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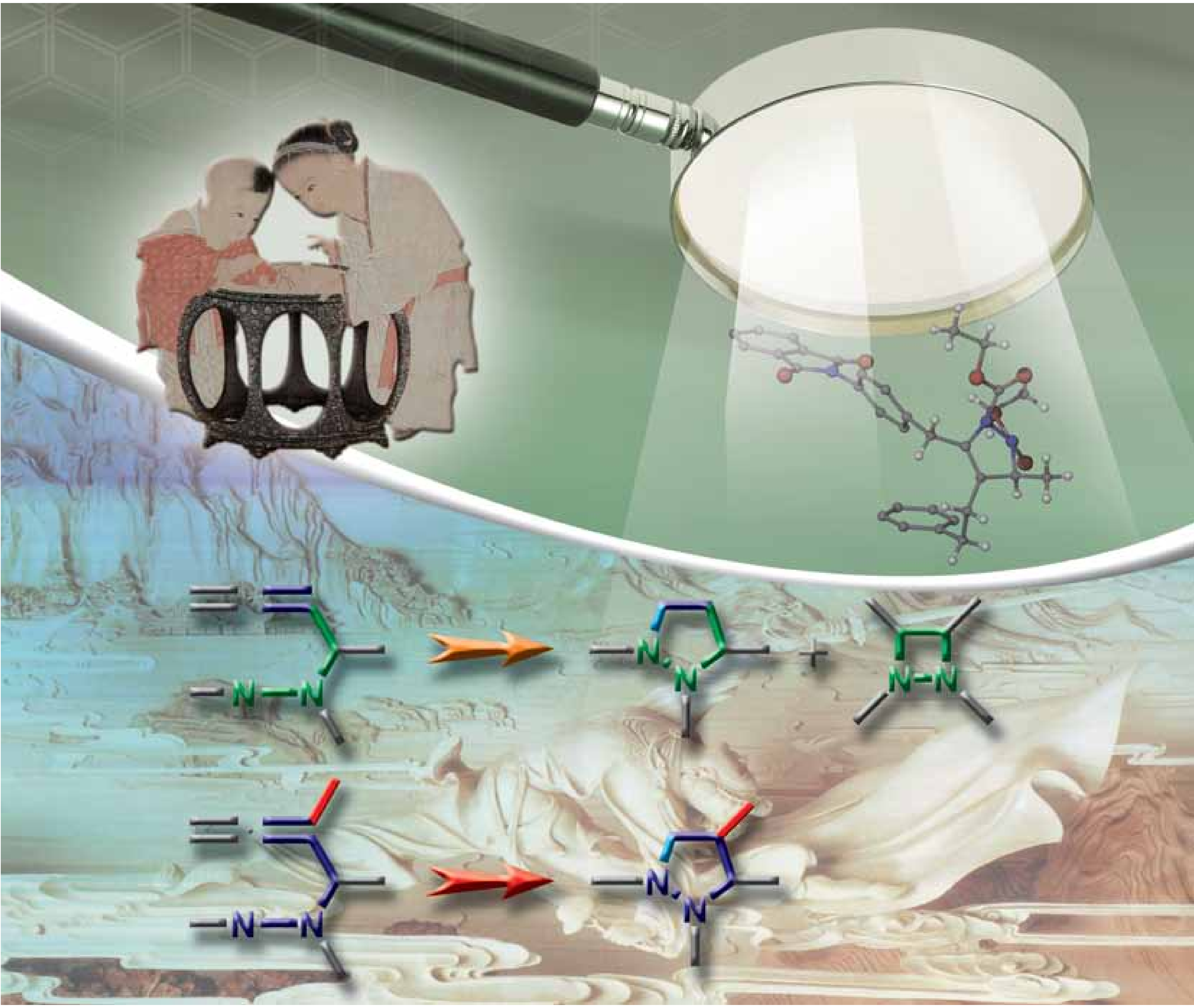

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Efficient synthesis of 2,3-dihydro-1*H*-pyrazoles *via* a highly selective Pd(0)-catalyzed coupling-cyclization reaction of terminal 2-substituted 2,3-allenyl hydrazines with aryl iodides†‡

Xin Cheng and Shengming Ma*

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2,3-Dihydro-1*H*-pyrazoles were highly selectively synthesized *via* the Pd(0)-catalyzed coupling-cyclization reaction of 4-non-substituted 2-substituted 2,3-allenyl hydrazines with aryl iodides in moderate to good yields.

Pyrazoles and dihydro-1*H*-pyrazoles, two important classes of nitrogen-containing heterocycles, show extensive applications in the pharmaceutical and agrochemical industries due to their biological properties.[1] Although 2,3-dihydro-1*H*-pyrazoles derivatives have been prepared by the 1,3-dipolar cycloaddition of azomethine imines with alkynes,[2] reaction of pyrazolium salts with silyllithium reagents,[3] and reaction of Huisgen zwitterions with chalcones,[4] development of efficient methodologies for the synthesis of functionalized 2,3-dihydro-1*H*-pyrazoles under mild conditions is still of high interest.

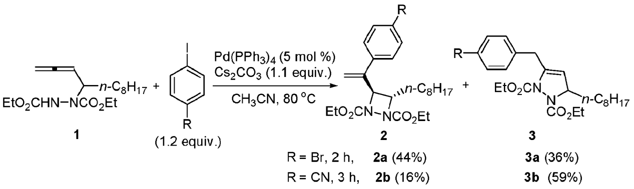
Recently, much attention has been paid to the coupling–cyclization reaction of functionalized allenes with organic halides.[5–7] During the course of our study on the chemistry of allenes, we and others[5–7] have demonstrated that allenes with a nucleophilic functionality are versatile building blocks for the synthesis of some potentially important carbo- and heterocyclic compounds such as γ-butenolides,[7a,b] γ-lactams,[7c,d] vinylic epoxides,[7e] 2,5-dihydrofurans,[7f,g] furans,[7h,i] vinylic cyclopropanes,[7j–l] 2,3-dihydropyrroles,[7m,n] *etc*. Recently, we have described that the Pd(0)-catalyzed coupling-cyclization of 2,4-non-substituted 2,3-allenyl hydrazines with electron-donating aryl iodides or phenyl iodide affords *trans*-1,2-diazetidines in a highly regio- and *trans*-diastereoselective manner.[8] Here we wish to report our most recent observation on the Pd(0)-catalyzed coupling-cyclization reaction of 4-non-substituted 2-substituted 2,3-allenyl hydrazines with aryl iodides, in which a different regioselectivity was observed.

Stimulated by our previous successful results,[8] we then continued to investigate the reaction of 2,4-non-substituted 2,3-allenyl hydrazine **1** with electron-withdrawing aryl iodides under identical conditions to those described in ref. 8 (Conditions A: **1** (1.0 equiv.), aryl halide (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (1.1 equiv.), MeCN, 80 °C) (Scheme 1). As can be seen from Scheme 1, a mixture of four-membered *trans*-1,2-diazetidine **2** and five-membered 2,3-dihydro-1*H*-pyrazole product **3** were formed when electron-withdrawing aryl iodides were used. A trend was observed that the yield of five-membered product **3** increased with the enhancement of electron-withdrawing ability of substituents attached to the *para* position of aryl iodides.

Based on these results, we were intrigued by the possibility that the five-membered 2,3-dihydro-1*H*-pyrazole products could be obtained exclusively after introducing substituents to the 2-position of 2,3-allenyl hydrazines. Thus, we synthesized 4-non-substituted 2-substituted 2,3-allenylic hydrazine **4a**[8,9] and investigated its reaction with 4-nitroiodobenzene under Conditions A. As anticipated, after 3 h the reaction afforded the five-membered ring 2,3-dihydro-1*H*-pyrazole product **5a** in 74% yield exclusively (Scheme 2). Compound **5a** was fully characterized by $^1H/^{13}C$ NMR, IR, MS and HRMS methods. It should be noted that we did not observe the formation of four-membered *trans*-1,2-diazetidine product **2c**.

Some typical results of the Pd(0)-catalyzed coupling-cyclization reaction of **4a** with other differently substituted aryl halides under Conditions A are summarized in Table 1. It can be seen from Table 1 that both electron-withdrawing aryl iodides and phenyl iodide can react efficiently to afford the corresponding 2,3-dihydro-1*H*-pyrazole products (entries 1–6, Table 1). When electron-donating 4-methyliodobenzene or 4-methoxyiodobenzene was used to react with **4a**, 2,3-dihydro-1*H*-pyrazole product **5h** or **5i** was also obtained solely but the yields dropped to 49 and 38%, respectively (entries 7 and 8, Table 1). However, the formation of four-membered products was not observed.

To further investigate the scope of this reaction, the cyclization reaction of various 4-non-substituted 2-substituted 2,3-allenyl hydrazines with a number of aryl iodides were



Scheme 1

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai, 200032, P. R. China,.
E-mail: masm@mail.sioc.ac.cn; Fax: (+86) 21-6416-7510

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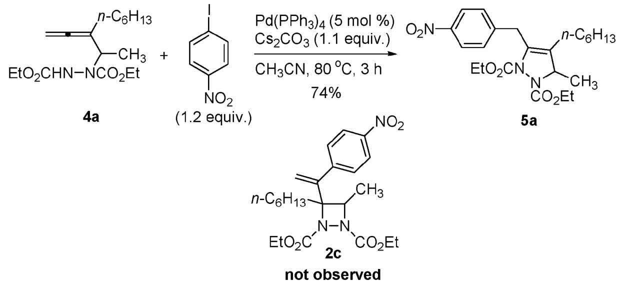
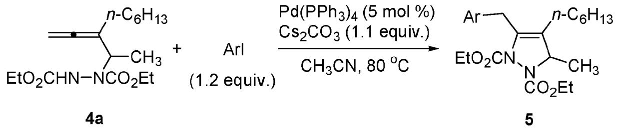
‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products. CCDC 716723. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b903634b



Scheme 2

Table 1 Pd(0)-catalyzed coupling-cyclization reaction of **4a** with aryl iodides



Entry	Ar	t/h	Product **5**	Yield of 5^a (%)
1	p-NCC_6H_4	2.5	**5b**	79
2	p-$Me(O)CC_6H_4$	2.5	**5c**	73
3	p-$MeO_2CC_6H_4$	2.5	**5d**	77
4	o-$MeO_2CC_6H_4$	3	**5e**	76
5	p-BrC_6H_4	3	**5f**	72
6	Ph	3	**5g**	68
7	p-MeC_6H_4	7	**5h**	49
8	p-$MeOC_6H_4$	5	**5i**	38

[a] Isolated yield based on **4a**.

performed under Conditions A and the results are listed in Table 2. All reactions afforded five-membered products exclusively in 47–86% yields. The reaction is pretty general: R^1 can be an alkyl or a cycloalkyl group; R^2 can be hydrogen, an alkyl or cycloalkyl group; R^3 can be an ethyl, isopropyl or *tert*-butyl group. When heteroaromatic halides such as 4-iodopyridine or iodopyrazine were used in this transformation, the yields were slightly higher (entries 11 and 12, Table 2). When 4-phthalimidoiodobenzene was used, the yield of product dropped to 47% (entry 13, Table 2). It is interesting to observe that even when an aryl iodide with a methoxy group at the *meta* position, *i.e.*, 3-methoxyphenyl iodide was used, 2,3-dihydro-1*H*-pyrazole product **5w** was formed in 72% yield (entry 14, Table 2). The 2,3-dihydro-1*H*-pyrazole structure of product **5** was unambiguously established by the single-crystal X-ray diffraction study of **5v** (Fig. 1).[10]

Additional studies were conducted to investigate the possibility of synthesizing optically active 2,3-dihydro-1*H*-pyrazoles. Optically active (*R*)- or (*S*)-**4** can be easily prepared by the reaction of diethyl azodicarboxylate with the corresponding highly optically active (*S*)- or (*R*)-2,3-allenols, which are easily available from the kinetic enzymatic resolution of the racemic 2,3-allenols.[11] Some typical results are shown in Table 3. From Table 3, both *R* and *S* substrates can smoothly afford the corresponding products with the yields ranging

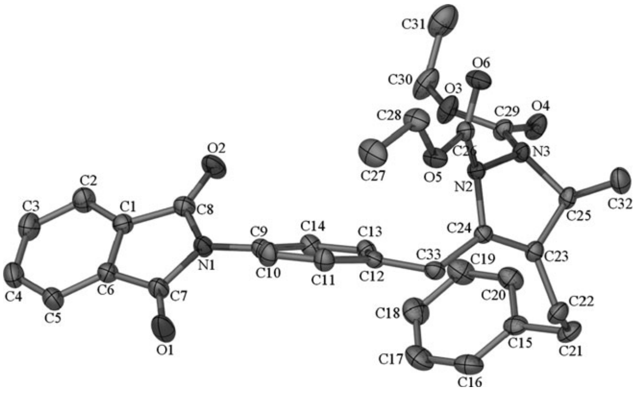
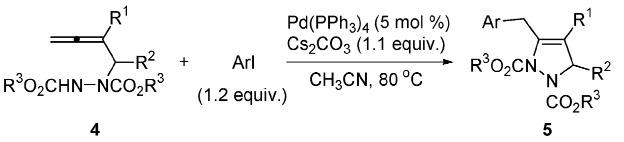


Fig. 1 ORTEP representation of the product **5v**.

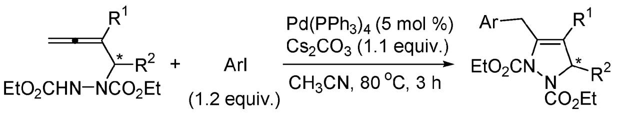
Table 2 Pd(0)-catalyzed coupling-cyclization reaction of **4a** with aryl iodides



	4					
Entry	R^1	R^2	R^3	Ar	t/h	Yield of 5^a (%)
1	n-C_6H_{13}	Me	i-Pr (**4b**)	p-$Me(O)CC_6H_4$	3	76 (**5j**)
2	n-C_6H_{13}	Me	t-Bu (**4c**)	p-$Me(O)CC_6H_4$	5	70 (**5k**)
3	n-C_4H_9	n-C_5H_{11}	Et (**4d**)	p-$O_2NC_6H_4$	3.5	66 (**5l**)
4	Cyclopropyl	n-C_5H_{11}	Et (**4e**)	p-$O_2NC_6H_4$	3.5	63 (**5m**)
5	n-C_5H_{11}	n-C_8H_{17}	i-Pr (**4f**)	p-$O_2NC_6H_4$	7	72 (**5n**)
6	n-C_5H_{11}	Cyclohexyl	i-Pr (**4g**)	p-NCC_6H_4	4	76 (**5o**)
7	n-C_4H_9	Me	Et (**4h**)	p-$BnO_2CC_6H_4$	3	78 (**5p**)
8	n-C_4H_9	Et	Et (**4i**)	o-$MeO_2CC_6H_4$	3	76 (**5q**)
9	n-C_5H_{11}	Me	Et (**4j**)	p-NCC_6H_4	3	82 (**5r**)
10	n-C_5H_{11}	H	Et (**4k**)	p-NCC_6H_4	3	73 (**5s**)
11	n-C_5H_{11}	Me	t-Bu (**4l**)	4-Pyridyl	11	86 (**5t**)
12	$Ph(CH_2)_2$	Me	Et (**4m**)	Pyrazinyl	4	84 (**5u**)
13	$Ph(CH_2)_2$	Me	Et (**4m**)	p-$PhthNC_6H_4$	7	47 (**5v**)
14	n-C_5H_{11}	Me	Et (**4j**)	m-$MeOC_6H_4$	5	72 (**5w**)

[a] Isolated yield based on **4**.

Table 3 Synthesis of optically active 2,3-dihydro-1*H*-pyrazoles



(*R*)- or (*S*)-4 **(*R*)- or (*S*)-5**

Entry	(*R*)- or (*S*)-**4** R^1	R^2	ee (%)	Ar	Yield of (*R*)- or (*S*)-**5**[a] (%)	ee[b] (%)
1	*n*-C_4H_9	Me (*R*-**4h**)	>99	*p*-$BnO_2CC_6H_4$	77 (*R*-**5p**)	99
2	*n*-C_4H_9	Me (*S*-**4h**)	96	*p*-$BnO_2CC_6H_4$	77 (*S*-**5p**)	95
3	*n*-C_5H_{11}	Me (*R*-**4j**)	>99	*p*-NCC_6H_4	82 (*R*-**5r**)	98
4	*n*-C_5H_{11}	Me (*S*-**4j**)	>99	*p*-NCC_6H_4	83 (*S*-**5r**)	96
5	*n*-C_6H_{13}	Me (*R*-**4a**)	>99	*p*-Me(O)CC_6H_4	71 (*R*-**5c**)	97

[a] Isolated yield. [b] The ee value was determined by HPLC.

from 71 to 83%. Racemization of the chiral centers in (*R*)- or (*S*)-**4** is not clearly evident.

In conclusion, we have developed a mild and efficient method for the regioselective synthesis of 2,3-dihydro-1*H*-pyrazoles. By using the readily available enantiomerically enriched 2,3-allenyl hydrazines, optically active 2,3-dihydro-1*H*-pyrazoles with high ee values can be synthesized conveniently. The reaction may proceed *via* oxidative addition followed by carbopalladation forming a π-allylic palladium intermediate or by a nucleometalation–reductive elimination pathway.[5c] Further studies in this area are being conducted in our laboratory.

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