries 6 and 7). In addition, acid-sensitive pyrroles **2d** and **2e** underwent C2 functionalization exclusively without any polymerization (entries 8 and 9). Notably, pyrrole **2d** reacted with two equivalents of chalcone **2a** at the C2 and C5 positions of the pyrrole (entry 8).

Table 4. Substrate scope or the reaction



Entry	Acceptor R1	Acceptor R2		Nucleophile		Yield (%)[a]
1	Ph	Ph	**1a**		**2a**	88 (**3a**)
2	Me	H	**1b**			89 (**3b**)
3			**1c**			80 (**3c**)
4	Me	H	**1b**		**2b**	88 (**3d**)
5			**1c**			85 (**3e**)
6	Ph	Ph	**1a**		**2c**	50 (**3f**)
7			**1c**			64 (**3g**)
8	Ph	Ph	**1a**		**2d**	72 (**3h**)
9			**1c**		**2e**	51 (**3i**)

[a] Isolated yield.

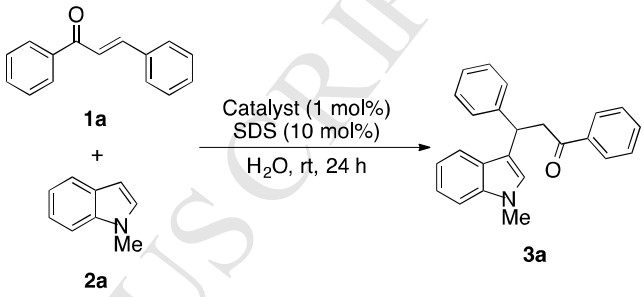


3h

A plethora of catalysts have been developed for 1,4-addition reactions with indoles, including Lewis acid[21] or Brønsted acid[22] catalysts. The postulated reaction pathway shown in Scheme 1 involves a nucleophilic attack process for which the notion of Lewis acidity is already present; an acceptor is expected to coordinate to and be activated by the palladium(II) core. However, the inherently low Lewis acidic nature of palladium(II) restricts its use as a Lewis acid catalyst. The behavior of cationic palladium(II) complexes as a Lewis acid catalyst has been embodied in oxa-Michael[23] or aza-Michael[24] reactions. It has been found that single-electron-transfer processes are not involved in palladium(II)-induced activation of an acceptor.[24e,25] Thus, the proposed palladium(II)-acceptor complex would undergo protonolytic cleavage, which should be accelerated by acids.[25,26] The low hydrolysis constant of cationic palladium(II)[27] means that it can release a sufficient amount of acid to facilitate this cleavage.[28] Acids should be also required for the final protonolytic cleavage.

To gain insight into the reaction pathway, the reaction was also carried out in the presence of Lewis acid or Brønsted acid (Table 5). It was verified that SDS alone did not catalyze the reaction (entry 1). Scandium tris(dodecyl sulfate) $Sc(DS)_3$ is known to be a typical Lewis acid that forms a colloidal dispersion and yields C3-functionalized indoles in the reaction with electron-deficient alkenes.[21e] However, when 1 mol% $Sc(DS)_3$ was used as catalyst, the reaction proceeded in low yield (entry 3). In contrast, 2 mol% trifluoroacetic acid catalyzed the reaction smoothly to give a comparable yield (entry 4). On the other hand, in the reaction of 3-methylindole (**2f**) with β-nitrostyrene (**1c**), palladium(II) catalysis provided C2-functionalized product **3j** (Table 6) in higher yield than that achieved under acid catalysis.

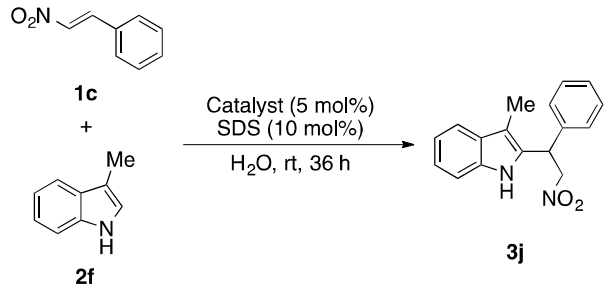
Table 5. Comparison of catalytic activity for the reaction of **1a** with **2a**



Entry	Catalyst	Yield (%)[a]
1	–	NR
2	$Pd(TFA)_2$	88
3[b]	$Sc(DS)_3$	16
4[c]	TFA	91

[a] Yield based on NMR spectroscopic analysis. [b] Reaction conducted in the absence of SDS. [c] With 2 mol% TFA.

Table 6. Comparison of catalytic activity for the reaction of **1c** with **2f**



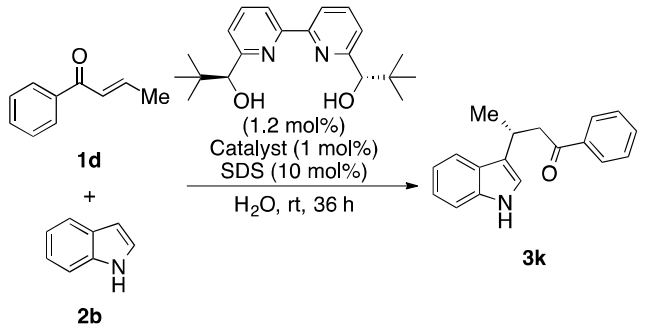
Entry	Catalyst	Yield (%)[a]
1	$Pd(TFA)_2$	32
2[b]	TFA	23

[a] Isolated yield. [b] With 10 mol% TFA.

Finally, the system was extended to asymmetric catalysis (Table 7). Indole **2b** could be functionalized at the C3 position in 78% yield with 72% ee through the reaction with **1d** in the presence of a chiral palladium(II) complex formed with chiral 2,2′-bipyridine (entry 1). Given that cationic palladium(II) is known to form a stable complex with 2,2′-bipyridine,[29] chiral 2,2′-bipyridine,[30] which is effective for the reaction performed in water, was chosen as a chiral ligand. Chiral information was not delivered to the product under Brønsted acid catalysis (entry 2).

Although the generated acid is expected to play a pivotal role in protonolytic cleavage to release the desired product, these results clearly suggest the involvement of palladium(II) in a nucleophilic attack, although this conclusion is based on an unoptimized reaction with the chiral ligand.

Table 7. Toward asymmetric C–H bond functionalization of indole in water



Entry	Catalyst	Yield (%)[a]	Ee (%)[b]
1[c]	$Pd(TFA)_2$	78	72
2[d]	TFA	89	0

[a] Isolated yield. [b] Determined by HPLC analysis. [c] 2.4 mol% of 2,6-di-*tert*-butylpyridine was added. [d] 2 mol% TFA was used as catalyst.

3. Conclusion

The catalytic behavior of cationic palladium(II) in a micellar system was studied in detail. The combination of catalyst with anionic surfactant was effective in inhibiting the formation of Pd black. The electrophilic palladium(II) was stabilized in the micelles and exploited to functionalize indoles and pyrroles in water. The inherent tendency of palladium(II) complexes to undergo hydrolysis means that it can release Brønsted acid, which would be required to effect the final protonolytic cleavage to produce the product. Although the observed activity was equivalent to that obtained under Brønsted acid catalysis, chiral information obtained by using an asymmetric variant of the reaction was clearly retained. The enhanced reactivity observed compared with that obtained with a typical Lewis acid implies that an unusual form of catalysis is operating in this system that is distinct from that of Lewis acid and Brønsted acid catalysis.

4. Experimental section

4.1. General information

NMR spectra were recorded with a JEOL ECX-600 or a ECX-500 spectrometer, operating at 600 or 500 MHz for ^{1}H and at 150 or 125 MHz for ^{13}C NMR in $CDCl_3$, unless otherwise noted. $CDCl_3$ served as the internal standard (δ = 7.24 ppm) for ^{1}H NMR and (δ = 77.0 ppm) for ^{13}C NMR. HPLC was carried out with SHIMADZU LC-10ATvp (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R8A (Chromatopac) using Daicel Chiralpak® or Chiralcel® columns. Preparative thin-layer chromatography (PTLC) was carried out with Wakogel B-5F from Wako Pure Chemical Industries, Ltd. Deionized water from a MILLIPORE Milli-Q machine (Gradient A 10) was used as solvent without further treatment. All organic solvents used were commercially available anhydrous solvents, which were distilled appropriately under an argon atmosphere or were stored over molecular sieves prior to use. All reagents used as substrates were either distilled or recrystallized before use. *N*-Methylindole was prepared by using reported procedures.[31] Chiral 2,2′-bipyridine was synthesized by using reported procedures.[30] $Sc(OSO_3C_{12}H_{25})_3$[32] was also prepared by a known method.

4.2. General procedure for Pd(II)-catalyzed reaction of indoles with Michael acceptors in water

A mixture of $Pd(OCOCF_3)_2$ (1.0 mg, 0.003 mmol) and SDS (8.7 mg, 0.03 mmol) was stirred in water (0.6 mL) for 1 h at room temperature. After successive addition of **1a** (62.5 mg, 0.3 mmol) and indole **2a** (47.2 mg, 0.36 mmol), the mixture was stirred vigorously for 24 h at room temperature. The reaction was quenched with saturated aq $NaHCO_3$ and brine. The aqueous layer was extracted with dichloromethane (three times), and the combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (elution: *n*-hexane/ethyl acetate = 3:1) to give the corresponding product **3a** (89.5 mg, 88% yield).

*4.2.1. 3-(1-Methyl-1H-indol-3-yl)-1,3-diphenylpropan-1-one (**3a**)*[33]

White solid; mp 181–182 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 6.9 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.44–7.41 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.26–7.24 (m, 3H), 7.19–7.14 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.83 (s, 1H), 5.06 (t, 1H, *J* = 6.9 Hz), 3.80 (dd, *J* = 6.5, 16.9 Hz, 1H), 3.74 (dd, *J* = 7.6, 16.5 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 198.5, 144.4, 137.3, 137.1, 133.0, 128.5, 128.4, 128.1, 127.8, 127.0, 126.2, 121.7, 120.0, 118.8, 117.8, 109.1, 45.3, 38.1, 32.7.

*4.2.2. 4-(1-Methyl-1H-indol-3-yl)butan-2-one (**3b**)*[34]

Colorless oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.50 (d, *J* = 7.6 Hz, 1H), 7.22–7.14 (m, 2H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.77 (s, 1H), 3.66 (s, 3H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 208.8, 137.0, 127.5, 126.3, 121.6, 118.7, 113.6, 109.2, 44.3, 32.6, 30.0, 19.2.

*4.2.3. 1-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole (**3c**)*[35]

Pinkish oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.45 (d, *J* = 8.0 Hz, 1H), 7.33–7.22 (m, 7H), 7.07 (dd, *J* = 7.5 Hz, 1H), 6.86 (s, 1H), 5.18 (t, *J* = 8.0 Hz, 1H), 5.05 (dd, *J* = 8.0, 12.6 Hz, 1H), 4.93 (dd, *J* = 8.6, 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 139.3, 137.2, 128.9, 127.7, 127.5, 126.5, 126.3, 122.2, 119.4, 118.9, 112.7, 109.5, 79.5, 41.5, 32.8.

*4.2.4. 4-(1H-Indol-3-yl)butan-2-one (**3d**)*[36]

White solid; mp 93–95 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.97 (br s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.97 (s, 1H), 3.05 (t, *J* = 7.7 Hz, 2H), 2.84 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 208.8, 136.3, 127.1, 122.0, 121.4, 119.3, 118.6, 115.2, 111.1, 44.1, 30.0, 19.3.

*4.2.5. 3-(2-nitro-1-phenylethyl)-1H-indole (**3e**)*[37]

Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.07 (br s, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.33–7.25 (m, 6H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.01 (s, 1H), 5.18 (t, *J* = 8.0 Hz, 1H), 5.06 (dd, *J* = 8.0, 12.6 Hz, 1H), 4.94 (dd, *J* = 8.6, 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 139.1, 136.4, 128.9, 127.7, 126.1, 122.7, 121.6, 119.9, 118.9, 114.4, 111.4, 79.5, 41.5.

*4.2.6. 3-(5-Bromo-1H-indol-3-yl)-1,3-diphenylpropan-1-one (**3f**)*[33]

White solid; mp 158–160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.00 (br s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.56–7.54 (m, 2H), 7.45–7.42 (m, 2H), 7.33–7.17 (m, 7H), 7.02 (s, 1H), 5.00 (t, *J* = 7.2 Hz, 1H), 3.78 (dd, *J* = 7.4, 16.6 Hz, 1H), 3.70 (dd, *J* = 7.4, 16.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.4, 143.8, 136.9, 135.2, 133.1, 128.6, 128.6, 128.4, 128.1, 127.7, 126.5, 125.0, 122.6, 122.0, 118.9, 112.7, 112.6, 45.2, 38.0.

*4.2.7. 5-Bromo-3-(2-nitro-1-phenylethyl)-1H-indole (**3g**)*[35]

Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.16 (br s, 1H), 7.54 (s, 1H), 7.34–7.20 (m, 7H), 7.06 (d, *J* = 1.2 Hz, 1H), 5.12 (t, *J* = 8.0 Hz, 1H), 5.02 (dd, *J* = 8.1, 12.6 Hz, 1H), 4.92 (dd, *J* = 8.0, 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.7, 135.1, 129.0, 127.9, 127.8, 127.6, 125.7, 122.7, 121.5, 114.1, 113.3, 112.8, 79.4, 41.3.

*4.2.8. 3,3'-(1H-Pyrrole-2,5-diyl)bis(1,3-diphenylpropan-1-one) (**3h**)*[38]

Yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.90–7.88 (m, 4H), 7.55–7.52 (m, 2H), 7.44–7.41 (m, 4H), 7.30–7.20 (m, 10H), 5.70–5.64 (m, 2H), 4.67 (t, *J* = 6.6 Hz, 2H), 3.71 (dd, *J* = 7.7, 17.4 Hz, 2H), 3.51 (dd, *J* = 5.2, 17.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.9 (2C), 142.9, 136.9 (2C), 134.0 (2C), 133.1, 128.6, 128.5, 128.1, 128.0, 126.7, 105.1, 104.9, 45.3, 45.1, 39.4, 39.3.

*4.2.9. 1-Methyl-2-(2-nitro-1-phenylethyl)-1H-pyrrole (**3i**)*[37]

Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32–7.22 (m, 3H), 7.17–7.15 (m, 2H), 6.57 (s, 1H), 6.12 (s, 2H), 4.95 (dd, *J* = 8.3, 12.9 Hz, 1H), 4.87 (t, *J* = 7.7 Hz, 1H), 4.74 (dd, *J* = 8.3, 12.9 Hz, 1H) 3.34(s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.0, 129.3, 129.1, 127.9, 123.0, 106.9, 105.9, 79.5, 41.8, 33.8.

*4.2.10. 3-Methyl-2-(2-nitro-1-phenylethyl)-1H-indole (**3j**)*[37]

Yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.62 (br s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.40–7.09 (m, 8H), 5.25 (t, *J* = 8.0 Hz, 1H), 5.08 (dd, *J* = 7.5, 13.2 Hz, 1H), 4.95 (dd, *J* = 7.4, 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 137.0, 130.5, 129.4, 129.1, 128.1, 127.3, 122.3, 119.6, 118.7, 110.8, 109.5, 77.6, 41.1, 8.6.

4.3. General procedure for Pd(II)-catalyzed asymmetric reaction in water

A mixture of $Pd(OCOCF_3)_2$ (1.5 mg, 0.0045 mmol), chiral 2,2′-bipyridine (1.8 mg, 0.0054 mmol) and SDS (13 mg, 0.045 mmol) was stirred in water (0.9 mL) for 1 h at room temperature. After successive addition of **1d** (65.8 mg, 0.45 mmol) and indole **2b** (63.3 mg, 0.54 mmol), the reaction mixture was stirred vigorously for 24 h at room temperature. The reaction was quenched with saturated aq $NaHCO_3$ and brine. The aqueous layer was extracted with dichloromethane (three times), and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (elution: *n*-hexane/ethyl acetate = 3:1) to give the corresponding product **3k** (92.4 mg, 78%). The enantioselectivity (72% ee) was determined by chiral HPLC analysis.

*4.3.1. (R)-3-(1H-Indol-3-yl)-1-phenylbutan-1-one (**3k**)*[39]

White solid; mp 100–101 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98–7.93 (m, 3H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.55–7.51 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.00 (s, 1H), 3.86–3.79 (m, 1H), 3.47 (dd, *J* = 4.9, 16.3 Hz, 1H), 3.23 (dd, *J* = 9.2, 15.5 Hz, 1H), 1.45 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.8, 137.2, 136.5, 132.9, 128.5, 128.1, 126.3, 121.9, 121.4, 120.2, 119.2, 119.2, 111.3, 46.4, 27.1, 21.0; HPLC (Daicel Chiralcel OD-H; *n*-hexane/*i*-PrOH = 9:1, flow rate = 1.0 mL/min): t_R = 16.0 min (*S*), 22.5 min (*R*).

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