

Exploiting the Chemistry of Strained Rings: Synthesis of Indoles via Domino Reaction of Aryl Iodides with 2H-Azirines

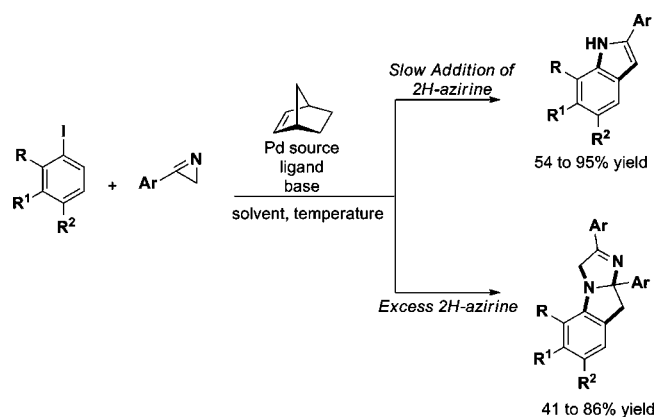
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ABSTRACT



The highly strained 2H-azirine ring system has been the source of considerable theoretical and synthetic work. The reaction of these strained heterocycles with transition metals has been documented to give rise to ring opening and subsequent formation of varied heterocycles. An interesting domino reaction is described wherein the strained bicyclic alkene, norbornene, mediates the reaction of 2H-azirines with aryl iodides under palladium catalysis to provide indole or polycyclic dihydroimidazole heterocycles.

There is often spectacular and unexpected reactivity that results from the drive to alleviate strain in an organic molecule. A major area of focus in our group has been the investigation of a palladium-catalyzed domino reaction of aryl electrophiles in which the strained bicyclic alkene, norbornene (~20 kcal/mol),^{1a} mediates a C–H activation event (Catellani reaction).² The correct sequence of events

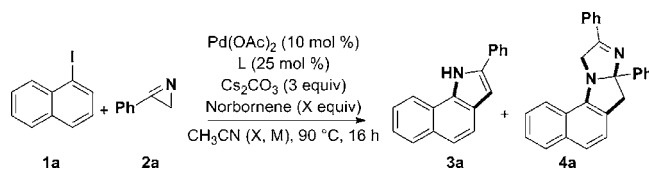
is of central importance in this domino reaction, and it is the fast and reversible carbopalladation of norbornene that allows for timely bond formation. Recently we disclosed a very efficient process for the formation of the phenanthridine nucleus via a sequence of direct arylation followed by N-arylation.³ We envisioned that the same strategy could be applied to the synthesis of indoles by alteration of the imine coupling partner.

Initial studies focused on the reaction of aryl iodides and α -haloimines. It was hypothesized that C-alkylation would occur followed by N-arylation and subsequent tautomerization to give the indole. To evaluate this hypothesis, io-

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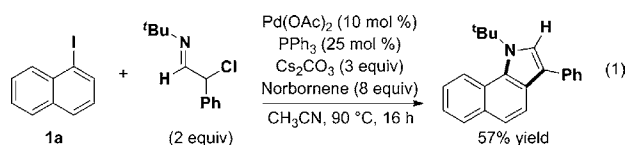
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Table 1. Optimization^a


entry	2 (equiv)	L	norbornene (equiv)	concn (M) ^b	yield (%) ^c	ratio 3a:4a ^e
1	2	P(C ₆ H ₅) ₃	8	0.05	66 ^d	0.7:1
2	1	P(C ₆ H ₅) ₃	8	0.025	36	0.7:1
3	1	P(C ₆ H ₅) ₃	8	0.0125	18	3.4:1
4	2	P(<i>o</i> -Me-C ₆ H ₄) ₃	8	0.05	<i>e</i>	
5	2	P(<i>p</i> -F-C ₆ H ₄) ₃	8	0.05	62	0.7:1
6	2	P(C ₆ F ₅) ₃	8	0.05	<i>e</i>	
7	2	P(<i>o</i> -CF ₃ -C ₆ H ₄) ₃	8	0.05	<i>e</i>	
8	2	P(<i>m</i> -Cl-C ₆ H ₄) ₃	8	0.05	71	0.7:1
9 ^f	1	P(<i>m</i> -Cl-C ₆ H ₄) ₃	8	0.05	74	>20:1
10 ^f	1	P(<i>m</i> -Cl-C ₆ H ₄) ₃	4	0.05	83	>20:1
11 ^f	1	P(<i>m</i> -Cl-C ₆ H ₄) ₃	2	0.05	95 ^d	>20:1
12 ^f	1	P(<i>m</i> -Cl-C ₆ H ₄) ₃	1	0.05	84	>20:1
13 ^g	1	P(<i>m</i> -Cl-C ₆ H ₄) ₃	2	0.05	90	10:1
14 ^h	2	P(<i>m</i> -Cl-C ₆ H ₄) ₃	8	0.05	95	1:2.5
15 ^h	4	P(<i>m</i> -Cl-C ₆ H ₄) ₃	8	0.05	99	1:5
16 ^h	4	P(<i>m</i> -Cl-C ₆ H ₄) ₃	8	0.10	84 ⁱ	<1:5
17 ^h	4	P(<i>m</i> -Cl-C ₆ H ₄) ₃	8	0.20	86 ^{d,i}	<1:5

^a Reaction conditions: reactions run in sealed tube on 0.2 mmol scale with respect to iodonaphthalene, unless otherwise noted. ^b Final total concentration based on iodonaphthalene. ^c Determined by HPLC. ^d Isolated yield. ^e Aryl iodide recovered. ^f Slow addition of solution of **2a** in MeCN (rate = 0.26 mL/h, 0.1 M in azirine) to refluxing reaction mixture. ^g Slow addition of solution of **2a** in MeCN (rate = 1.4 mL/h, 0.1 M in azirine) to refluxing reaction mixture. ^h 45 mol % of ligand used. ⁱ Yield of **4a**.

donaphthalene was reacted with a haloimine under previously developed conditions.³ The desired product was obtained in 57% yield (eq 1). As the investigation progressed it became evident that the synthesis of the requisite α -haloimines was low-yielding and often accompanied by decomposition of the imine, limiting this approach.



Conceptually, a 1,3-dipole is required to carry out the intended transformation. The ring cleavage reactions of highly strained 2*H*-azirines (44–48 kcal/mol of strain for the parent azirine)^{1b} under thermal, photochemical, and transition metal catalysis has been well documented, and varied heterocyclic structures are the outcome of such reactions.⁴ Pioneering work carried out by the groups of Hassner, Padwa, Alper, and others on the photochemical and transition-metal-catalyzed reactions of azirines suggested that cleavage of the azirine ring system under our reaction conditions would generate a 1,3-dipole equivalent that could

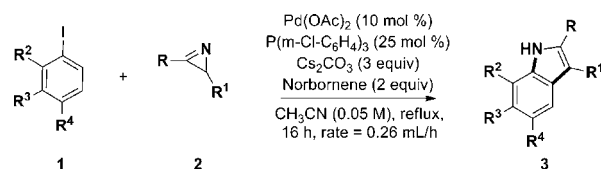
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go on to furnish the desired indole.⁵ To evaluate this hypothesis, iodonaphthalene was reacted with azirine **2a** (Table 1, entry 1). The desired indole **3a** was observed in 31% yield along with 35% of the unusual tetracyclic dihydroimidazole **4a**. The remainder of the mass balance was undefined byproducts and dimerized azirine.

Although the transition-metal-catalyzed intramolecular reaction of 2*H*-azirines to form indoles has been known for many years, the involvement of 2*H*-azirines in domino processes and their reactions with aryl palladium intermediates are, to our knowledge, unprecedented.⁵

An optimization of the reaction conditions was undertaken using **2a** and iodonaphthalene as a model system (Table 1). Attempts to reduce the amount of product **4a** by decreasing the total concentration of the reaction mixture were ineffective and led to a decrease in overall yield and only a modest shift in the product ratio (entries 1–3). Starting material was recovered when electron-deficient phosphines or phosphines

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Table 2. Scope of Indole Formation^a


entry	aryl iodide				azirine			3	yield (%) ^b
	1	R ₂	R ₃	R ₄	2	R	R ₁		
1	1a				2a	Ph	H	3a	95
2	1a				2b	4-F-C ₆ H ₄	H	3b	95
3	1a				2c	4-Cl-C ₆ H ₄	H	3c	86
4	1a				2d	4-MeO-C ₆ H ₄	H	3d	86
5	1a				2e	2-MeO-C ₆ H ₄	H	3e	67
6	1a				2f	2,5-Me ₂ -C ₆ H ₃	H	3f	60
7	1b	MeO	H	H	2a			3g	54
8	1c	Me	H	H	2a			3h	55
9	1d	Cl	H	H	2a			3i	64
10	1f	Me	CF ₃	H	2a			3j	64
11	1g	Me	F	H	2a			3k	55
12	1h	Me	H	NHAc	2a			3l	68
13	1a				2g	Ph	Me		c
14	1a				2h	Ph	CO ₂ Me		c
15	1a				2i	Bn	H		c
16	1a				2j	CO ₂ Bn	H		c
17	1a				2k	CONMe ₂	H		c

^a Reaction conditions: aryl iodide (0.2 mmol, 1.0 equiv), Pd(OAc)₂ (10 mol %), P(*m*-Cl-C₆H₄)₃ (25 mol %), Cs₂CO₃ (3 equiv), and norbornene (2 equiv) were heated to reflux (oil bath temperature = 110 °C) in MeCN (2 mL). The azirine (1.0 equiv, 0.1 M in MeCN) was added slowly via syringe pump (rate = 0.26 mL/h). ^b Isolated yields. ^c Aryl iodide recovered and azirine was consumed.

with *ortho* substituents were employed (entries 4–7). It was found that P(*m*-Cl-C₆H₄)₃ possessed the best combination of steric and electronic properties, and the optimization was continued using this ligand (entry 8). Slow addition of **2a** over 8 h effectively eliminated the formation of **4a** (entry 9). The crude reaction mixture revealed that byproducts resulting from the incorporation of norbornene accompanied **3a**, and reduction in the amount of norbornene led to a decrease in their formation and a corresponding increase in the yield of **3a** (entries 9–12). Ultimately, **3a** could be obtained in 95% isolated yield without the formation of **4a**.

With conditions in hand to obtain the indole product in good yield and selectivity, an investigation into the scope was undertaken (Table 2). Various 2*H*-azirines could be prepared in a straightforward manner via thermolysis of the corresponding vinyl azides or oxidation of the corresponding aziridine.⁶ Alkyl- and aryl-substituted azirines can be isolated and stored; however, 3-carbonyl-substituted azirines are unstable and in these cases the vinyl azides were pyrolyzed and the crude azirines (≥95% by NMR) were utilized immediately.⁶ Substitution of the aryl ring of the azirine

proved to be tolerated, as electron-donating and -withdrawing groups appeared to have little impact on the yields (entries 1–4). Furthermore, azirines with groups at the *ortho* position of the aryl ring were tolerated, although a decrease in yield was observed (entries 5 and 6). Variation of the aryl iodide was also possible; however, the yields were reduced when compared with the model system (entries 7–12). The yields reported were not optimized on a case by case basis, and despite this the developed reaction conditions were able to provide synthetically useful yields of the indoles. This method is suited to the rapid synthesis of a library of compounds where the aryl iodide can be readily varied. There are a number of cases in which the azirines failed to provide the desired indole products under the reaction conditions (entries 13–17). When a substituent is placed on the 2-position or when an alkyl or carbonyl group is placed at the 3-position of the azirine ring system, the starting azirine was completely consumed while the aryl iodide could be recovered (entries 13–17). Further, studies are required to determine the reason why these azirines did not undergo the desired reaction.

We have also identified conditions for the selective formation of **4a** (the structure of **4a** was confirmed by X-ray crystallography, see Supporting Information). As anticipated, the yield of **4a** increased with increasing the amount of **2a** present in the reaction mixture and by increasing the total concentration (Table 1, entries 14–17). It was also found

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Table 3. Scope of Dihydroimidazole Formation^a

	2	4	yield (%) ^b
1	2a	4a	86
2	2b	4b	63
3	2d	4c	41

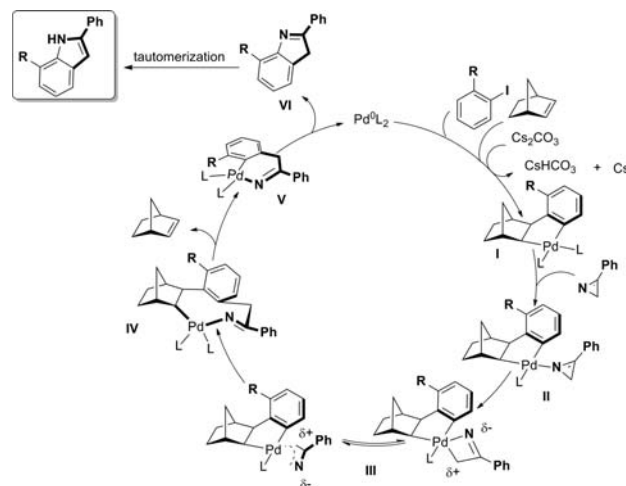
^a Reaction conditions: aryl iodide (0.2 mmol, 1.0 equiv), azirine (4 equiv), Pd(OAc)₂ (10 mol %), P(*m*-Cl-C₆H₄)₃ (45 mol %), Cs₂CO₃ (3.0 equiv), and norbornene (8 equiv) in MeCN (0.2 M) were heated in a sealed tube at 90 °C for 16–24 h. ^b Yield of isolated products

that increasing the amount of ligand present in the reaction mixture favored the formation of **4a**.

A few interesting polycyclic dihydroimidazoles could be formed selectively and efficiently (Table 3). It appears that the efficiency of the reaction to form products of type **4** is more sensitive to the electronic nature of the aryl substituent on the *2H*-azirine than observed for the formation of indoles **3**. In these cases it is difficult to completely preclude the formation of the indole product under the reaction conditions, and the crude reaction mixtures contain small amounts of the indole (~10% by NMR); however, careful chromatography is capable of removing the indole product.

The transformation requires that norbornene be present in the reaction mixture as in its absence the starting aryl iodide is recovered and the azirine is consumed, forming dimeric products. It is anticipated that this process follows a similar catalytic cycle to that of other norbornene mediated C–H functionalizations (Scheme 1).⁷ Oxidative addition of the aryl iodide, carbopalladation of norbornene, and electrophilic metalation followed by deprotonation can yield palladacyclic intermediate **I**. Complexes of azirines and palladium(II) are well-known and have been demonstrated to coordinate to the metal center through the nitrogen lone pair.^{5j,k} Binding of the *2H*-azirine is expected to yield complex **II** (L is taken to be any suitable ligand in the reaction mixture), and in doing so the bonds of the ligand are weakened, ultimately leading to fission of the N–C single bond via oxidative addition. The fission of the N–C single bond is commonly observed in the reactions of azirines with transition metals.^{5c,e,h–l} The complex resulting from metal-mediated

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Scheme 1. Proposed Mechanism of Indole Formation

ring opening of the azirine ligand can be formulated as complex **III** (other conformations of these representations cannot be excluded, and the ones depicted may not be the lowest in energy).^{5c,h,k} Chemoselective C–C bond formation is expected to yield **IV** initially, which can subsequently decarbopalladate to give intermediate **V**. Reductive elimination from **V** can provide **VI**, which tautomerizes to give the indole product (tautomerization of intermediates at an earlier stage of the catalytic cycle is also possible). The dihydroimidazoles **4** can be derived from a palladium(0)-catalyzed formal [3 + 2] reaction of an azirine with the C–N double bond of intermediate **VI**. Efforts toward mechanistic investigations are currently in progress.

In conclusion, we have described the first intermolecular reaction of aryl palladium intermediates with *2H*-azirines to furnish indoles and polycyclic dihydroimidazoles. It is interesting to note that in this reaction the strain energy in two small molecules is exploited to bring about a complex transformation. Further work in this area will focus on gaining insight into the mechanism and other synthetic applications of azirines when under the influence of transition metal catalysis.

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Supporting Information Available: Experimental procedures and full characterization for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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