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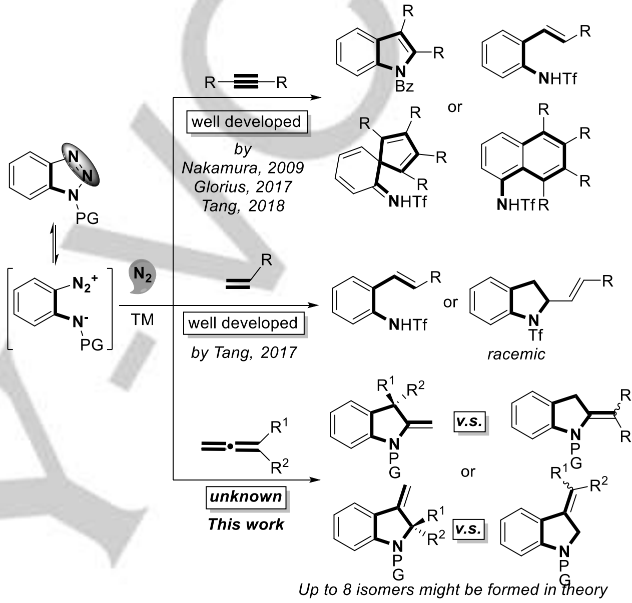
Pd/PC-Phos-Catalyzed Enantioselective Intermolecular Denitrogenative Cyclization of Benzotriazoles with Allenes or N-allenamides

Pei-Chao Zhang,[a] Jie Han[a] and Junliang Zhang*[a] [b]

Abstract: *Herein we reported an asymmetric Pd/PC-Phos-catalyzed denitrogenative cyclization of benzotriazoles with allennes and N-allenamides, which represents the first example of enantioselective denitrogenative cyclization of benzotriazoles. A series of optically active 3-methyleneindolines were obtained in good yields with high ees. The use of inexpensive and readily available starting materials, high regio- and enantioselectivity, a broad substrate scope, mild reaction conditions, base free, as well as versatile functionalization of the 3-methyleneindoline make this approach quite attractive.*

Benzotriazoles can undergo ring-chain isomerization to form the corresponding diazonium or diazo species via a Dimroth-type equilibrium. Over past years, many methodologies have been developed by the use of this unique chemical property of benzotriazoles via denitrogenation.[1-3] In this context, the development of new denitrogenative reactions of benzotriazoles with readily accessible unsaturated hydrocarbons have received much attention, which provide rapid access to various synthetic valuable compounds (Scheme 1). For example, Nakamura group[1c] demonstrated a Pd-catalyzed denitrogenative cyclization of benzotriazoles with internal alkynes. Glorius group[2b] then took the use of iridium-photocatalysis to achieve the denitrogenation of benzotriazoles and reacting with terminal alkynes. Recently, Tang and co-workers[3] developed an alternative seminal synergistic activating–stabilizing strategy to realize the denitrogenative reaction of benzotriazoles with alkyne[3a] and 1,3-diene[3b].

Allenes and N-allenamides, readily available unsaturated hydrodcarbons, bearing two cumulative unsaturation have emerged as highly important building blocks in organic synthesis.[4] However, to the best of our knowledge, allenes have not been applied to the denitrogenative cyclization of benzotriazoles so far.[5] As a part of our continual program in the discovery of new asymmetric cyclization reactions of allenes and N-allenamides,[6] we became interest in the enantioselective intermolecular denitrogenative cyclization reaction of benzotriazoles with allenes and N-allenamides. If success, 3-methyleneindolines and related skeleton which are ubiquitous structural motifs found in an array of biologically active natural products and pharmaceuticals, would become easily accessible (Figure 1).[7-14] However, the development of denitrogenative cyclization of benzotriazoles with allenes, especially in enantioselective manner, poses considerable challenge: 1) up to eight isomers (*er*, *rr*, *Z/E*) might be obtained in theory, how to control over the product distribution, 2) how to avoid the dimerization of allene, especially the allenamides,[15] 3) potential compatibility issue between phosphine ligands and diazonium salts intermediate,[16] 4) how to achieve high enantioselectivity.



The main challenges for denitrogenative cyclization of benzotrizaoles with allenes:

- *control over the product distribution*
- *compatibility of ligand with intermediate*
- *possible dimerization of allene*
- *acheive high enantioselectivity*

Scheme 1. Denitrogenative reactions of benzotriazoles with unsaturated hydrocarbon.

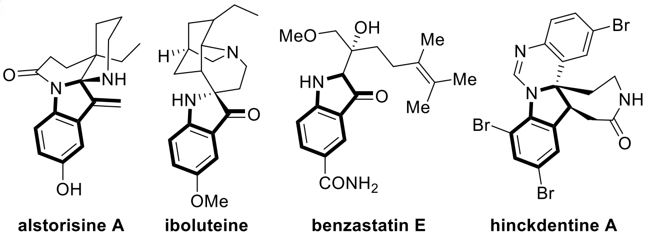


Figure 1. Biologically active natural products featuring functionalized indolines.

Our investigation began with the cyclization of N1-Tf benzotriazole **1a** and allene **2a** with the use of $Pd_2(dba)_3$ as a precatalyst. A series of commercially or readily available chiral ligands were systematically investigated, and our developed chiral sulfinamidephosphine type ligands [17-19] delivered **3a** in up to 90% yield and up to 75% ee (see Supporting Information (SI), Figure S1). Further screening showed that **PC-Phos**[6a,20] could give relatively higher ees (Table 1). For example, (*Sc, Rs*)-**PC3** could give **3a** in 91% yield with 92% *ee* (Table 1, entry 3). Moreover, (*Sc, Rs*)-N-Me-**PC3** lacking the hydrogen-bonding site delivered 31% *ee* (Table 1, entry 4). However, (*Rs*)-**PC7** with chirality only at the sulfur atom give a racemic product, indicating that carbon chirality is quite important for obtaining high enantio–

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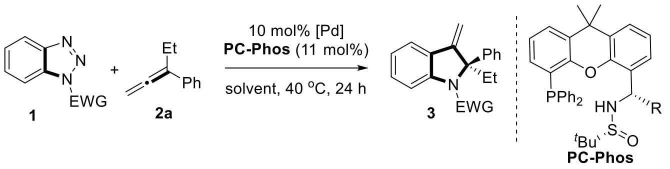
Table 1. Optimization of the reaction conditions. [a]



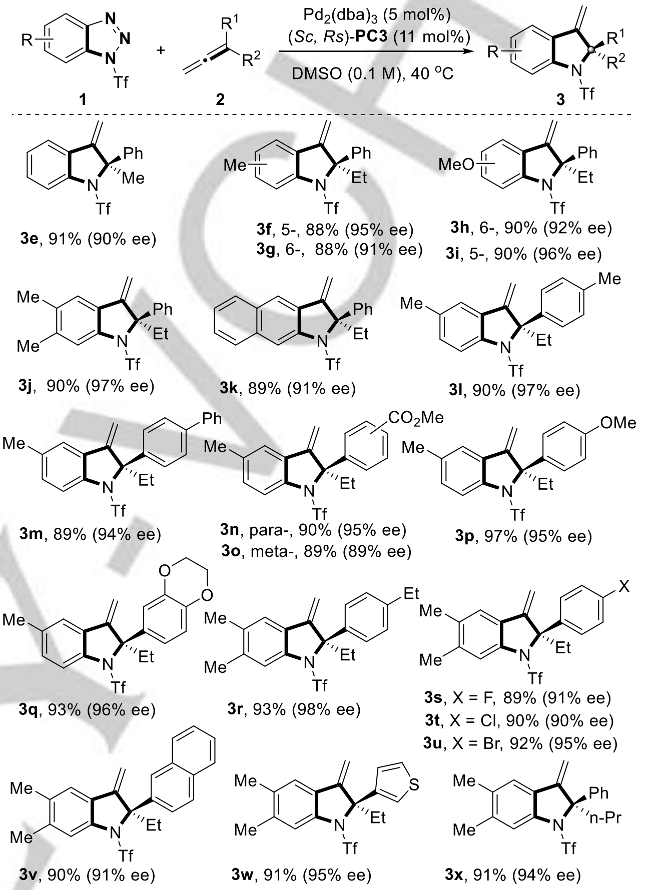
PC1: R = Ph; **PC2**: R = 4-MeOC$_6$H$_4$; **PC3**: R = 4-^{t}BuC$_6$H$_4$; **PC4**: R = 2-^{i}PrC$_6$H$_4$; **PC7**: R = H

Entry	EWG^b	[M]	L	Solvent	Yield *(Ee)* [%]^{c,d}
1	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC1**	DMSO	90(82)
2	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC2**	DMSO	89(86)
3	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC3**	DMSO	91(92)
4	Tf (**1a**)	Pd$_2$(dba)$_3$	N-Me-**PC3**	DMSO	87(31)
5	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC4**	DMSO	88(37)
6	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC7**	DMSO	85(0)
7	Tf (**1a**)	Pd(dba)$_2$	**PC3**	DMSO	89(91)
8	Tf (**1a**)	Pd$_2$(dba)$_3$•CHCl$_3$	**PC3**	DMSO	90(91)
9	Tf (**1a**)	Pd(OAc)$_2$	**PC3**	DMSO	-
10	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC3**	DMF	85(73)
11	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC3**	MeOH	86(78)
12	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC3**	CH$_3$CN	-
13^e	Tf (**1a**)	Pd$_2$(dba)$_3$	**PC3**	DMSO	90(89)
14	Ts (**1b**)	Pd$_2$(dba)$_3$	**PC3**	DMSO	-
15	Bz (**1c**)	Pd$_2$(dba)$_3$	**PC3**	DMSO	-
16	Tfb (**1d**)	Pd$_2$(dba)$_3$	**PC3**	DMSO	-

[a] Unless otherwise noted, all reactions were carried out with 0.1 mmol of **1** and 0.12 mmol of **2a**, 10 mol% of catalyst ([Pd] to **PC-Phos** = 1:1.1) in 1.0 mL of solvent at 40 ºC for 24 h; [b] Tf: trifluoromethylsulfonyl; Ts: *p*-tolylsulfonyl; Bz: benzoyl; Tfb: 4-(trifluoromethyl)phenylsulfonyl. [c] Isolated yield. [d] Determined by chiral HPLC. [e] At 30 ºC.

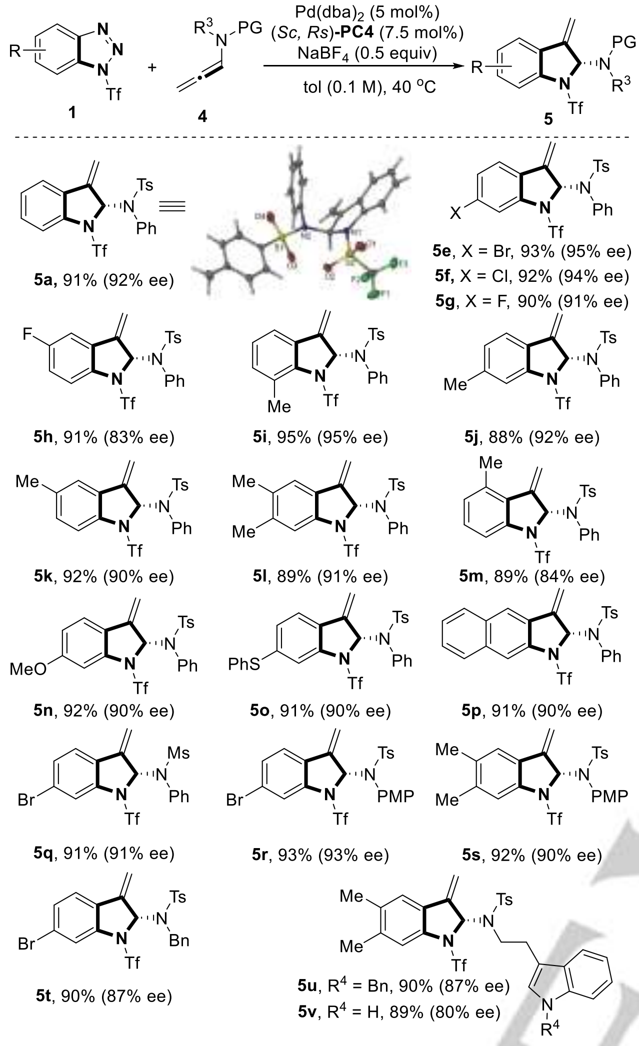
selectivity (Table 1, entry 6). Other palladium salts such as Pd(dba)$_2$, Pd$_2$(dba)$_3$•CHCl$_3$ and Pd(OAc)$_2$ were then examined as precatalysts under the identical reaction conditions (Table 1, entries 7–9), among which Pd$_2$(dab)$_3$ exhibited the best enantioselectivity. Subsequently, other polar solvents such as DMF, MeOH and CH$_3$CN were then examined but faild to give better result (Table 1, entries 10–12). Lowering the temperature to 30 ºC slightly decreased the ee to 89% (Table 1, entry 13). Finally, the adjustment of the N1-electron-withdrawing group of benzotriazole (**1b**, **1c** and **1d)** from Tf to Ts, Bz and Tfb could not deliver the corresponding products **3b**-**3d**, indicating that the electron-withdarwing group also plays crucial role for this denitrogentive cyclization (Table 1, entries 14–16).[3c]

With the optimized reaction conditions in hand, the scope of this asymmetric denitrogenative cyclization reaction was then investigated, and the results are shown in **Scheme 2**. In general, high yields (88-97%) with 89–98%ees were exclusively obtained for the new aza-quaternary stereogenic center. For example, the benzotriazoles bearing one or two electron-donating groups (Me, OMe) at the *para*-positions of N1 or N3, generally react well to furnish the desired products **3f**–**3j** in 88-90% yields with 91–97% ees. Notably, naphthotriazole worked also well, furnishing the corresponding product **3k** in 89% yield with 91% ee. Next, the scope of 1,1-disubstituted allene **2** was further investigated. A tolerance towards both electron-donating and electron-withdrawing aryl group of allene was observed, furnishing **3l**–**3r** in excellent yields (89–97%) with 89-98% *ee*. Especially, the halogens (F, Cl, Br) of the phenyl ring are also compatible to deliver the desired **3s**–**3u** in high yields with 90–95% *ees*. Gratifyingly, 2-naphthyl and 3-thienyl derived allenes delivered the cyclization products **3v**–**3w** in 90−91% yields with 91–95% ees. The structure and absolute configuration of **3x** were determined by single-crystal X-ray diffraction analysis.[21]



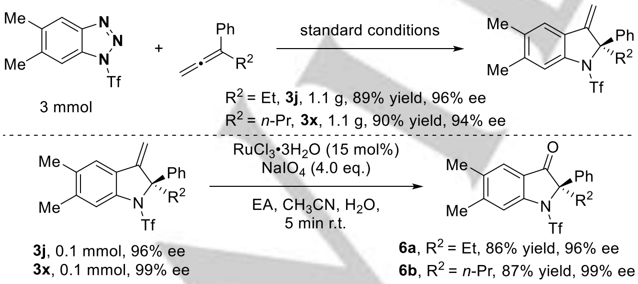
Scheme 2. Cyclization reaction of benzotriazoles with allenes.

We next turned to examine whether *N*-allenamides[22] **4** were applicable to the present reaction. We found that only trace amount of the corresponding cyclization product **5a** was detected under the above conditions. After many attempts (see SI, Figure S2 and Table S1), we finally identified the following reaction conditions : Pd(dba)$_2$ (5 mol%), **PC4** (7.5 mol%), **1a**, and 1.2 equiv of **4a** in toluene at 40 ºC for 48 h, could well deliver **5a** in 91% yield and 92% *ee*. The structure and absolute configuration of **5a** were determined by single-crystal X-ray diffraction analysis.[21] The scope of this reaction was then examined (Scheme 3). Notably, those benzotriazoles bearing diverse functional groups (R), such as the halogens (F, Cl, Br), and electron-donating groups (Me, OMe, SPh) at the various positions of the phenyl ring were compatible to deliver the desired **5a**-**5o** in high yields with 84–95% *ees*. Naphthotriazole worked also well, furnishing the corresponding product **5p** in 91% yield with 90% ee. Then, by changing the substitution on the sulfonyl group (PG), the reaction could proceed **5q** in 91% yield with 91% ee. Next, variation of R^3 on the N-allenamides from phenyl to PMP and Bn did not led big difference and the desired products **5r**-**5t** were produced in high yields with good *ees*. Interestingly, the R^4 group of attached indoles of N-allenamide,[6a] which is several bonds away, still affect the enantioselectivity in some sense (**5u**-**5v**).



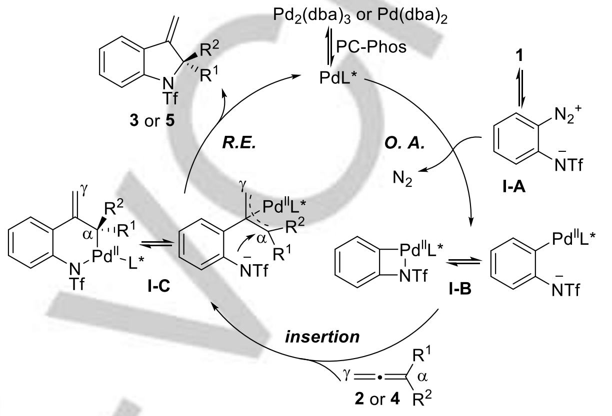
Scheme 3. Cyclization reaction of benzotriazoles with N-allenamides.

To demonstrate the practical utility of our protocol, gram-scale reactions were carried out under standard conditions, furnishing1.1 g of **3j** in 89% yield with 97% *ee* and 1.1 g of **3x** in 90% yield with 94% *ee*, respectively (Scheme 4). Treatment of compounds **3j** and **3x** with RuCl$_3$/NaIO$_4$ gave good yields of the chiral ketones **6**, which are common skeleton in biologically relevant products. [23]



Scheme 4. Gram-scale synthesis and synthetic derivatization of the products.

To elucidate the proposed mechanism, several control reactions were conducted by addition of external nucleophiles or using 1,3-disubstituted allenes W/O nucleophile, but no other type of products with the reaction the other nucleophiles were detected. (See SI). Based on the above results and some relevant precedents,[3b,24] we proposed a plausible mechanism to account for this palladium-catalyzed denitrogenative cyclization reaction (Scheme 5). Benzotriazoles **1** would undergo a ring-chain isomerization to form the corresponding diazonium **I-A** via a Dimroth-type equilibrium.[3c,25] Oxidative addition of **I-A** with palladium complex and extrusion of nitrogen gas would generate the intermedaite **I-B.** The insertion of allene or allenamide into the C-Pd bond would deliver a π-allylpalladium complex **I-C**, which upon allylic substitution would produce the cyclization product **3** or **5** and regenerate the palladium catalyst.



Scheme 5. Proposed mechanism.

In summary, we have developed the first highly chemo-, regio-, and enantioselective palladium-catalyzed denitrogenative cyclization reaction of benzotriazoles with allenes or *N*-allenamines with the use of chiral sulfinamidephosphine type ligand **PC-Phos**. A series of optically active 3-methyleneindolines were obtained in high yields and with excellent ees. This method can be expected to find wide synthetic applications, in view of the high efficiency, simple operation, mild reaction conditions, base free, high chemo- and enantioselectivity. Inspired by this work, we anticipate that more catalytic asymmetric and synthetically valuable transformations of benzotriazoles will be developed in near future.

Acknowledgements

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Keywords: Denitrogenative cyclization • Allene • Allenamide• Palladium•Benzotriazole

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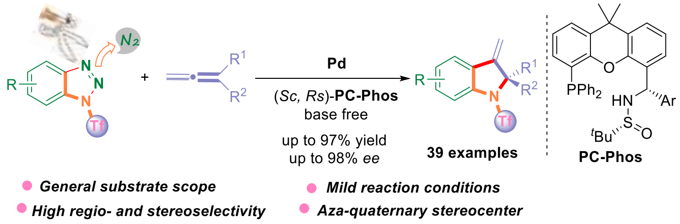

The first example of enantioselective denitrogenative cyclization of benzotriazoles with allennes and N-allenamides was enabled by Pd/PC-Phos catalysis, which provides a rapid access to optically active 3-methyleneindolines in good yields with high ees.

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