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Palladium-Nanoparticle-Catalyzed 1,7-Palladium Migration Involving C−H Activation, Followed by Intramolecular Amination: Regioselective Synthesis of *N*1-Arylbenzotriazoles and an Evaluation of Their Inhibitory Activity toward Indoleamine 2,3-Dioxygenase

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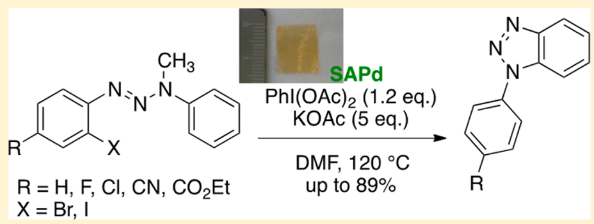
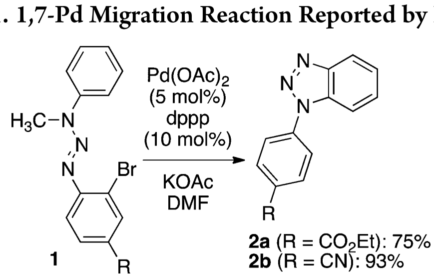
Supporting Information

ABSTRACT: A sulfur-modified gold-supported palladium material (SAPd) has been developed bearing palladium nanoparticles on its surface. Herein, we report for the first time the use of SAPd to affect a Pd-nanoparticle-catalyzed 1,7-Pd migration reaction for the synthesis of benzotriazoles via C−H bond activation. The resulting benzotriazoles were evaluated in terms of their inhibitory activity toward indoleamine 2,3-dioxygenase.



The metal-catalyzed direct functionalization of aromatic C−H bonds is one of the most common and straightforward methods for the formation of carbon−carbon and carbon−heteroatom bonds in organic synthesis.[1] Larock[2] and Gallagher[3] reported the development of a 1,4-palladium migration reaction for the synthesis of fused polycycles. The key step in this particular process involves the Pd-catalyzed activation of a C−H bond via a five-membered palladacycle intermediate.[4] In 2011, Ren et al.[5] reported the development of a novel 1,7-palladium migration/cyclization/dealkylation sequence for the regioselective synthesis of benzotriazoles (Scheme 1), and this reaction has subsequently been used extensively for the synthesis of important molecules in synthetic organic chemistry, materials science, and pharmaceutical science. We recently developed an interest in the N1-substituted benzotriazole **2b**, which can be readily prepared according to the transformation depicted in Scheme 1, because compounds of this particular type exhibit inhibitory activity toward indoleamine 2,3-dioxygenase (IDO), which is an important new therapeutic target for the treatment of cancer.[6]

Scheme 1. 1,7-Pd Migration Reaction Reported by Ren et al.[5]



Immobilized catalysts such as supported Pd nanoparticles (NPs) have been used effectively for the activation of C−H bonds because these catalysts can function efficiently in the absence of a ligand. Although there have been several studies in the literature pertaining to the use of Pd-NPs as catalysts for the activation of $C(sp^2)$−H bonds,[7] there have been no reports describing the use of Pd-NPs for the Pd-catalyzed activation of C−H bonds with the activation occurring via a key five-membered palladacycle intermediate.

Herein, we report for the first time the development of a Pd-NP-catalyzed ligand-free 1,7-palladium migration/cyclization/dealkylation sequence for the regioselective synthesis of N-substituted benzotriazoles. We recently described the development of a sulfur-modified Au-supported Pd material (SAPd),[8] which is essentially an immobilized Pd catalyst bearing Pd-NPs of approximately 5 nm in size on its surface. This material was prepared via the mixing of piranha-treated Au with $Pd(OAc)_2$ in xylene (Figure 1).

We initially examined the reaction of triazene **1a** under Ren's homogeneous reaction conditions in a glovebox, where the oxygen and moisture levels were less than 1 ppm. As shown in Table 1, a solution of **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), dppp ligand (10 mol %), and KOAc (1.2 equiv) in DMF was stirred at 110 °C. Disappointingly, however, these conditions resulted in no reaction, even when the reaction time was

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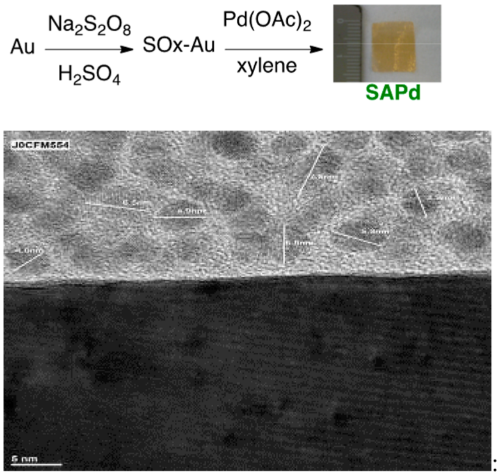
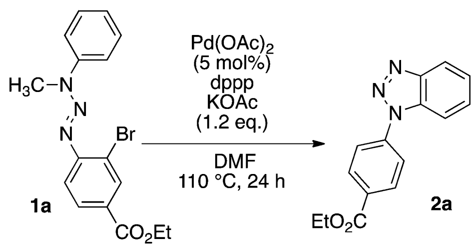


Figure 1. Preparation of SAPd and a transmission electron microscopy image of the resulting material.

Table 1. 1,7-Pd Migration Reaction To Yield Benzotriazoles Using a Homogeneous Pd Catalyst



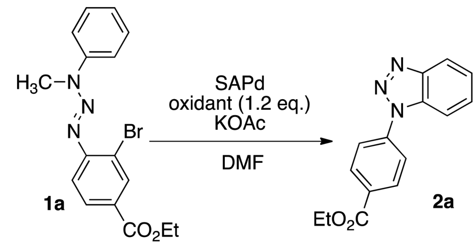
entry	dppp (mol %)	atmosphere (1 atm)	yield of **2a** (%)[a]	unreacted **1a** (%)[a]
1	10	glovebox[b]	0	99
2	10	air	64	19
3	10	O_2	48	32
4	10	Ar	69	4
5	0	air	12	78

[a]Isolated yield. [b]Argon atmosphere where the oxygen and moisture levels were less than 1 ppm.

extended to 24 h (Table 1, entry 1). In contrast, the desired product **2a** could be isolated in 64, 48, or 69% yields, together with 19, 32, and 4% of the starting material **1a** when the reaction was conducted under an atmosphere of air, oxygen, or argon (1 atm), respectively (Table 1, entries 2–4). A control experiment was performed in the absence of the ligand (Table 1, entry 5), which gave a much lower yield of **2a** when the reaction was conducted in air. This reaction revealed that the presence of oxygen and the dppp ligand was critical to allow this 1,7-Pd migration reaction to proceed smoothly using the homogeneous Pd catalyst, $Pd(OAc)_2$.

To establish appropriate ligand-free reaction conditions using the Pd-NP catalyst SAPd instead of $Pd(OAc)_2$, we screened SAPd as a catalyst for the conversion of **1a** to **2a** in the presence of various oxidants (Table 2). The SAPd catalyst was screened in the presence of an oxidant because most of the C–H activation reactions are catalyzed by a Pd(II) species, and the Pd-NPs in SAPd are in the Pd(0) oxidation state. When a solution of **1a** (0.16 mmol), KOAc (1.2 equiv), and SAPd (14 mm × 12 mm mesh, ~50 μg of Pd-NPs immobilized on the surface) in DMF was heated at 110 °C for 1 day in the presence of air, oxygen, AgOAc, or benzoquinone as an oxidant,

Table 2. Ligand-Free Synthesis of Benzotriazoles via the 1,7-Pd Migration Reaction of Triazine 1a Using SAPd as a Catalyst



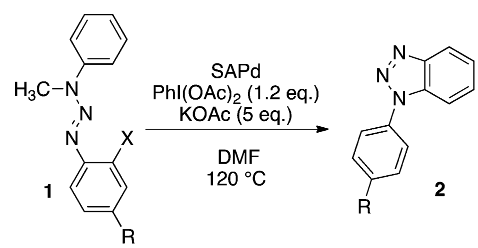
entry	oxidant	KOAc (equiv)	temp (°C)	time (days)	yield of **2a** (%)[a]	unreacted **1a** (%)[a]
1	air[b]	1.2	110	1	0	99
2	O_2[b]	1.2	110	1	0	99
3	AgOAc	1.2	110	1	0	99
4	benzoquinoline	1.2	110	1	0	99
5	$PhI(OAc)_2$	1.2	110	1	14	63
6	$PhI(OAc)_2$	1.2	120	1	32	65
7	$PhI(OAc)_2$	1.2	120	3	39	27
8	$PhI(OAc)_2$	3.0	120	3	92	4
9	$PhI(OAc)_2$	5.0	120	3	89	trace

[a]Isolated yield. [b]An excess of the gas oxidant was used.

the reaction did not proceed at all (Table 2, entries 1–4). However, when the reaction was performed with $PhI(OAc)_2$ as the oxidant at 110 °C for 1 day, compound **2a** was generated in an isolated yield of 14%, with 63% of the starting material **1a** also being recovered (Table 2, entry 5). Subsequent optimization of the reaction conditions revealed that increasing the amount of base to 3 equiv as well as an increasing in the reaction temperature and reaction time to 120 °C and 3 days, respectively, led to an increase in the isolated yield of product **2a** to 92% (Table 2, entries 5–9).

To examine the scope and generality of this SAPd-catalyzed 1,7-Pd migration reaction, we examined the reaction using triazenes **1b–i** (Table 3) as substrates under the optimized con-

Table 3. Scope of the 1,7-Pd Migration Reaction Using SAPd as a Catalyst



entry	substrate			time (h)	yield of **2** (%)[a]
		R	X		
1	**1a**	CO_2Et	Br	72	**2a** (89)
2	**1b**	CN	Br	36	**2b** (80)
3	**1c**	F	Br	96	**2c** (70)
4	**1d**	Cl	Br	96	**2d** (49)
5	**1e**	H	Br	96	**2e** (18)
6	**1f**	CO_2Et	I	26	**2a** (79)
7	**1g**	CN	I	10	**2b** (76)
8	**1h**	F	I	36	**2c** (67)
9	**1i**	Cl	I	26	**2d** (73)
10	**1j**	H	I	17	**2e** (67)

[a]Isolated yield.

ditions described in entry 9 of Table 2. Pleasingly, all of these reaction proceeded as anticipated to give the corresponding 1-arylbenzotriazole products **2b−e**. The aryl iodide substrates **1f−j** were more reactive than the aryl bromides **1a−e**, with the corresponding products being formed over a shorter reaction time. Furthermore, the aryl bromide substrates bearing a Cl or H at the *para*-position (i.e., **1d** or **1c**) gave the corresponding products in low yields of 49 and 18%, respectively, whereas the corresponding aryl iodide substrates **1i** and **1j** gave the same benzotriazole products in 73 and 67% yields, respectively, over a shorter reaction time.

The structure of compound **2e** was unambiguously determined by X-ray crystallography (Supporting Information Figure S1). With a novel series of 1-arylbenzotriazoles **2a−e** in hand, we studied their activity using a colorimetric in vitro IDO inhibition assay.[9] Briefly, the inhibitors were incubated (6 min, 37 °C) with IDO and L-Trp, which is the natural substrate for IDO. Trichloroacetic acid (TCA) was then added to quench the reaction, and the resulting *N*-formylkynurenine was hydrolyzed to kynurenine over a period of 30 min. *p*-Dimethylaminobenzaldehyde was then added to the reaction mixture to form a Schiff base with kynurenine. The residual IDO activity was measured at 490 nM, with the activity corresponding to the amount of Schiff base formed. 4-Phenylthiazole-2-thiol,[17] which is a known inhibitor of IDO (IC_{50} = 50 μM), was used as a positive control in the experiment.

Compounds **2a−e** were tested at 100 μM, and the results revealed that none of these compounds inhibited IDO at more than 30% at this concentration. Compound **2a** showed the highest inhibitory activity of all of the compounds tested in the current study (Figure 2).

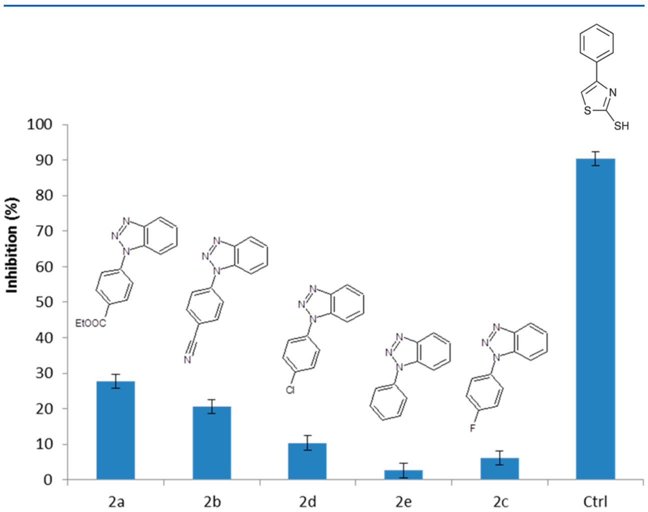


Figure 2. Inhibition of IDO at 100 μM by compounds **2a−e**.

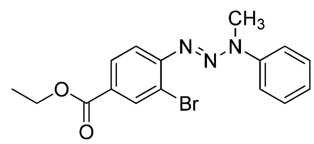
In summary, we have developed a new strategy for the synthesis of benzotriazoles using a Pd-NP-catalyzed 1,7-Pd migration reaction, which proceeded via the activation and functionalization of a $C(sp^2)$−H bond. It is noteworthy that this reaction required the addition of an oxidant and provided good to excellent yields of the desired 1-arylbenzotriazole products. Furthermore, the inhibitory activities of these compounds toward IDO were evaluated in vitro. Because this procedure involves the unique combination of Pd-NPs with a hypervalent iodine reagent, it could be used in several other systems for the activation of $C(sp^2)$−H bonds, which could lead to the development of new methods in synthesis. Further studies toward developing a better understanding of the scope and utility of this system are currently underway in our laboratory.

■ EXPERIMENTAL SECTION

General Considerations. Unless otherwise indicated, all reactions were carried out with magnetic stirring and under argon atmosphere. Reactions were monitored by thin layer chromatography (TLC).

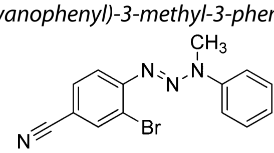
General Procedure for the Preparation of 1-Aryl-3-methyl-3-phenyltriazenes. According to modified Ren's procedure,[5] aniline drivative (1.0 equiv) was dissolved in CH_3CN (1.0 M) at 0 °C, then concentrated hydrochloric acid (5.0 equiv) was added. The solution was stirred and cooled to −10 °C. After 15 min, an aqueous solution of $NaNO_2$ (1.2 equiv, 1.0 M) was added dropwise. The resulting mixture of the diazonium salt was stirred for 30 min, and then it was added to a solution of *N*-methyl aniline (1.1 equiv) and K_2CO_3 (2.5 equiv in CH_3CN/H_2O, 1.0 M), which was previously cooled to 0 °C. The reaction mixture was warmed to rt and stirred for 30 min. After completion, the reaction mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/AcOEt or hexane/CH_2Cl_2) to afford 1-aryl-3-methyl-3-phenyltriazene.

*1-(2-Bromo-4-ethoxycarbonylphenyl)-3-methyl-3-phenyltriazene (**1a**).*



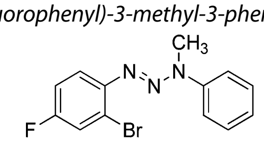
A yellow solid [4.09 g, 11.3 mmol, 75% from ethyl 4-amino-3-iodobenzoate[10] (3.66 g, 15.0 mmol)]; mp = 120−121 °C from CH_2Cl_2/hexane (lit.[5] 115−116 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.59 (d, *J* = 8.50 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.43 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.20(t, *J* = 7.5 Hz, 1H), 4.38 (q, *J* = 7.3 Hz, 2H), 3.77 (s, 3H), 1.41 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 151.0, 144.5, 134.7, 129.3, 129.2, 129.0, 124.7, 120.3, 118.5, 117.7, 61.2, 343.7, 14.3; LRMS (APCI) *m*/*z* (relative intensity, %) 366.06 (16), 365.05 [(M + H)$^+$, 99], 363.04 (16), 362.04 [(M + H)$^+$, 100].

*1-(2-Bromo-4-cyanophenyl)-3-methyl-3-phenyltriazene (**1b**).*



An orange solid [2.54 g, 8.06 mmol, 70% from 4-amino-3-bromobenzonitrile[11] (2.28 g, 11.6 mmol)]; mp = 126−127 °C from CH_2Cl_2/hexane (lit.[5] 124−125 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.50−7.41 (m, 4H), 7.23 (t, *J* = 7.2 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 144.2, 136.8, 131.5, 123.3, 125.2, 120.7, 119.0, 118.0, 117.8, 110.0, 34.1; LRMS (APCI) *m*/*z* (relative intensity, %) 318.02 (15), 317.02 [(M + H)$^+$, 100], 316.02 (15), 315.02 [(M + H)$^+$, 98].

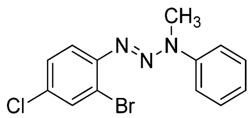
*1-(2-Bromo-4-fluorophenyl)-3-methyl-3-phenyltriazene (**1c**).*



An orange solid [758 mg, 2.46 mmol, 93% from 2-bromo-4-fluoroaniline[5] (500 mg, 2.63 mmol)]; mp = 59−60 °C from CH_2Cl_2/hexane (lit.[5] 59−60 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.9, 5.6 Hz, 1H), 7.47 (dd, *J* = 8.9, 1.0 Hz, 2H), 7.43−7.37 (m, 3H), 7.17 (dd, *J* = 7.25 Hz, 1H), 7.04 (td, *J* = 8.5, 2.73 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 159.7, 144.8, 144.3, 144.3, 129.2, 124.1, 120.8, 120.7, 120.1, 119.9, 119.6, 119.5, 117.3, 115.1, 115.0, 33.2;

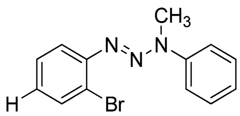
LRMS (APCI) m/z (relative intensity, %) 311.02 (14), 310.02 $[(M + H)^+$, 96], 309.02 (14), 308.02 $[(M + H)^+$, 100].

*1-(2-Bromo-4-chloro)-3-methyl-3-phenyltriazene (**1d**).*



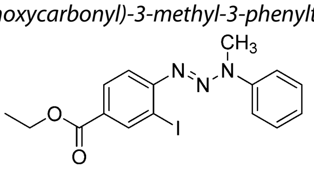
An orange solid [1.04 g, 3.19 mmol, 94% from 2-bromo-4-chloroaniline[12] (700 mg, 3.39 mmol)]; mp = 59−60 °C from CH_2Cl_2/hexane (lit.[5] 76−77 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.47−7.44 (m, 2H), 7.43−7.38 (m, 2H), 7.26 (dd, J = 8.8, 2.1 Hz, 2H), 7.19−7.15 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 144.7, 132.7, 132.0, 129.2, 128.1, 124.3 121.0, 119.5, 117.5, 33.4; LRMS (ESI) m/z (relative intensity, %) 327.99 $[(M + H)^+$, 24], 325.99 $[(M + H)^+$, 100], 323.99 $[(M + H)^+$, 76].

*1-(2-Bromo)-3-methyl-3-phenyltriazene (**1e**).*



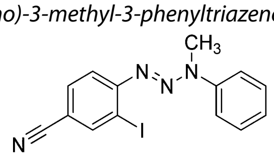
A red oil, 92% [3.12 g, 10.8 mmol, 92% from commercially available 2-bromoaniline (2.0 g, 11.6 mmol)]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, 1H, J = 8.4, 1.4 Hz), 7.57 (dd, 1H, J = 8.4, 1.4 Hz), 7.49 (d, 2H, J = 8.7 Hz), 7.41 (dd, 2H, J = 8.7, 7.5 Hz), 7.31 (ddd, 1H, J = 8.4, 7.2, 1.4 Hz), 7.17 (t, 1H, J = 7.5 Hz), 7.09 (ddd, 1H, J = 8.4, 7.2, 1.4 Hz), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 144.8, 133.2, 129.2, 127.8, 127.5, 124.0, 120.7, 119.0, 117.3, 33.1; LRMS (APCI) m/z (relative intensity, %) 293.03 (14), 292.03 $[(M + H)^+$, 98], 291.03 (14), 290.03 $[(M + H)^+$, 100].

*1-(2-Iodo 4-ethoxycarbonyl)-3-methyl-3-phenyltriazene (**1f**).*



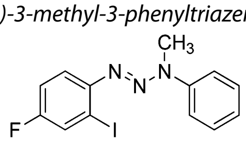
A yellow solid [586 mg, 1.43 mmol, 48% from ethyl 4-amino-3-iodobenzoate[13] (831 mg, 3.00 mmol)]; mp = 124−125 °C from CH_2Cl_2/hexane; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 1.3 Hz, 1H), 8.00 (dd, J = 7.2, 1.3 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 4.37 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 1.40 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 152.9, 144.5, 140.7, 130.2, 129.3, 129.3, 124.7, 117.8, 117.4, 96.7, 61.2, 34.0, 14.3; LRMS (APCI) m/z (relative intensity, %) 412.03 (16), 410.03 $[(M + H)^+$, 100], 382.03 (12). Anal. Calcd for $C_{16}H_{16}IN_3O_2$: C, 46.96; H, 3.94; N, 10.27. Found: C, 46.80; H, 3.90; N, 10.21.

*1-(2-Iodo-4-cyano)-3-methyl-3-phenyltriazene (**1g**).*



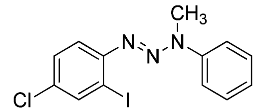
An orange solid [1.97 g, 5.43 mmol, 91% from 4-amino-3-iodobenzonitrile[14] (1.46 g, 6.00 mmol)]; mp = 165−166 °C from CH_2Cl_2/hexane; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 1.0 Hz, 1H), 7.61−7.57 (m, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.44 (dd, J = 8.8, 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 144.3, 142.8, 132.5, 129.4, 125.3, 118.0, 118.0, 117.7, 110.6, 96.8, 34.5; LRMS (APCI) m/z (relative intensity, %) 364.01 (14), 363.01 $[(M + H)^+$, 100], 335.00 (18). Anal. Calcd for $C_{14}H_{11}IN_4$: C, 46.43; H, 3.06; N, 15.47. Found: C, 46.48; H, 3.09; N, 15.51.

*1-(2-Iodo-4-fluoro)-3-methyl-3-phenyltriazene (**1h**).*



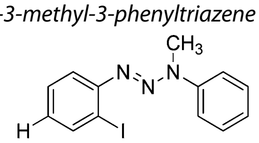
An orange solid [1.01 g, 2.86 mmol, 95% from 4-fluoro-2-iodoaniline[15] (711 mg, 3.00 mmol)]; mp = 61−62 °C from CH_2Cl_2/hexane; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.3, 2.8 Hz, 1H), 7.48 (dd, J = 8.3, 5.8 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.39 (dd, J = 8.5, 7.2 Hz, 2H), 7.15 (t, J = 7.2 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 159.7, 146.2, 146.2, 144.7, 129.2, 125.8, 125.6, 124.1, 118.3, 118.3, 117.3, 116.0, 115.8, 96.9, 96.8, 33.5; LRMS (APCI) m/z (relative intensity, %) 357.00 (13), 356.01 $[(M + H)^+$, 100], 328.00 (12). Anal. Calcd for $C_{13}H_{11}FIN_3$: C, 43.96; H, 3.12; N, 11.83. Found: C, 44.01; H, 3.13; N, 11.88.

*1-(2-Iodo-4-chrolo)-3-methyl-3-phenyltriazene (**1i**).*



A red solid [999 mg, 2.69 mmol, 90% from 4-chloro-2-iodoaniline[16] (760 mg, 3.00 mmol)]; mp = 73−74 °C from CH_2Cl_2/hexane; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 2.7 Hz, 1H), 7.45−7.42 (m, 3H), 7.41−7.37 (dd, J = 9.3 Hz, 2H), 7.29 (dd, J = 10.8, 2.7 Hz, 1H), 7.16 (t, J = 9.3 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 144.6, 138.4, 132.2, 129.2, 129.0, 124.3, 118.4, 117.5, 97.41, 33.7; LRMS (APCI) m/z (relative intensity, %) 373.97 (31), 372.98 (13), 371.98 $[(M + H)^+$, 100], 343.97 (12). Anal. Calcd for $C_{13}H_{11}ClIN_3$: C, 42.02; H, 2.98; Cl, 9.54; N, 11.31. Found: C, 42.29; H, 3.00; Cl, 9.81; N, 11.36.

*1-(2-Iodophenyl)-3-methyl-3-phenyltriazene (**1j**).*



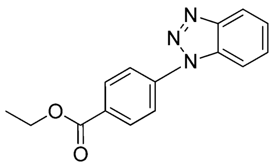
An orange oil [968 mg, 2.87 mmol, 96% from commercially available 2-iodoaniline (657 mg, 3.00 mmol)]; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7.5 Hz, 1H), 7.52 (dd, J = 7.5, 1.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.39 (dd, J = 8.3, 7.5 Hz, 2H), 7.33 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.92 (dd, J = 7.5, 7.5 Hz,1H), 3.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 144.8, 139.3, 129.2, 128.8, 127.9, 124.0, 118.1, 117.3, 97.5, 33.4. Anal. Calcd for $C_{13}H_{12}IN_3$: C, 46.31; H, 3.59; N, 12.46. Found: C, 46.52; H, 3.57; N, 12.57.

Preparation of Sulfur-Modified Au-Supported Pd Material (SAPd). SAPd was prepared according to the literature.[8d] The Au (100 mesh, 14 × 12 mm^2, 100.7 mg) was placed in the piranha solution for 5 min and then washed first with H_2O (3.0 mL × 10) and then with EtOH (3.0 mL × 6). The Au mesh was placed in a round-bottom flask and dried for 10 min under reduced pressure (ca. 6 mmHg). The sulfur-modified Au mesh was placed in a solution of $Pd(OAc)_2$ (5.3 mg, 0.023 mmol) in xylene (3.0 mL) and stirred at 100 °C for 12 h. Then it was rinsed with xylene (3.0 mL × 50), and after vacuum drying, it was placed in xylene (3.0 mL) and heated at 135 °C for 12 h. Finally, it was rinsed with xylene (3.0 mL × 50) and dried under vacuum for 10 min to give sulfur-mocdified Au-supported Pd material (SAPd, 100.8 mg), and only this SAPd was used throughout this research.

General Procedure for the Synthesis of Benzotriazoles with $Pd(OAc)_2$. According to Ren's procedure,[5] **1a** (72.5 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 10 μmol, 5 mol %), dppp (8.2 mg, 20 μmol, 10 mol %), and KOAc (23.6 mg, 0.24 mmol, 1.2 equiv) were dissolved in 800 μL of dried DMF. The reaction mixture was stirred at 110 °C. After being heated, the reaction mixture was cooled to rt and 2.0 mL of H_2O was added. The resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/AcOEt = 9/1−3/1).

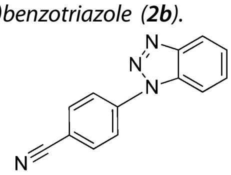
General Procedure for the Synthesis of Benzotriazoles with SAPd. In the presence of SAPd, to a solution of **1** (0.16 mmol) in 1.5 mL of dried DMF were added and stirred at 120 °C KOAc (78.5 mg, 0.8 mmol, 5.0 equiv) and $PhI(OAc)_2$ (61.8 mg, 0.192 mmol, 1.2 equiv). After 30 min, SAPd was removed and the reaction mixture was stirred at 120 °C. After completion of the reaction, the reaction mixture was cooled to rt and 2.0 mL of H_2O was added. The resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/AcOEt).

*1-(4-Ethoxycarbonylphenyl)benzotriazole (**2a**).*



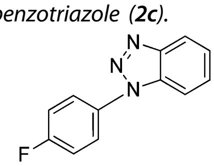
A white solid [34.0 mg, 0.13 mmol, 79% from **1f** (65.4 mg, 0.16 mmol)]; mp = 90−91 °C from CH_2Cl_2/hexane (lit.[5] 87−88 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.61 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.48 (dd, *J* = 8.3, 7.5 Hz, 1H) 4.45 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 146.7, 140.4, 132.0, 131.3, 130.3, 128.7, 124.7, 121.9, 120.6, 110.3, 61.4, 14.3; LRMS (ESI) *m/z* (relative intensity, %) 291.09 (17), 290.09 [(M + Na)$^+$, 100], 268.11 [(M + H)$^+$, 48].

*1-(4-Cyanophenyl)benzotriazole (**2b**).*



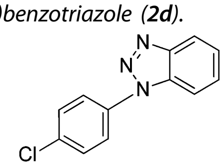
A white solid [26.8 mg, 0.12 mmol, 76% from **1g** (57.9 mg, 0.16 mmol)]; mp = 192−193 °C from CH_2Cl_2/hexane (lit.[5] 189−190 °C)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.94 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.65 (ddd, *J* = 8.3, 8.3, 1.0 Hz, 1H), 7.51 (ddd, *J* = 8.3, 8.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 140.4, 134.0, 131.6, 129.1, 125.0, 122.5, 120.8, 117.9, 112.0, 110.1; LRMS (ESI) *m/z* (relative intensity, %) 222.09 (16), 221.08 [(M + H)$^+$, 100].

*1-(4-Fluoropheny)benzotriazole (**2c**).*



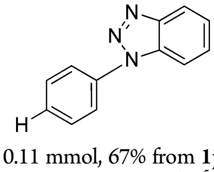
A white solid [23.0 mg, 0.11 mmol, 67% from **1h** (56.8 mg, 0.16 mmol)]; mp = 102−103 °C from CH_2Cl_2/hexane (lit.[5] 101−102 °C)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 1H) 7.80−7.74 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.46 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.355−7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 161.4, 146.4, 133.1, 132.4, 128.4, 124.9, 124.8, 124.5, 120.4, 117.0, 116.8, 110.0; LRMS (ESI) *m/z* (relative intensity, %) 237.06 (14), 236.06 [(M + Na)$^+$, 100], 214.08 [(M + H)$^+$, 27].

*1-(4-Chlorophenyl)benzotriazole (**2d**).*



A white solid [27.4 mg, 0.12 mmol, 75% from **1i** (59.5 mg, 0.16 mmol)]; mp = 156−157 °C from EtOAc (lit.[5] 151−152 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.77−7.72 (m, 3H), 7.61−7.56 (m, 3H), 7.46 (dd, *J* = 8.5, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 135.5, 134.4, 132.1, 130.1, 128.5, 124.5, 123.9, 120.5, 110.1; LRMS (ESI) *m/z* (relative intensity, %) 254.03 (33), 252.03 [(M + Na)$^+$, 100], 232.05 (17), 230.05 [(M + H)$^+$, 52].

*1-Phenylbenzotriazole (**2e**).*



A white solid [20.9 mg, 0.11 mmol, 67% from **1j** (53.9 mg, 0.16 mmol)]; mp = 89−90 °C from CH_2Cl_2/hexane (lit.[5] 86−87 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.62 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.55 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.51 (t, *J* = 7.1 Hz, 1H), 7.44 (dd, *J* = 7.5, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 137.0, 132.3, 129.8, 128.6, 128.2, 124.4, 122.9, 120.3, 110.3; LRMS (ESI) *m/z* (relative intensity, %) 219.07 (14), 218.07 [(M + Na)$^+$, 100], 196.09 [(M + H)$^+$, 47].

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all compounds and crystallographic data of compound **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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