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1,7-Palladium Migration via C−H Activation, Followed by Intramolecular Amination: Regioselective Synthesis of Benzotriazoles

Jun Zhou, Jianjun He, Binjie Wang, Weijun Yang, and Hongjun Ren*

Department of Chemistry, Zhejiang University, 38 Zheda Road, Hangzhou 310027, P. R. China

Supporting Information

ABSTRACT: A novel 1,7-palladium migration−cyclization−dealkylation sequence for the regioselective synthesis of benzotriazoles has been developed. These reactions proceed in excellent yields with high regioselectivities. The mechanism of the reaction has also been investigated.

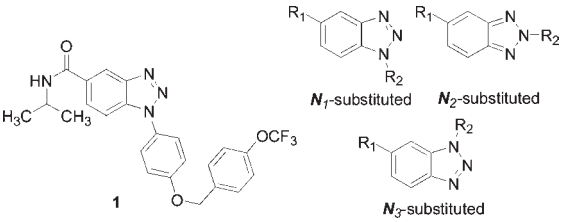
Because of their interesting structures, high reactivity, and anticancer properties, N-substituted benzotriazoles are widely used in synthetic organic chemistry,[1] materials science,[2] and pharmaceutical science.[3] For example, benzotriazole **1** is an inhibitor of c-Kit protooncogene[4] and exists as either the N_1-, N_2-, or N_3-substituted isomer (Scheme 1). N-Substituted benzotriazoles can be prepared by copper-catalyzed Buchwald−Hartwig-type reactions,[5] a transition-metal-free procedure using aryne chemistry for N-arylation,[6] the [3 + 2] cycloaddition reaction between aryne and organic azides,[7] and the reaction of (*Z*)-1-aryl-3-hexen-1,5-diynes with sodium azide.[8] However, the products are formed as a mixture of N_1-, N_2-, and N_3-arylation isomers in all cases except the synthesis involving Buchwald−Hartwig-type reactions.

Larock[9] and Gallagher[10] recently reported the 1,4-palladium migration for the synthesis of fused polycycles. This process involves a Pd-catalyzed C−H activation proceeding via a key five-membered-ring palladacycle intermediate.[11] Aryltriazenes are unique compounds that have been used in medicinal chemistry,[12] combinatorial chemistry,[13] organic synthesis,[14] and molecular architectures synthesis[15] and as precursors to heterocycles.[16] Herein we report a regioselective synthesis of benzotriazoles from aryltriazenes via a novel 1,7-palladium migration and intramolecular amination−dealkylation sequence.

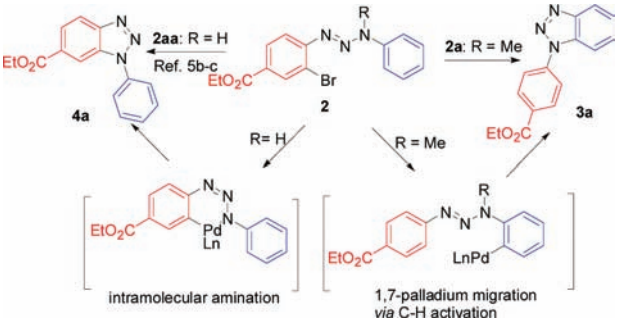
When R = H, the cis/trans isomerization of 1,3-diphenyltriazene occurs under basic conditions,[17] and the intramolecular amination is possible (Scheme 2).[5b,c] Thus, heating triazene **2aa** in the presence of $Pd(OAc)_2$ gave the direct amination product **4a** in 96% yield. We envisioned that if the H were to be replaced by an alkyl group, the reaction of triazene **2a** (with R = Me) would give benzotriazole **3a** via a 1,7-palladium migration−cyclization−dealkylation sequence involving a C−H activation (Scheme 2).

To probe the viability of this envisioned intramolecular 1,7-palladium migration and the subsequent amination reaction, palladium complexes derived from various ligands and bases were screened in toluene or *N*,*N*-dimethylformamide (DMF). The results are summarized in Table 1. The desired benzotriazole

Scheme 1. The Structure of Benzotriazole 1, an Inhibitor of c-Kit Protooncogene, and its Three Isomers



Scheme 2. Regioselective Synthesis of Benzotriazoles



3a was obtained in a trace amount with Cs_2CO_3 as the base and dppp as the ligand in toluene or DMF (Table 1, entries 1 and 7). After the base was changed from Cs_2CO_3 to K_2CO_3, **3a** was formed in 64% yield (entry 2). Both bidentate ligands such as dppb, dppe, dppp, and dppf (entries 3−5 and 9) and a monophosphorus ligand (PPh_3, entry 6) led to the formation of compound **3a** in 31−75% yield using toluene as solvent. The best result was obtained with dppp as the ligand in the presence of KOAc as the base and DMF as the solvent (entry 8).

To explore the reaction scope, a number of 3-methyl-1,3-diphenyltriazenes **2b**−**2p** were examined under the optimal reaction conditions. The substituents on the two aromatic groups had different effects on the yields (**3b**−**3g** in Table 2). Electron-donating groups on the bromo-substituted aromatic ring (shown in red) decreased the yield (**3l**, **3o**, and **3p**; the yield could be improved by running the reaction at high temperature), while on the other aromatic system (shown in blue), the yields increased to up to 98% (**3n**) under the optimal reaction conditions. The

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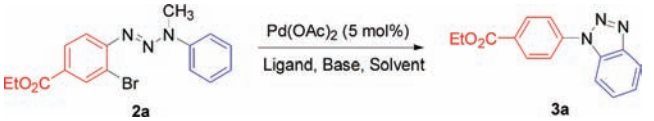
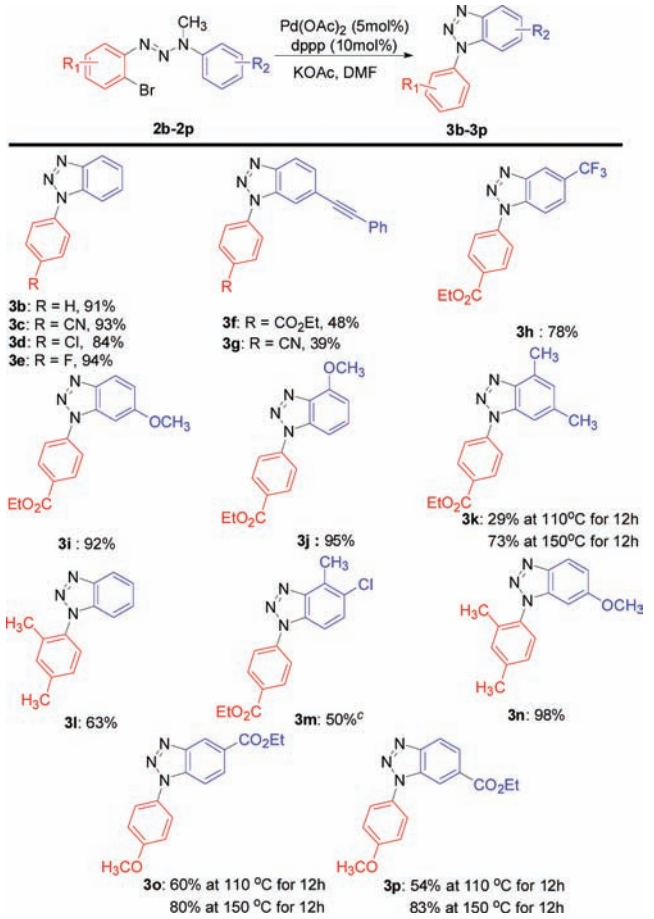
Table 1. Screen of 1,7-Palladium Migration Reaction Variables[a]



entry	base	solvent	ligand	yield (%)[b]
1	Cs_2CO_3	toluene	dppp	trace
2	K_2CO_3	toluene	dppp	64
3	K_2CO_3	toluene	dppb	32
4	K_2CO_3	toluene	dppe	56
5	K_2CO_3	toluene	dppf	40
6	KOAc	toluene	PPh_3	31
7	Cs_2CO_3	DMF	dppp	trace
8	KOAc	DMF	dppp	75
9	KOAc	toluene	dppp	55

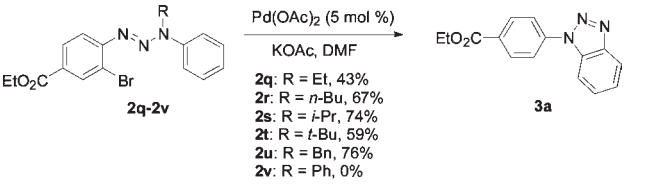
[a] All of the reactions were carried out with **2a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol), and base (1.2 mmol) in 4 mL of solvent at 110 °C for 12 h. [b] Yield of isolated product after chromatography.

Table 2. Substrate Scope of the 1,7-Palladium Migration Reaction[a,b]

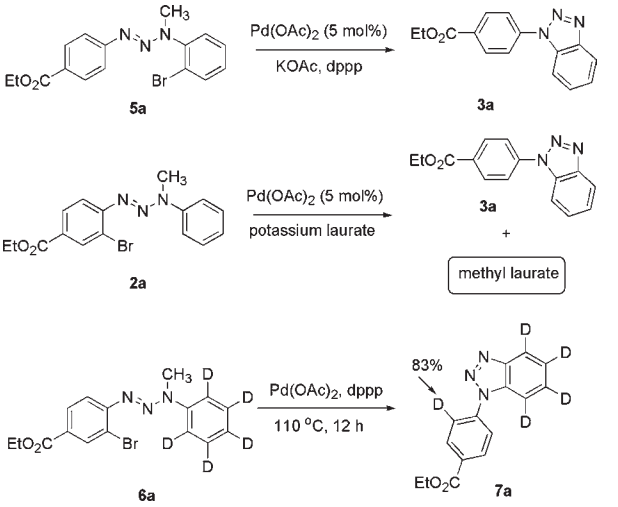


[a] All of the reactions were carried out with substrate (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), dppp (0.1 mmol), and KOAc (1.2 mmol) in DMF (4 mL) at 110 °C for 12 h. [b] Yields of isolated products after chromatography are shown. [c] The reaction was carried out at 150 °C for 12 h.

Scheme 3. Reaction of Substrates with Groups Other Than Me on the Triazene



Scheme 4. Reaction of Substrates 5a and 2a and Deuterium Substrate 6a



structure of **3h** was determined by X-ray analysis (see the Supporting Information). Lower yields were obtained when steric hindrance was introduced near the reaction site (**3k** and **3m**), and higher temperatures gave better yields. Gratifyingly, 1-(4-methoxyphenyl)-1*H*-benzotriazole-5-carboxylic acid ethyl ester (**3o**), the important intermediate leading to benzotriazole **1**, was obtained in 80% yield after treatment with $Pd(OAc)_2$ and dppp at 150 °C.

Furthermore, we also used substrates with groups other than Me on the triazene motif. All of the substrates with alkyl groups such as Et, *n*-Bu, *i*-Pr, and Bn gave the desired product **3a** in good yields from 43 to 76% (Scheme 3). Even with a very bulky group like *t*-Bu, the desired product was obtained in 59% yield. However, *N*-phenyltriazene (**2v**) did not produce the desired product **3a**.

To probe the reaction mechanism, substrate **5a** was subjected to the standard reaction conditions, and N-substituted benzotriazole **3a** was formed in 97% yield. This result strongly indicates that the same intermediate is formed when the substrates **2a** and **5a** are treated with $Pd(OAc)_2$ in the presence of base and ligand. When we changed the base to potassium laurate, the byproduct methyl laurate was observed along with **3a** using GC−MS analysis. Furthermore, d_5-triazene **6a** was synthesized and subjected to the standard reaction conditions (using toluene as the solvent), and 83% deuterium incorporation at the ortho position of **7a** was observed using ^{1}H NMR and GC−MS analysis (Scheme 4).

On the basis of these results, a plausible reaction mechanism for this fascinating process is depicted in Scheme 5. Presumably, Pd(0) would first undergo oxidative addition to bromotriazene

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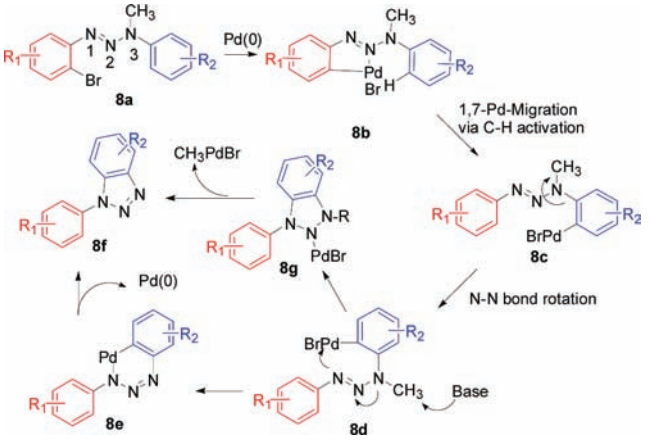
Scheme 5. Plausible Mechanism for the 1,7-Palladium Migration−Cyclization−Dealkylation Sequence (The Coordinated Ligand Has Been Omitted for Clarity)



8a, generating the intermediate **8b**. The coordination of palladium with the middle nitrogen of the triazene moiety would bring the C−H bond of the other aromatic ring close enough allow the 1,7-palladium migration via C−H bond activation and reductive elimination, giving **8c** (an eight-membered-ring palladacycle intermediate[18] may be involved). After N_2-N_3 bond rotation, intermediate **8d** would be formed, and it could be converted to **8e**, which would provide the desired product **8f** and release Pd(0). An alternative reaction pathway from **8f** via the insertion intermediate **8g** and β-CH_3 elimination would also be possible and cannot be excluded on the basis of the present results, especially for the *t*-Bu-substituted substrates.

In conclusion, we have developed a novel 1,7-palladium migration−cyclization−dealkylation sequence for the regioselective synthesis of benzotriazoles. These reactions occurred in excellent yields with high regioselectivities. Further investigations of the mechanism and synthetic applications are underway.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra for all products, complete ref 3d, and crystallographic data for compound **3h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
renhj@zju.edu.cn

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