Iron-Catalyzed Direct Alkenylation of 2-Substituted Azaarenes with *N*-Sulfonyl Aldimines via C—H Bond Activation

Bo Qian,[†] Pan Xie,[†] Yinjun Xie,[†] and Hanmin Huang^{*,†,‡}

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, P. R. China, and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, P. R. China

hmhuang@licp.cas.cn

Received March 15, 2011



A novel iron-catalyzed alkenylation of 2-substituted azaarenes through sp³ C–H bond activation has been developed. A favorable E2-elimination is proposed as a key step to cleavage of C–H and C–N bonds for the construction of a C=C bond in high stereoselectivity. This transformation represents an efficient way to synthesize 2-alkenylated azaarenes from simple starting materials.

Pyridine and quinoline derivatives have been widespread and have growing applications in drug discovery and material sciences due to their special physical, chemical, and biological properties.¹ Among them, 2-alkenyl pyridine and quinoline derivatives not only are ubiquitous structural motifs in biologically relevant molecules but also serve as valuable precursors for a wide range of 2-alkyl heterocycles.² Transition-metal-catalyzed cross-coupling reactions, such as the Heck reaction and Suzuki coupling, rank as one of the most reliable approaches to the target molecules. Recently, the transition-metal-catalyzed direct alkenylation of activated pyridines and quinolines via sp² C–H bond activation has been proven to be an expedient approach to achieve the alkenylated azaarenes.³ In most cases, however, nonterminal symmetric alkynes, Heck acceptors, and special alkenyl iodides are required as coupling partners. Moreover, a "nitrogen atom activation" group is required to activate the pyridine or quinoline core in most of the reported procedures.^{3,4}

ORGANIC LETTERS

2011 Vol. 13, No. 10

2580-2583

Very recently, we have developed a palladium and Lewis acid catalyzed direct C–H functionalization of 2-substituted azaarenes with aldimines in the absence of a nitrogen atom activation group.⁵ Mechanism studies on this reaction

[†]Lanzhou Institute of Chemical Physics.

[‡]Lanzhou University.

 ^{(1) (}a) Campeau, L.-C.; Fagnou, K. Chem. Soc. Rev. 2007, 36, 1058.
(b) Bagley, M. C.; Glover, C.; Merritt, E. A. Synlett 2007, 2459. (c) Laird, T. Org. Process Res. Dev. 2006, 10, 851. (d) Henry, G. D. Tetrahedron 2004, 60, 6043. (e) Michael, J. P. Nat. Prod. Rep. 2005, 22, 627.

^{(2) (}a) Carey, J. S.; Laffan, L.; Thompson, C.; Williams, M. T. Org. Biomol. Chem. 2006, 4, 2337. (b) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. Org. Process Res. Dev. 2005, 9, 253. (c) Buffat, M. G. P. Tetrahedron 2004, 60, 1701. (d) Felpin, F.-X.; Lebreton, J. Eur. J. Org. Chem. 2003, 3693.

^{(3) (}a) Mousseau, J. J.; Bull, J. A.; Charette, A. B. Angew. Chem., Int. Ed. 2010, 49, 1115. (b) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. J. Am. Chem. Soc. 2009, 131, 13888. (c) Cho, S. H.; Hwang, S. J.; Chang, S. J. Am. Chem. Soc. 2008, 130, 9254. (d) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. J. Am. Chem. Soc. 2008, 130, 2448. (e) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. Angew. Chem., Int. Ed. 2007, 46, 8872. (f) Murakami, M.; Hori, S. J. Am. Chem. Soc. 2003, 125, 4720. (g) Kim, M.; Kwak, J.; Chang, S. Angew. Chem., Int. Ed. 2009, 48, 8935.

⁽⁴⁾ For selected examples, see: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. J. Am. Chem. Soc. 2005, 127, 18020. (b) Leclerc, J.-P.; Fagnou, K. Angew. Chem., Int. Ed. 2006, 45, 7781. (c) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. J. Am. Chem. Soc. 2008, 130, 3266. (d) Campeau, L.-C.; Shipper, D. J.; Fagnou, K. J. Am. Chem. Soc. 2008, 130, 3266. (e) Larivée, A.; Mousseau, J. J.; Charette, A. B. J. Am. Chem. Soc. 2008, 130, 52. (f) Mousseau, J. J.; Larivée, A.; Charette, A. B. Org. Lett. 2008, 10, 1641. (g) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. Chem.— Eur. J. 2009, 15, 333. (h) Tobisu, M.; Hyodo, I.; Chatani, N. J. Am. Chem. Soc. 2009, 131, 12070.

revealed that a metal-enamide species was involved as a key reactive intermediate to react with imines forming the amine product **3**, where the sp³ C–H bond was activated by the transition metal and the proton was abstracted by an endogenous basic counteranion of the metal complexes. On the basis of these results a working hypothesis was conceived that the product **3** could further interact with the appropriate catalyst MX_n that could activate the C–H bond again, thus leading to the formation of the intermediate **A** or **B**, in which the endogenous basic counteranion will act as a base or some outer base was involved to cleave the C–H bond and the C=C double bond will form through an E2-elimination process in high regioselectivity (Scheme 1).

Scheme 1. New Strategy for Alkenylation of 2-Substituted Azaarenes



Iron complexes are inexpensive, nontoxic, and environmentally benign, which have been extensively used as catalysts to promote a broad range of reactions such as cross-couplings, allylations, hydrogenations, and direct C–H bond functionalizations.⁶ Iron salts are also wellknown as good Lewis acid catalysts for many classic reactions. These interesting features of iron catalysts have prompted us to envision that it may be suitable for promotion of the above-proposed reaction. Herein, we present a novel iron-catalyzed direct alkenylation of 2-substituted azaarenes with readily accessible *N*-sulfonyl aldimines through cleavage of two sp³ C–H bonds and one C–N bond,⁷ which is a very efficient route to synthesize 2-alkenyl azaarenes.

Our initial investigation focused on the reaction of 8-methoxy-2-methylquinoline 1a and tosylimine 4a with iron salt as catalyst. After some initial experiments, we found in the presence of $Fe(OAc)_2$, the coupling of 1a and 4a could afford the desired product 2aa in 68% yield at 120 °C. Significantly, the ¹H NMR analysis of the reaction mixture and X-ray crystallographic analysis of the product **2aa** indicated that only the (*E*)-isomer was formed (Figure 1). The interesting initial results encouraged us to optimize the reaction conditions based on the iron catalyst. A screen of solvents revealed that the experiments performed in DMF, DMA, dioxane, CH₂ClCH₂Cl, 2-PrOH, toluene, and mesitylene proceeded with more than 90% isolated vield (Table 1, entries 7-16). The effect of reaction temperature was examined, and it was confirmed that reactions conducted at 120 °C gave the best results (Table 1, entries 15, 17, and 18). Although the reactions ran at 80 and 100 °C can give high conversion, greater amounts of amine product 3aa were obtained in high yields. These results suggested that the alkenylation product 2 was most likely to be produced from the intermediate 3. The effect of catalyst loading was also examined, and we were delighted to find that when the catalyst loading of Fe(OAc)₂ was decreased to 1 mol %, 2aa was still obtained in 99% yield, the same as that obtained with 10 mol % catalyst, although a longer reaction time was required in the latter case (Table 1, entries 19 and 20). Control experiments revealed that no reaction was observed in the absence of $Fe(OAc)_2$.



Figure 1. X-ray crystal structure of 2aa.

To eliminate the contaminants which may affect the catalysis, a high purity $Fe(OAc)_2$ (>99.995%, from Aldrich) was used under the standard conditions, and the yield remained unchanged. Furthermore, when Cu(OAc)_2, CuCl, CuCl_2, CuBr, and Cu(OTf)_2 were tested as catalysts under the standard conditions, both conversion and yield became relatively low (less than 60% yield), thus suggesting that Cu salts were much less effective catalysts for this transformation (see the Supporting Information). These results further indicate that the Fe catalyst plays a crucial role in this alkenylation reaction.

^{(5) (}a) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. J. Am. Chem. Soc. 2010, 132, 3650. (b) Qian, B.; Guo, S.; Xia, C.; Huang, H. Adv. Synth. Catal. 2010, 352, 3195. Other groups reported similar reactions using the same strategy: (c) Rueping, M.; Tolstoluzhsky, N. Org. Lett. 2011, 13, 1095. (d) Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. Org. Lett. 2011, 13, 1706.

⁽⁶⁾ For reviews: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. Chem. Rev. 2004, 104, 6217. (b) Fürstner, A.; Martin, R. Chem. Lett. 2005, 34, 624. (c) Correa, A.; García Mancheno, O.; Bolm, C. Chem. Soc. Rev. 2008, 37, 1108. (d) Enthaler, S.; Junge, K.; Beller, M. Angew. Chem., Int. Ed. 2008, 47, 3317. (e) Sherry, B. D.; Fürstner, A. Acc. Chem. Res. 2008, 41, 1500. (f) Fürstner, A. Angew. Chem., Int. Ed. 2009, 48, 1364. (g) Czaplik, W. M.; Mayer, M.; Cvengroš, J.; Jacobi von Wangelin, A. ChemSusChem 2009, 2, 296. (h) Nakamura, E.; Yoshikai, N. J. Org. Chem. 2010, 75, 6061. (i) Buchwald, S. L.; Bolm, C. Angew. Chem., Int. Ed. 2009, 48, 5586. (j) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Chem. Rev. 2011, 111, 1293.

⁽⁷⁾ For C=C bond formation through cleavage of C-N bond: (a) Bestmann, H. J.; Seng, F. Angew. Chem., Int. Ed. 1963, 2, 393. (b) Dong, D.-J.; Li, H.-H.; Tian, S.-K. J. Am. Chem. Soc. 2010, 132, 5018. (c) Dong, D.-J.; Li, Y.; Wang, J.-Q.; Tian, S.-K. Chem. Commun. 2011, 47, 2158. The C-N cleavage was also involved in Hofmann elimination, Cope elimination, and Bamford-Stevens-Shapiro olefination; see reviews: (d) Cope, A. C.; Trumbull, E. R. Org. React. 1960, 11, 317. (e) Shapiro, R. H. Org. React. 1976, 23, 405. (f) Adlington, R. M.; Barrett, A. G. M. Acc. Chem. Res. 1983, 16, 55.

Table 1. Optimization of the Reaction Conditions^a



entry	cat. (mol %)	solvent	<i>t</i> (°C)	yield $(\%)^b$
1	$\operatorname{FeCl}_{3}(10)$	CH_3NO_2	120	56
2	$FeBr_{3}(10)$	CH_3NO_2	120	37
3	$Fe(OTf)_3(10)$	CH_3NO_2	120	30
4	$Fe(acac)_3(10)$	CH_3NO_2	120	64
5	Fe(OTs) ₃ (10)	CH_3NO_2	120	31
6	$Fe(OAc)_2(10)$	CH_3NO_2	120	68
7	$Fe(OAc)_2(10)$	THF	120	57
8	$Fe(OAc)_2(10)$	CH_3CN	120	42
9	$Fe(OAc)_2(10)$	DME	120	87
10	$Fe(OAc)_2(10)$	DMF	120	93
11	$Fe(OAc)_2(10)$	DMA	120	97
12	$Fe(OAc)_2(10)$	dioxane	120	96
13	$Fe(OAc)_2(10)$	CH ₂ ClCH ₂ Cl	120	91
14	$Fe(OAc)_2(10)$	2-PrOH	120	97
15	$Fe(OAc)_2(10)$	toluene	120	99
16	$Fe(OAc)_2(10)$	mesitylene	120	96
17^c	$Fe(OAc)_2(10)$	toluene	100	41
18^d	$Fe(OAc)_2(10)$	toluene	80	9
19	$Fe(OAc)_2(5)$	toluene	120	99
20^e	$\operatorname{Fe}(\operatorname{OAc})_2(1)$	toluene	120	99

^{*a*} General conditions: **1a** (0.3 mmol), **4a** (0.36 mmol), solvent (1.5 mL), 24 h. ^{*b*} Isolated yield. ^{*c*} The amine product **3aa** was obtained in 57% yield. ^{*d*} The amine product **3aa** was obtained in 90% yield. ^{*e*} For 30 h.

The scope of this transformation with various N-sulfonyl aldimines was first examined under the optimized conditions (Table 2). Treatment of 8-methoxy-2-methylquinoline 1a with a series of N-sulfonyl aldimines 4a-qafforded the corresponding products 2aa-2aq in good to excellent yields. The reaction was not significantly influenced by the substitutents on the aromatic ring of the used aldimines. Both electron-poor (Table 2, entries 2-9) and electron-rich (Table 2, entries 10 and 11) aryl-substituted aldimines were effective to furnish the desired products. The reaction also proceeded well with naphthyl aldimine (Table 2, entry 12) and aldimine with either a heteroaromatic substituent (Table 2, entry 13) or an alkenyl substituent (Table 2, entry 17). Furthermore, the replacement of the tosyl group in imine with another group was investigated. Under the standard conditions, the reactions of aldimines 4n-4q, which were protected with *p*-nitrobenzenesulfonyl (Ns), proceeded smoothly to give the corresponding olefins in more than 90% yields (Table 2, entries 14-17). However, the Boc and Cbz protected aldimines were not useful substrates for this transformation (Table 2, entries 18 and 19).

Next, the reaction scope of 2-substituted azaarenes was also investigated. The reaction was examined with a series of 2-substituted azaarenes 1b-1r, which were treated with (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide **4a** under the optimized conditions (Scheme 2). The alkenylation reaction worked smoothly with 2-methylquinolines Table 2. Substrate Scope of N-Sulfonyl Aldimines^a



entry	4 , Ar, R	product	yield $(\%)^b$
1	$4a, C_6H_5, Ts$	2aa	99
2	4b , 4 -ClC ₆ H ₄ , Ts	2ab	97
3	4c, 2-ClC ₆ H ₄ , Ts	2ac	94
4	4d, 3 -ClC ₆ H ₄ , Ts	2ad	94
5	4e, 4 -BrC ₆ H ₄ , Ts	2ae	99
6	4f, 2-BrC ₆ H ₄ , Ts	2af	81
7	$4g, 3-BrC_6H_4, Ts$	2ag	99
8	4h , 2,4-Cl ₂ C ₆ H ₃ , Ts	2ah	79
9	$4i$, 2,6- $Cl_2C_6H_3$, Ts	2ai	99
10	4j, 4-MeC ₆ H ₄ , Ts	2aj	96
11	$4\mathbf{k}$, 4-MeOC ₆ H ₄ , Ts	2ak	92
12	4l, 1-naphthyl, Ts	2al	99
13	4m , 2-furyl, Ts	2am	99
14	4n, 4 -MeC ₆ H ₄ , Ns	2aj	96
15	$40, 2-BrC_6H_4, Ns$	2af	94
16	4p, 4-MeOC ₆ H ₄ , Ns	2ak	97
17	4q, (E) -C ₆ H ₅ CH=CH, Ns	2aq	94
18	$4\mathbf{r}, \mathrm{C}_{6}\mathrm{H}_{5}, \mathrm{Boc}$	2aa	21
19	$\mathbf{4s}, \mathrm{C}_{6}\mathrm{H}_{5}, \mathrm{Cbz}$	2aa	<5

^{*a*}General conditions: **1a** (0.3 mmol), **4** (0.36 mmol), Fe(OAc)₂ (5 mol %), solvent (1.5 mL), 24 h. ^{*b*} Isolated yield, only *E*-isomer was observed in all cases.

bearing a variety of substituent groups on the ring of quinoline, thus leading to the formation of 2-alkenylated quinolines in good to excellent yields with high regioselectivities (only the *E*-isomer was observed in all cases). The 2-methylquioxaline was compatible, although with a slightly lower yield (40%) under the standard reaction conditions. As for 2-ethylquinoline, it only gave **2na** in 11% yield using the standard conditions, However, the modified conditions which used KOt-Bu as a cocatalyst can regioselectively furnish the corresponding trisubstituted alkene **2na** in 59% yield.⁸ Finally, the process is not limited to quinolines and quioxalines. A series of 2-substituted pyridines could also react with **4a** under the modified conditions to form the corresponding 2-alkenylated pyridines **20a**–**2ra** in good yields.

To explore how the C–H and C–N bond cleavage occurred in the present transformation, radical scavengers, such as TEMPO and 1,1-diphenylethylene, were employed in the standard reaction, and the desired product **2aa** was still obtained in 87% and 92% yields, respectively (see Supporting Information). This result suggested that a free radical process was not involved in the present reaction. The benzylic addition product amine **3ba** and deuterium-labeled **3ba-d** were prepared and then subjected to the standard conditions (Scheme 3), respectively. The reactions afforded the desired 2-alkenylated products **2ba** and **2ba-d**, which confirmed our proposal that the amino

⁽⁸⁾ In the case where only KOt-Bu was used, no reaction occurred.

Scheme 2. Substrate Scope of Azaarenes^a



^{*a*} Reaction conditions: **1** (0.3 mmol), **4a** (0.36 mmol), Fe(OAc)₂ (5 mol %), Toluene (1.5 mL), 120 °C, 24 h; isolated yield. ^{*b*}Reaction conditions: **1** (0.3 mmol), **4a** (0.36 mmol), Fe(OAc)₂ (10 mol %), KOt-Bu (20 mol %), DMA (1.5 mL), 150 °C, 48 h. ^cReaction conditions: **1** (0.3 mmol), **4a** (0.36 mmol), Fe(OAc)₂ (5 mol %), KOt-Bu (20 mol %), Toluene (1.5 mL), 120 °C, 48 h.

compound **3** was responsible for the final olefin product. Moreover, kinetic isotope effect (KIE) experiments were carried out under the standard conditions (see Supporting Information). The significant isotopic effects ($k_{\rm H}/k_{\rm D}$ = 7.6) shown here indicated that the C–H bond cleavage is the rate-determining step of this transformation and a concerted E2-elimination is most likely to be involved in the C–H and C–N cleavage step, providing the alkenylated products in absolute regioselectivity.⁹





In summary, we have developed the first novel iron(II)catalyzed coupling reaction of 2-substituted azaarenes and readily accessible *N*-sulfonyl imines to give (*E*)-2-alkenylated azaarenes in high regioselectivity through cleavage of C–H and C–N bonds. This transformation provides a facile method for the synthesis of 2-alkenylated azaarenes that are of tremendous importance in medicinal chemistry. These results highlight the potential of Lewis acids in promoting new reactions via C–H bond activation, and the explorations of new catalytic reactions involving C–H and C–N bond activation pave the way to a new class of coupling reactions.

Acknowledgment. Financial support provided by the National Natural Science Foundation of China (2080-2085) and Chinese Academy of Sciences is gratefully acknowledged.

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

⁽⁹⁾ For discussion on E2-elimination mechanism, see review: Saunders, W. H., Jr. Acc. Chem. Res. **1976**, *9*, 19.

 $[\]left(10\right)$ For a detailed discussion of the mechanism, see the Supporting Information.