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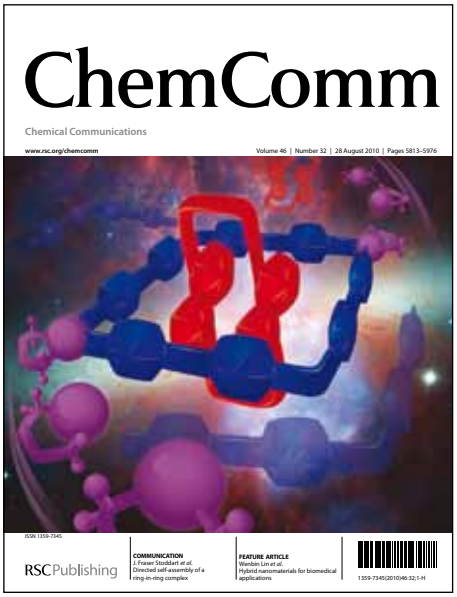

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ARTICLE TYPE

Highly Efficient Vinylaromatics Generation *via* Iron-Catalyzed sp^3 C-H Bond Functionalization CDC Reaction: A Novel Approach to Preparing Substituted Benzo[*α*]phenazines

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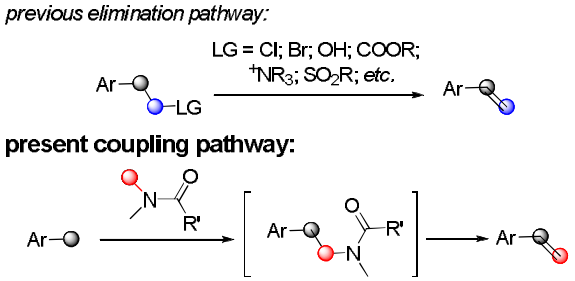
An iron-catalyzed benzylic vinylation was developed to transfer the carbon atom in N,N-dimethyl moiety of *N*,*N*-dimethylacetamide (or *N*,*N*-dimethylformamide) to 2-methyl azaarenes to generate 2-vinyl azaarenes.

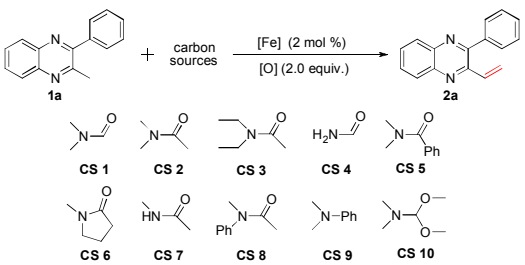
Vinylaromatics are important structural motifs for C-C bond construction *via* cross-coupling reactions, such as Heck reaction, and have been widely applied in the synthesis of natural products. Traditional formation of terminal alkenes were studied extensively including the elimination of haloalkanes, alcohols, quaternary ammonium salts, carboxylic esters, epoxyethanes and sulfones, for instance. However, most of these procedures are impaired by prefunctional starting materials, which limit their applications. Hence, this study investigated a new concise pathway employing a cross-dehydrogenative-coupling (CDC) reaction between a 2-methyl azaarene and an *N*,*N*-dimethyl amide with tandem elimination to generate vinylarene compounds (Scheme 1).

Given their remarkable advance and significance, iron catalysts, especially hydrous iron salts, have been given significant attention in studies involving direct C-H bond activation reaction.[1] Although several efforts have been made in recent years to develop efficient strategies for the transition metal-catalyzed, selective oxidation of C-H bonds adjacent to heteroatoms,[2] the use of eco-friendly iron as catalyst is still rare and little attention has been given to employing the more stable *N*-substituted amides as CDC partner.[3, 4] Prompted by the results of our previous work on the sp^2 C-H bond nitration of quinoxalines,[5] we continued our research on the quinoxaline structure, this time focusing on sp^3 C-H bond functionalization.[6]



Scheme 1. Synthesis strategies.

Table 1. Optimization of the Reaction Condition [a]

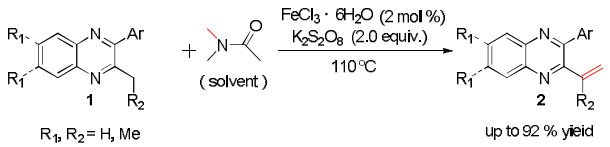


Entry	Iron	Carbon sources	Yield (%) [b]
1 [c]	$FeCl_3$	CS 1	n.d. [d]
2	$FeCl_3$	CS 1	90 (81[e])
3	$FeCl_3$	CS 2	94
4	$FeCl_3$	CS 3	n.d.
5	$FeCl_3$	CS 4	n.d.
6	$FeCl_3$	CS 5	83
7-11 [f]	$FeCl_3$	CS 6-CS10	n.d.
12	$FeCl_3·6H_2O$	CS 2	***94(87[e])***
13	$FeCl_2·4H_2O$	CS 2	91
14	$FeSO_4·7H_2O$	CS 2	91
15	>99.99%, $FeCl_3$	CS 2	94
16	--	CS 2	4
17	$FeCl_3·6H_2O$ [g]	CS 2	n.d.

[a] Reaction condition : **1a** (0.2 mmol), [Fe] (0.004 mmol), $K_2S_2O_8$ (0.4 mmol), solvent / carbon source (1.5 mL), 110 ℃, 3h, under air (unless otherwise noted). [b] GC-MS yields. [c] 10 mol % $FeCl_3$ were used, r. t. for 24 h, under argon. [d] n.d. = not detected. [e] Isolated yields. [f] CS6 – CS10 were used respectively. [g] Without oxidants.

No desired product was initially obtained (entry 1) when the model substrate **1a** was treated with $FeCl_3$ as catalyst (10 mol%) and *N*,*N*-dimethylformamide (DMF) using $K_2S_2O_8$ (2.0 *equiv.*) as an oxidant under argon at room temperature for 24 hours, as shown in Table 1. However, the desired vinyl aromatic, **2a**, was isolated at 81% yield within a shorter complete substrate consumption time of 3 hours (entry 2) when the temperature was increased to 110 °C and the catalyst loading was reduced to 2 mol%. Alternative amides were employed to test this notable

Table 2. Vinylation of benzylic C-H bond [a]



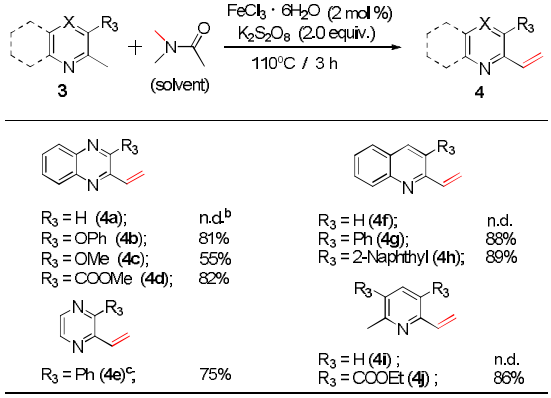
Entry	Ar (**2**)	R_1	R_2	Yield (%) [b]
1	Phenyl (**2a**)	H	H	87
2	4'-OMe Phenyl (**2b**)	H	H	89
3	4'-Me Phenyl (**2c**)	H	H	86
4	2', 4'-DiMe Phenyl (**2d**)	H	H	92
5	4'-Ph Phenyl (**2e**)	H	H	87
6	4'-F Phenyl (**2f**)	H	H	86
7	4'-Cl Phenyl (**2g**)	H	H	84
8	4'-Br Phenyl (**2h**)	H	H	83
9	4'-I Phenyl (**2i**)	H	H	81
10	2'-Br Phenyl (**2j**)	H	H	87
11	3'-NO_2 Phenyl (**2k**)	H	H	83
12	3'-CF_3 Phenyl (**2l**)	H	H	75
13	Phenyl (**2m**)	Me	H	91
14	2-Thienyl (**2n**)	H	H	73
15	Phenyl (**2o**)	H	Me	60 [c]

[a] Reaction condition : **1** (0.2 mmol), $FeCl_3{\cdot}6H_2O$ (0.004 mmol), $K_2S_2O_8$ (0.4 mmol), DMA (1.5 mL), 110 ℃, 3h, under air (unless otherwise noted). [b] Isolated yields. [c] 10 mol % $FeCl_3{\cdot}6H_2O$ was used, 8h.

transformation. Vinylation was found to occur only in the presence of *N*,*N*-dimethyl amides, particularly *N*,*N*-dimethylacetamide (DMA), suggesting that the extended carbon atom was donated by the *N*,*N*-dimethyl moiety rather than by the carbonyl carbon in the amides (entries 3–5). Although other *N*-methyl sources were also investigated, only *N*,*N*-dimethyl amides were found feasible (entries 6–11).[7] Having established the optimal carbon source for vinylation, various combinations of iron salts and oxidants were subsequently surveyed. To our delight, $FeCl_3{\cdot}6H_2O$ was found as effective as the anhydrous one and other hydrous iron salts also provided comparable results (entries 12–14). About 99.99% $FeCl_3$ was used to avoid metal impurities in the catalyst (entry 15). The reaction failed in the absence of catalysts or oxidants (entries 16 and 17). Notably, $K_2S_2O_8$ was the only applicable compound among a series of oxidants, including organic and inorganic compounds (see Supporting Information).[7] Thus, this study developed a unique benzylic vinylation reaction using *N*,*N*-dimethyl in amides as a new one-carbon source.[8]

Under optimal conditions, the scope of the vinylation was then explored (Table 2). Both electron-donating and electron-withdrawing aromatic rings afforded vinylation products in good to excellent yields (entries 1–13). No observable steric effect was observed for substrates bearing ortho-substituted aryl rings (entries 4 and 10). Heterocyclic rings, e.g., thiophene, were also tolerated at 73% isolated yield (entry 14). Notably, ethyl-substituted quinoxaline was still available to produce the desired vinylaromatic product at 60% yield (entry 15).

Table 3. Scope of substituted 2-methyl azaarenes [a]



[a] Reaction condition : **3** (0.2 mmol), $FeCl_3{\cdot}6H_2O$ (0.004 mmol), $K_2S_2O_8$ (0.4 mmol), DMA (1.5 mL), 110 ℃, 3h, under air, isolated yields. [b] n.d. = not detected. [c] 7.5 mol % $FeCl_3{\cdot}6H_2O$ was used, 8h.

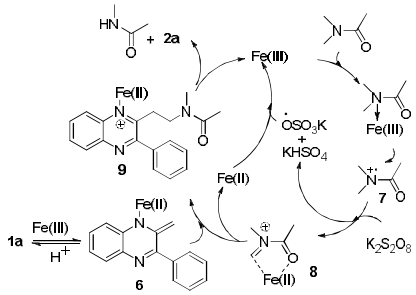
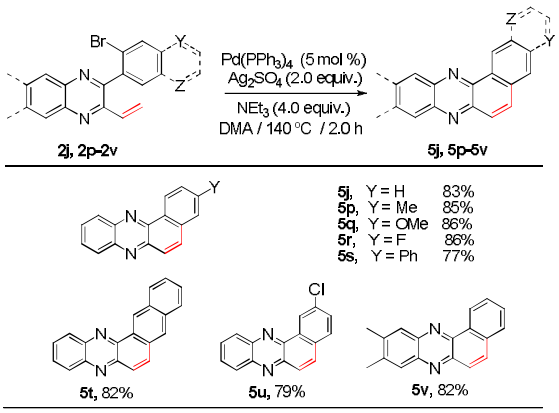


Figure 1. Proposed mechanism

More substituted 2-methyl azaarenes were employed to investigate the versatility of the present method (Table 3). Azaarenes without any substituents at the C3-position failed to generate the terminal olefines (**4a**, **4f**, **4i**). However, vinylation was feasible when 2-methyl quinoxalines were substituted with phenoxylate, methoxylate, or carboxylate (**4b–4d**). Other azaarenes, e.g., pyrazine, quinoline, and pyridine, were also subjected to the same conditions, and no obstacles were encountered (**4e**, **4g**, **4h**, and **4j**). Remarkably, only one side of the benzylic C-H bond in diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**3j**) was vinylated, even when 4.0 *equiv.* oxidant and 10 mol% catalyst were loaded onto the system. A steric effect made the secondary vinylation of **3j** sluggish.

Preliminary mechanistic investigations were carried out subsequently. The reaction failed when 2.0 *equiv.* 2,2,6,6-tetramethylpiperidine-*N*-oxyl, a radical scavenger,[9] was employed in the system, suggesting that a radical mechanism may be involved in this reaction. A series of deuterated experiments were carried out to get further insight of the transformation, the results indicated that the C-H bond in both coupling partners were activated, and the terminal vinyl carbon was produced by the *N*,*N*-dimethyl moiety of amides.[7] Furthermore, KIE studies showed that the cleavage of the C-H bond of *N*,*N*-dimethyl amides may be involved in the rate-determining step ($k_H/k_D \approx$

Table 4. Synthesis of Substituted Benzo[α]phenazine [a]



[a] Reaction condition : **2** (0.2 mmol), $Pd(PPh_3)_4$ (0.004 mmol), Ag_2SO_4 (0.4 mmol), Degassed NEt_3 (0.8 mmol), Degassed DMA (2.5 mL), 140 ℃, under argon. [b] Isolated yields.

2.0)[7]. In addition, the formation of the CDC intermediate was detected by mass spectrometry.[7]

Based on the above information, a proposed mechanism is depicted in Figure 1. The in-situ generated enamine **6**[6] attacked the iminium species **8**[4] to form the intermediate **9**, which then underwent elimination to give the product **2a**.

Benzo[α]phenazine derivatives have attracted considerable attention because of their remarkable biological activities.[10] To our knowledge, previous studies on the synthesis of substituted benzo[α]phenazines are limited,[10] because of the challenges posed by substituent compatibility and fussy procedures. Based on the 2-(2-bromophenyl)-3-vinylquinoxaline (**2j**) obtained, the Heck reaction may be the ideal method for preparing benzo[α]phenazines. After using a modified procedure described in a previous report,[11] the Heck closure occurred smoothly between the terminal vinyl and bromobenzene under the said conditions using degassed DMA as alternative solvent (Table 4). The direct C-H bond ortho-bromination of the *O*-methyl oximes developed by Sanford[12] provided a general way to the corresponding 2-(2-bromoaromatic)-3-methylquinoxalines.[7] After vinylation and Heck cyclization, the desired substituted benzo[α]phenazines were collected at 77%-86% isolated yields based on vinylaromatics (**2j**, **2p**–**2v**).

In conclusion, we have developed a novel and facile procedure for synthesizing terminal aromatic alkenes at high yields through the direct iron-catalyzed vinylation of benzylic C-H bond using the *N*-Methyl group in amides as a novel carbon source. In addition, a general pathway initiated from simple propiophenone and *o*-phenylenediamine to the synthesis of substituted benzo[α]phenazines using the proposed vinylation approach as a key step was presented as a promising synthetic strategy. As of this writing, further studies on the detailed mechanism and expanded substrate variations are under way.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and analysis data for new compounds. See DOI: 10.1039/b000000x/

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