Heterocycles

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Surfactant-Type Brønsted Acid Catalyzed Stereoselective Synthesis of *trans*-3-Alkenyl Indazoles from Triazenylaryl Allylic Alcohols in Water**

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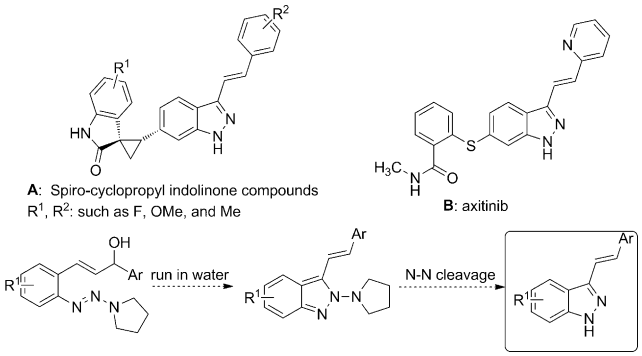
Dedicated to Professor Paul Knochel

3-Alkenyl 1-unsubstituted 1*H*-indazoles, such as spiro-cyclopropyl indolinone (**A**, Scheme 1)[1] and axitinib (**B**),[2] display a wide array of biological activities, including antiangiogenesis, antitumor, and multikinase inhibitor activity.



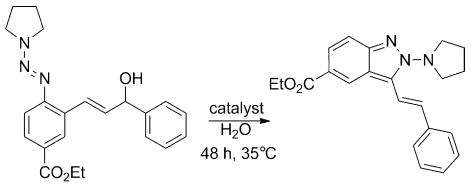
Scheme 1. The structures of some indazoles and our strategy for the preparation 1-unsubstituted 3-alkenyl indazoles.

Although several of methods, such as palladium-,[3] copper-,[4] iron-,[5] and rhodium-catalyzed[6] reactions, have been used for the synthesis of the core of indazole,[7] the existing synthetic routes to 3-alkenyl indazoles are limited to the palladium-catalyzed Heck and Suzuki–Miyaura cross-coupling reactions of protected 3-halogenated indazoles.[1,8] These methods suffer from several disadvantages, such as harsh reaction conditions, narrow substrate tolerance, and the lack of methods for breaking the Aryl–N bond[6a] to form 1-unsubstituted indazoles. Additionally, if these methods are used in the synthesis of pharmaceuticals, the trace contaminants leached from the catalyst must be removed by additional processes, otherwise it would seriously affect the quality of the product, particularly pharmaceutical and material properties.[9] As a part of a new approach to indazoles, transition-metal-free protocols are attractive but the reported methods are mainly confined to specific examples, such as diazotization or nitrosation of 2-alkyl anilines,[10] condensation of *ortho*-substituted benzaldehydes or ketones with hydrazines,[11] and dipolar cycloaddition of arynes.[12] Recently, Bolm and co-workers provided a facile and efficient K_2CO_3-catalyzed route for the synthesis of 1-unsubstituted 1*H*-indazoles from *o*-halo arylhydrazones.[13]

Recently, we have focused on environmentally friendly reactions of triazenes and they have provided a highly valuable approach to the formation of nitrogen-containing heterocycles.[14,15] The use of an environmentally friendly reaction medium, especially water, has attracted much attention.[16] Various types of reactions, including dehydration,[17] Mannich,[18] and multicomponent reactions[19] in water have been achieved by the group of Kobayashi and others. However, direct nucleophilic substitution of allylic alcohols[20] in water remains unexploited. Herein, we present a useful dodecyl benzene sulfonic acid (DBSA) catalyzed intramolecular cyclization of triazenylaryl allylic alcohols for the formation of 3-alkenyl-2-pyrrolidine-2*H*-indazoles in water. In addition, the cleavage of the N–N bond results in the efficient generation of 1-unsubstituted 3-alkenyl-1*H*-indazoles (Scheme 1).

Initially, we treated the 3-triazenylaryl allylic alcohol (**1a**) with DBSA (5 mol%) in water at 35°C and it led to the formation of the desired 3-alkenyl-2-pyrrolidine-2*H*-indazole

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



1a 2a

Entry	Catalyst [mol%]	Yield[b] [%]
1	DBSA (5)	30
2	DBSA (10)	70
3	DBSA (20)	90
4	HCl (20)	20
5	TsOH (20)	5
6	CF_3COOH (20)	40

[a] All reactions were carried out with **1a** (0.5 mmol) and the catalyst in water (2 mL) at 35°C for 48 h. [b] Yield of the isolated product after flash column chromatography. Ts = 4-toluenesulfonyl.

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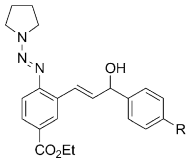
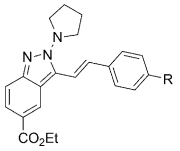
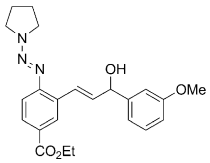
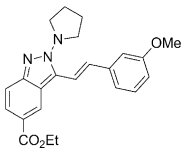
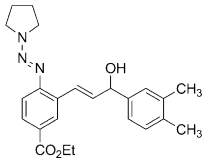
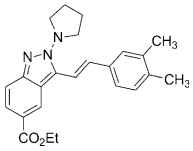
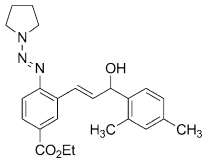
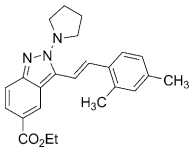
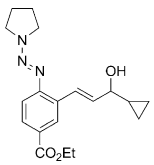
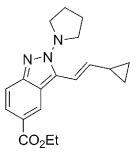
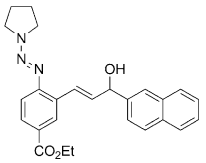
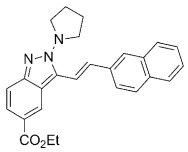
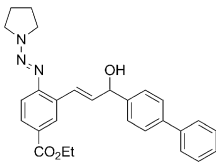
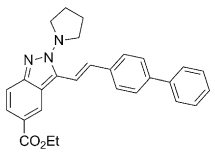
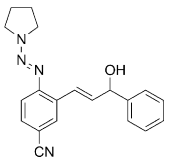
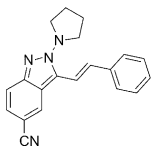
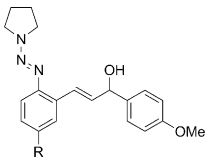
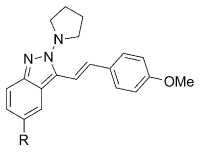
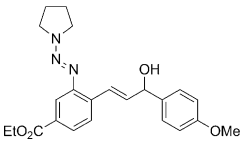
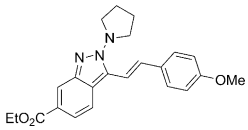
(**2a**) in 30% yield (Table 1, entry 1). To our delight, when the amount of the DBSA catalyst was doubled to 10 mol%, the yield of **2a** was increased to 70% (entry 2). When it was increased to 20 mol%, only the *trans* isomer was obtained and the yield increased to 90%. As expected, the treatment of **1a** with the simple Brønsted acid HCl (20 mol%) led to the formation of **2a** in a lower yield (20%, entry 4). Use of TsOH and CF_3COOH did improve the yield, thus leading to the desired product **2a** in 5% (entry 5) and 40% (entry 6) yield, respectively. Thus, the best result was obtained when the reaction was carried out in water at 35°C using DBSA (20 mol%) as the catalyst (entry 3).

With the optimized reaction conditions in hand, the scope of this reaction was investigated, and the results are summarized in Table 2. All the substrates give *trans*-type compounds.

Table 2: Scope of synthesis of the functionalized 3-alkenyl-2-pyrrolidine-2*H*-indazoles from 3-triazenylaryl allylic alcohols.[a]

Entry	Substrate	Product	Yield[b] [%]
			
1[c]	**1b**: R = F	**2b**: R = F	83
2[d]	**1c**: R = Cl	**2c**: R = Cl	77
3[d]	**1d**: R = Br	**2d**: R = Br	59
4[d]	**1e**: R = I	**2e**: R = I	57
5	**1f**: R = CH_3	**2f**: R = CH_3	92
6	**1g**: R = OCH_3	**2g**: R = OCH_3	95
			
7	**1h**	**2h**	83
			
8	**1i**	**2i**	99
			
9	**1j**	**2j**	79
			

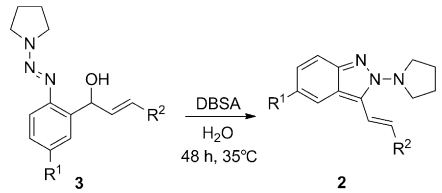
Entry	Substrate	Product	Yield[b] [%]
10	**1k**	**2k**	92
			
11	**1l**	**2l**	98
			
12	**1m**	**2m**	84
			
13	**1n**	**2n**	99
			
14	**1o**: R = Br	**2o**: R = Br	99
15	**1p**: R = Cl	**2p**: R = Cl	99
16	**1q**: R = H	**2q**: R = H	78
17	**1r**: R = CH_3	**2r**: R = CH_3	52
			
18	**1s**	**2s**	79

[a] All reactions were carried out with the triazenylaryl allylic alcohol **1** (0.5 mmol) and DBSA (0.1 mmol, 20 mol%) in water (2 mL) at 35°C for 24 h. [b] Yield of the isolated product after flash column chromatography. [c] The reaction was carried out with DBSA (0.2 mmol, 40 mol%) in water (2 mL) for 48 h. [d] The reactions were carried out with DBSA (0.2 mmol, 40 mol%) in water (2 mL) for 4 d.

The transformation was sensitive to the electronic nature of benzyl alcohol substituents: substrates with electron-donating substituents such as CH_3 (92%, Table 2, entry 5), OCH_3 (95%, entry 6), and dimethyl groups (99%, entry 8) showed higher reactivity than those with electron-withdrawing groups (57–83%, entries 1–4) because the benzylic carbocation intermediates are stabilized by the electron-donating substituents. Owing to the relatively weak stability of the *m*-OCH_3-substituted benzylic carbocation intermediate, **1h** gave the desired product **2h** in a lower yield (83%, entry 7)

compared to the *p*-OCH_3-substituted substrate **1g**. In the case of the dimethyl-substituted substrate **1j**, the yield decreased to 79% compared to that of the substrate **1i** (entries 8 and 9). In particular, the substrate **1k**, bearing a cyclopropyl group, can also be converted into the corresponding product in 92% yield (entry 10). Aromatic motifs, such as naphthyl and biphenyl groups, were successfully incorporated into the 3-alkenyl-2-pyrrolidine-2*H*-indazole products in 84–98% yields, as shown by the formation of the products **2l**,**m** (entries 11 and 12). The electronic character of the aryl triazene substituents also influenced the yield of the transformation. A decreased yield was observed (entries 14–17) when the electron-withdrawing ability of the substituents on the aryl triazene motif was decreased. In addition, the substrates with a cyano (99%, entry 13) and *m*-CO_2Et (79%, entry 18) group were successfully converted into the corresponding products. The structure of **2a** was confirmed unambiguously by X-ray diffraction analysis (see the Supporting Information).

Following the success of the formation of 3-alkenyl-2-pyrrolidine-2*H*-indazoles from the allylic alcohols substrates **1**, the reaction of the allylic alcohols **3** (Scheme 2) were carried out under the same reaction conditions. After stirring for 48 hours in water, the intramolecular amination proceeded and the alcohols **3** were converted into the corresponding 3-alkenyl-2-pyrrolidine-2*H*-indazole products in

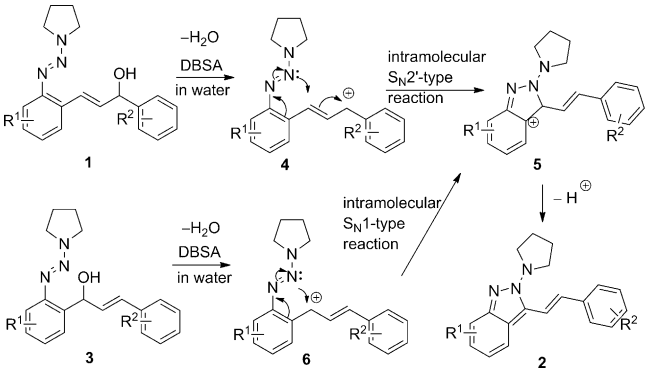


Scheme 2. Synthesis of 3-alkenyl-2-pyrrolidine-2*H*-indazoles from 1-aryl triazene cinnamyl alcohols.

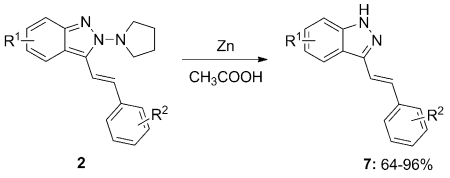
moderate to good yields under the similar reaction conditions (Scheme 2).

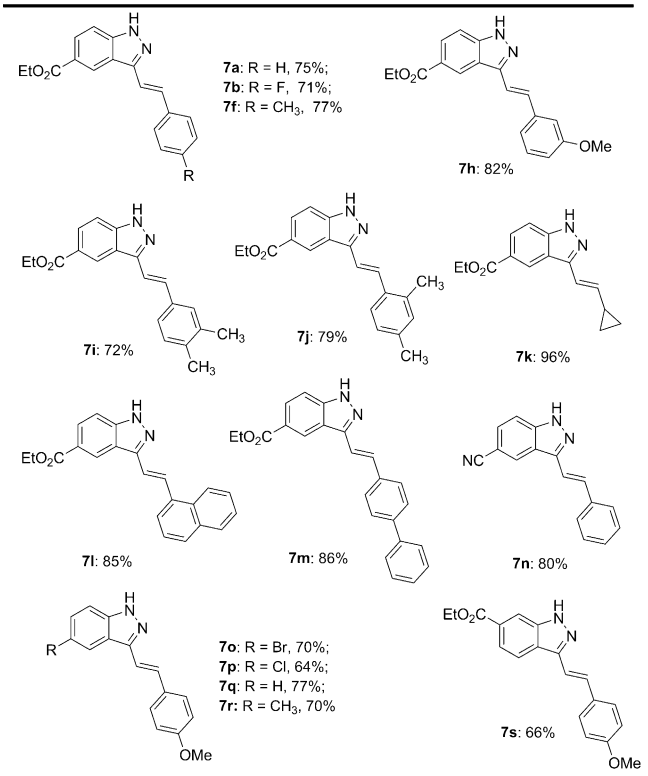
On the basis of the above-mentioned results, a plausible reaction mechanism for this process is depicted in Scheme 3. The interaction between the hydroxy group of **1** and the Brønsted acid DBSA leads to the activation of the hydroxy group and formation of the carbocation intermediate **4**, which undergoes an intramolecular S_N2'-type reaction to give the intermediate **5**. When the reaction was carried out using **3** instead of **1**, the intermediate **6** is formed and then the attack by the middle nitrogen atom of the triazene motif through an intramolecular S_N1-type reaction results in the formation of **5.** The formation of the carbocation intermediates **4** and **6** are the rate-determining steps. The final product **2** is obtained after further deprotonation of **5**.

Next we extended the work to construct 3-alkenyl-1*H*-indazoles. The removal of the pyrrolidine protecting group from the 3-alkenyl-2-pyrrolidine-2*H*-indazoles **2** in acetic acid



Scheme 3. A plausible reaction mechanism.





Scheme 4. Cleavage of pyrrolidine from 3-alkenyl-2-pyrrolidine-2*H*-indazoles to form 3-alkenyl-1*H*-indazoles. Yields are those of the isolated products.

with active zinc provided the corresponding 3-alkenyl-1*H*-indazoles **7** in 64–96% yield (Scheme 4). Good functional-group compatibility was observed. Functional groups, such as ester (**7a**,**b**, **7f**, **7h**–**m**, and **7s**), cyano (**7n**), alkenyl (**7a**,**b**, **7f**, and **7h**–**s**), methoxy (**7h**, and **7o**–**s**), fluoro (**7b**), chloro (**7p**), and bromo (**7o**) groups all are well tolerated.

In summary, we have developed a DBSA-catalyzed approach to the efficient synthesis of *trans*-3-alkenyl-2-pyrrolidine-2*H*-indazoles in water from triazenylaryl allylic alcohols. These reactions are *trans* stereoselective and carried out under mild reaction conditions. Additionally, *trans*-3-alkenyl-1*H*-indazoles were obtained in excellent yields by reduction of 3-alkenyl-2-pyrrolidine-2*H*-indazoles with Zn in CH_3COOH. Further investigation of the reaction mechanism and synthetic applications are underway.

Experimental Section

DBSA (33 mg, 0.1 mmol) was added to a glass vial containing 3-(*E*)-3-hydroxy-3-phenylprop-1-enyl)-4-(*E*)-pyrrolidin-1-yldiazenyl)benzonitrile (**1n**; 166 mg, 0.5 mmol) and water (2 mL). The reaction mixture was stirred at 35 °C for 24 h. After completion, as monitored by TLC, the reaction mixture was extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Purification by column chromatography (5–20 % EtOAc/Petroleum ether) gave (*E*)-2-(pyrrolidin-1-yl)-3-styryl-2*H*-indazole-5-carbonitrile (**2n**; 155 mg, 99 %) as a light-yellow solid. $R_f = 0.29$ (5:1 Petroleum ether/EtOAc).

Freshly activated Zn (407 mg, 6.25 mmol) was added to a solution of **2n** (79 mg, 0.25 mmol) in CH_3COOH (2 mL). The reaction mixture was stirred at 100 °C for 12 h. After cooling to room temperature, water was added and the reaction mixture was neutralized with saturated $NaHCO_3$. The resulting mixture was extracted with ethyl acetate (20 mL × 3). The organic fractions were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (20–50 % EtOAc/petroleum ether) gave (*E*)-3-styryl-1*H*-indazole-5-carbonitrile (**7n**; 49 mg, 0.2 mmol, 80 %) as a white solid. $R_f = 0.20$ (3:1 petroleum ether/EtOAc).

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