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Domino N−H/C−H Bond Activation: Copper-Catalyzed Synthesis of Nitrogen-Bridgehead Heterocycles Using Azoles and 1,4-Dihalo-1,3-dienes

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ABSTRACT

Copper-catalyzed tandem coupling of 1,4-dihalo-1,3-dienes with azoles *via* an N−H bond and its adjacent C−H bond activation has been described. The reaction exhibits good regioselectivity when unsymmetrical 1,4-dihalo-1,3-diene is employed. This method provided a novel route to the synthesis of nitrogen-bridgehead azolopyridine derivatives.

Direct transition-metal-catalyzed functionalization of C−H bonds in heterocycles has received significant attention in modern organic chemistry owing to its atom economy, high functional group tolerance, and the possibilities for transformation of the unreactive C−H bonds into diverse functions in one operation. Significant progress was accomplished by recently developed methodologies for the general use of aryl (pseudo)halides in direct arylation reactions.[1,2] In contrast to the much more developed palladium-catalyzed C−H arylation reaction of various heterocycles, direct alkenylations of heteroaromatics with vinyl (pseudo)halides have received much less attention.[2a,3] In particular, copper-catalyzed direct *C*-alkenylation of free (NH)-azoles with vinyl halides was unknown, to the best of our knowledge. Cu-catalyzed alkenylation of free (NH)-azoles to afford *N*-alkenylation products has been reported.[4] In this case, no *C*-alkenylation products were obtained. As part of a general

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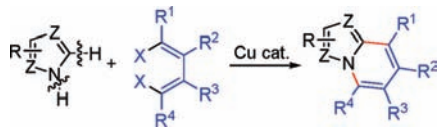
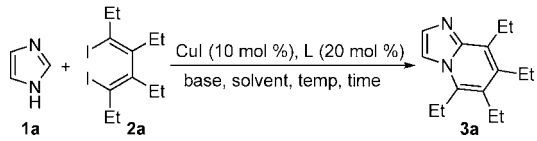
study of the construction of heterocyclic compounds using 1,4-dihalo-1,3-dienes,[5] we envisioned that a domino reaction of free (NH)-azole with 1,4-dihalo-1,3-diene could afford an annulated heterocycle through N−H and C−H cleavage. Herein, we report a novel copper-catalyzed domino reaction[2d,e,6] for the synthesis of N-bridgehead azolopyridine.[7] This approach involves a consecutive *N*-alkenylation and *C*-alkenylation by using readily available azoles and 1,4-dihalo-1,3-dienes (Scheme 1).

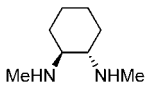
Scheme 1



To probe the viability of the envisioned domino reaction, imidazole **1a** and (3*Z*,5*Z*)-4,5-diethyl-3,6-diiodoocta-3,5-diene **2a** were used as the model substrates for the optimization of the reaction conditions (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	base	solvent	temp /°C	time /h	yield /%[b]
1	acac	Cs_2CO_3	DMF	140	24	65
2	acac	Cs_2CO_3	DMF	140	48	66
3	acac	K_3PO_4	DMF	140	48	49
4	acac	^{t}BuONa	DMF	140	48	36
5	acac	Cs_2CO_3	DMA	140	24	41
6	acac	Cs_2CO_3	DMSO	140	24	41
7	acac	Cs_2CO_3	NMP	140	24	53
8	PPh_3	Cs_2CO_3	DMF	140	24	77
9	proline	Cs_2CO_3	DMF	140	24	78
10	2,2-dipyridine	Cs_2CO_3	DMF	140	24	79
11		Cs_2CO_3	DMF	140	24	75
12	1,10-phen	Cs_2CO_3	DMF	140	24	79
13	acac	Cs_2CO_3	DMF	160	24	78
14	none	Cs_2CO_3	DMF	160	24	80
15[c]	none	Cs_2CO_3	DMF	160	24	89 (83)
16[d]	none	Cs_2CO_3	DMF	160	24	0

[a] Reaction conditions: 1,4-diiodo-1,3-diene (1.0 equiv), imidazole (1.0 equiv), CuI (10 mol %), Ligand (20 mol %), Cs_2CO_3 (3 equiv), DMF (2 mL). [b] ^{1}H NMR yields using $Cl_2C{=}CHCl$ as an internal standard; the isolated yields are given in parentheses. [c] Imidazole (1.5 equiv). [d] Without CuI.

It is noted that the requested 1,4-dihalo-1,3-dienes were conveniently prepared in high yields with high regioselectivity and stereoselectivity through halogenation of zirconacyclopentadienes derived from two alkynes, according to the reported methods.[8]

As summarized in Table 1, substrate **1a** and **2a** were first subjected to the following typical conditions: 10 mol % of CuI, 20 mol % of acetyl acetone (acac), dimethylformamide (DMF) as a solvent, and Cs_2CO_3 as a base at 140 °C. 5,6,7,8-Tetraethylimidazo[1,2-*a*]pyridine **3a** was obtained in 65% yield after 24 h (entry 1). Prolonging the reaction time to 48 h did not help (entry 2). However, when the reaction was carried out in DMF at 160 °C for 24 h, the expected coupled product **3a** was achieved in 78% yield (entry 13). Other polar solvents also resulted in the formation of the product (entries 6−7), while they are not as efficient as DMF. Among the bases, Cs_2CO_3 proved to be superior. Usually, ligands play an important role in the copper-catalyzed coupling reactions; thus different types of ligands were screened. Surprisingly, all the ligands screened gave similar results (entries 1, 8−12). These results let us suspect that the ligands might not participate in the coupling reaction. Indeed, we were pleased to find that, in the absence of a ligand, the reaction proceeded smoothly, and azolopyridine **3a** formed also in high yield (entry 14). The above data also suggested that azole itself might function as the ligand in the reaction. Increasing the amount of imidazole to 1.5 equiv gave a product **3a** in excellent yield (entry 15). On the other hand, without the use of CuI, the reaction did not proceed (entry 16).

Having established an effective catalytic system for the coupling reactions, we next synthesized a variety of 1,4-dihalo-1,3-dienes[8] to explore the scope of tandem alkenylation under the optimized conditions (CuI as a catalyst, Cs_2CO_3 as a base, and DMF as a solvent, with the reaction temperature at 160 °C). The results are summarized in Table 2. At the beginning, 1,4-diiodo-1,3-dienes with an ethyl and a propyl substituent were examined, and the corresponding azolopyridine formed in high yields (entries 1−2). When a diiododiene fused with a six-membered ring **2c** was used, the reaction smoothly occurred to afford imidazo[1,2-*b*]isoquinoline derivative **3c** in a high yield (entry 3). When 2,2′-diiodobiphenyl **2d**[9] was used, and the reaction also proceeded smoothly under the conditions to afford imidazo[1,2-*f*]phenanthridine **3d** in moderate yield (entry 4). The reaction of 1,4-dibromo-1,3-diene **2e** with azole **1a** also

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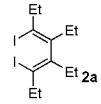
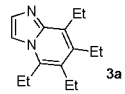
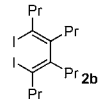
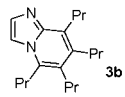
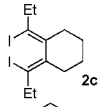
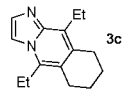
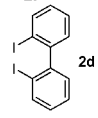
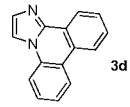
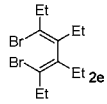
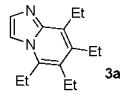
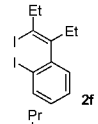
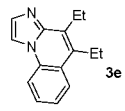
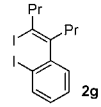
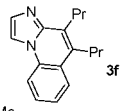
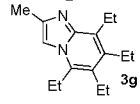
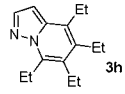
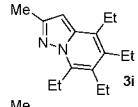
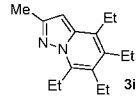
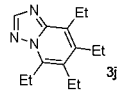
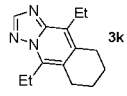
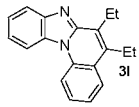
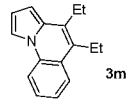
Table 2. Tandem Synthesis of Diversely Substituted Azolopyridines Catalyzed by CuI[a]

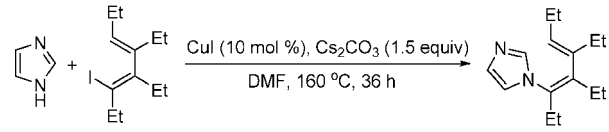
entry	azole	dihalide	time /h	product	yield /%[b]
1	 **1a**	 **2a**	36	 **3a**	89 (83)
2	**1a**	 **2b**	50	 **3b**	65 (60)
3	**1a**	 **2c**	30	 **3c**	82 (78)
4	**1a**	 **2d**	36	 **3d**	30 (29)
5	**1a**	 **2e**	48	 **3a**	86 (80)
6	**1a**	 **2f**	24	 **3e**	80 (78)
7	**1a**	 **2g**	32	 **3f**	70 (59)
8	 **1b**	**2a**	24	 **3g**	40 (39)
9	 **1c**	**2a**	36	 **3h**	30 (25)
10[c]	 **1d**	**2a**	24	 **3i**	40 (38)
11[c]	**1d**	**2e**	96	 **3i**	39
12	 **1e**	**2a**	60	 **3j**	33 (28)
13[c]	**1e**	**2c**	48	 **3k**	53 (50)
14[c]	 **1f**	**2f**	36	 **3l**	25 (22)
15	 **1g**	**2f**	48	 **3m**	-- (15)

[a] Reaction conditions: diiododiene (1.0 equiv), azole (1.5 equiv), CuI (10 mol %), Cs_2CO_3 (3 equiv), DMF (2 mL). [b] ^{1}H NMR yields, using $Cl_2C{=}CHCl$ as an internal standard; the isolated yields are given in parentheses. [c] Azole (2.0 equiv), CuI (20 mol %), *N*-phenylpyridin-2-methylimine (20 mol %) as ligand.

afforded azolopyridine **3a** in high yield (entry 5). Furthermore, when (*Z*)-1-iodo-2-(2-iodovinyl)benzenes[10] (**2f** and **2g**) were used, the reactions smoothly occurred to afford imidazo[1,2-*a*]quinoline derivative **3e** and **3f** in high yields, respectively (entries 6−7). The structure of product **3e** was confirmed by ^{1}H NMR, ^{13}C NMR, HSQC, and HMBC experiments,[11] which indicated that aryl iodide coupled with the N−H bond and then the alkenyl iodide coupled with the C−H bond. The reaction could be extended to substituted imidazole and other azoles, such as pyrrole, pyrazole, and triazole. The reaction of 4-methylimidazole **1b** with **2a** gave 5,6,7,8-tetraethyl-2-methylimidazo[1,2-*a*]pyridine **3g** regioselectively, which could be rationalized by steric hindrance (entry 8). When 4-nitro-1*H*-imidazole and 1*H*-imidazole-4-carbaldehyde were treated under the condition, the desired products were not observed. Pyrazole **1c** and 3-methylpyrazole **1d** reacted with **2a** to form pyrazolo[1,5-*a*]pyridine **3h** and its methyl substituted derivative **3i** (entries 9−10), respectively. 1,4-Dibromo-1,3-dienes **2e** also reacted under the conditions with a slow reaction rate (entry 11). When 1,2,4-triazole **1e** was employed, N-1, C-2 annulated products were formed in moderate yields (entries 12−13) with a high loading of CuI and other ligand. The coupling reaction occurred in the N-1 position, other than N-3. These results are consistent with those reported by Buchwald.[12] Pyrrole **1g** could also perform in these conditions, and pyrrolo[1,2-*a*]quinoline **3m** was obtained with low yield.

To investigate the reaction process, a reaction of (3*Z*,5*E*)-4,5-diethyl-3-iodoocta-3,5-diene **2g** and imidazole **1a** was treated under the conditions. In this case *N*-coupled product **3n** was obtained as the sole product (Scheme 2). It is important to note that under the conditions we did not detect any formation of the *C*-coupled product. This result indicated that the N−H bond was activated preferentially in the

Scheme 2



1a **2g** **3n**, 50 % yield

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(11) HSQC and HMBC showed cross-peak correlation for product **3e**. See Supporting Information for details.

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reaction conditions. Therefore a proposed reaction course is first N−H bond alkenylation followed by a sequent C−H bond alkenylation on azole with 1,4-dihalo-1,3-diene.

In summary, we have reported a novel copper-catalyzed domino reaction for the synthesis of annulated heterocycles that consists of N−H bond alkenylation and C−H bond alkenylation with readily available azoles and 1,4-dihalo-1,3-dienes. Notably, this approach constitutes an unprecedented direct alkenylation-based domino process that is applicable to synthesize nitrogen-bridgehead azolopyridine derivatives.

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Supporting Information Available: Experimental procedures and full characterization including ^{1}H NMR and ^{13}C NMR data for compounds **3a**−**3c**, **3e**−**3l**, and **3n**. HSQC and HMBC for **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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