DOI: 10.1002/adsc.200900066

Iron-Catalyzed Cross-Coupling Reaction of Vinyl Bromides or Chlorides with Imidazoles in the Absence of Ligands and Additives

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Received: February 1, 2009; Revised: April 10, 2009; Published online: June 2, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900066.

Abstract: Highly effective coupling of imidazoles with (*E*)-vinyl halides can be achieved by using readily available iron catalysts under ligand-free, copper-free and palladium-free conditions. Coupling of (*E*)-vinyl bromides led to (*Z*)-products predominantly, while the reactions of (*E*)-vinyl chlorides afforded (*E*)-isomers as the major products.

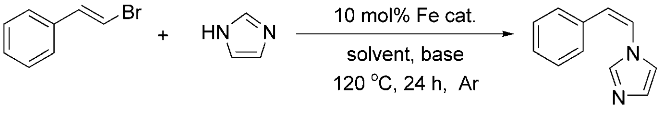
Keywords: cross-coupling; imidazoles; iron; ligand-free conditions; vinyl halides

N-(1-Alkenyl)imidazoles are versatile intermediates in the preparation of a wide variety of biologically and industrially valuable organic compounds.[1] The antifungal and antiparasitic properties of these types of compound are of great interest to medicine and agriculture.[2] Thus, a number of methods has been developed to create these synthetic units in the past decades.[3,4] Among these methods, vinylation reactions of imidazoles with vinyl halides were the most efficient and straightforward, since the traditional methods suffer from harsh reaction conditions or lack of stereocontrol of the double bond geometry.[4] To our astonishment, there are few reports about this direct coupling reaction until now.[5] Interestingly, we found that just 10 mol% of CuI could also effectively catalyze the coupling of nitrogen-containing heterocycles with vinyl bromides and chlorides under ligand-free and Pd-free conditions.[6] It is noteworthy that the double bond geometry of these vinyl halides was completely retained with our protocol: the coupling reactions of (*E*)-vinyl halides led to exclusive (*E*)-products, perhaps because the more stable (*E*)-isomer is more easily generated compared with the less stable (*Z*)-isomer of the corresponding product. This raises the question: how can we get the (*Z*)-products? Furthermore, the availability of ligand-free and readily available catalytic systems remains of interest when considering cost and operability.[7]

Iron is an abundant, economical, and environmentally friendly metal that shows increasingly promising catalytic abilities in many organic transformations, in particular for C–C bond-forming reactions.[8] However, the application for C–N coupling reactions has rarely been reported.[9–12] To the best of our knowledge, there is no example of a vinylation reaction of imidazoles with vinyl halides using this inexpensive catalyst through such an economic and effective method. Herein, we report the efficient $FeCl_3$-catalyzed ligand-free C–N couplings between (*E*)-vinyl halides[13] and imidazoles. In our hands and and in contrast to previous reports, couplings of vinyl bromides afforded (*Z*)-products predominantly and the couplings of vinyl chlorides resulted in (*E*)-isomers as the major products, which are different from the traditional reports. Thus, this new method could easily meet the demands of different isomers of *N*-(1-alkenyl)imidazoles simply by using different types of vinyl halides as starting materials.

In order to find the most active ligand-free catalyst system, various iron salts were screened for the *N*-arylation of imidazole with (*E*)-β-bromostyrene as the model reaction. Optimization data are listed in Table 1. Initially, a reagent combination of $FeCl_3$, K_3PO_4 and DMF was tested (Table 1, entry 1). To our delight, the corresponding product was obtained in 36% yield. The blank experiment indicated that the presence of iron salt is necessary in our protocol (entry 2). The use of other solvents such as toluene, NMP (*N*-methylpyrrolidone), DMSO, or glycol resulted in various yields (entries 3–6). Among them,

Table 1. Screening of iron catalysts for *N*-arylation of imidazole with (*E*)-β-bromostyrene.[a]



Entry	Fe cat.	Base	Solvent	T [°C]/ t [h]	Z/E	Yield [%][b]
1	$FeCl_3$	K_3PO_4	DMF	120/24	50:50	36
2	-	K_3PO_4	DMF	120/24	–	trace
3	$FeCl_3$	K_3PO_4	Toluene	120/24	–	0
4	$FeCl_3$	K_3PO_4	NMP	120/24	70:30	83
5	$FeCl_3$	K_3PO_4	DMSO	120/24	80:20	>99
6	$FeCl_3$	K_3PO_4	glycol	120/24	–	trace
7	$FeCl_3$	K_2CO_3	DMSO	120/24	–	trace
8	$FeCl_3$	KOH	DMSO	120/24	70:30	86
9	$FeCl_3$	Cs_2CO_3	DMSO	120/24	70:30	73
10	Fe powder	K_3PO_4	DMSO	120/24	80:20	80
11	$FeCl_2$	K_3PO_4	DMSO	120/24	80:20	90
12	$Fe(acac)_3$	K_3PO_4	DMSO	120/24	75:25	95
13	Fe_2O_3	K_3PO_4	DMSO	120/24	75:25	>99
14	$Fe_2(SO_4)_3$	K_3PO_4	DMSO	120/24	78:22	>99
15	$FeCl_3$	K_3PO_4	DMSO	100/24	67:33	40
16	$FeCl_3$	K_3PO_4	DMSO	140/24	60:40	81
17[c]	$FeCl_3$	K_3PO_4	DMSO	120/24	60:40	51
18	$FeCl_3$	K_3PO_4	DMSO	120/48	70:30	>99
19	$FeCl_3$	K_3PO_4	DMSO	100/48	80:20	52

[a] Iron catalyst (0.05 mmol), (*E*)-β-bromostyrene (0.5 mmol), imidazole (0.6 mmol), base (1.0 mmol), solvent (2 mL), 120 °C, 24 h, under an argon atmosphere.

[b] Isolated yield (based on vinyl bromide).

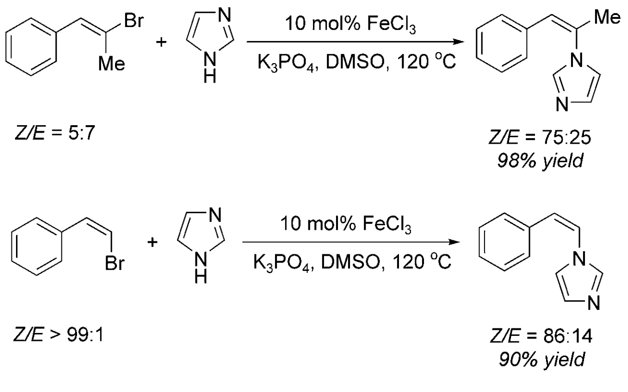
[c] The catalytic reaction was performed in air.

DMSO proved to be the best solvent with the desired product being obtained in almost quantitative yield (entry 5). It is noteworthy that the stereoselectivity of the product was 80:20 (*Z/E*). Subsequently, several bases (K_2CO_3, KOH, and Cs_2CO_3) were investigated (entries 7–9), but still K_3PO_4 gave the highest yield (entry 5). Different forms of iron were employed in the coupling reaction (entries 10–14). It can be seen that generally a higher oxidation state of iron is favorable for the catalytic reaction. All of the iron(III) salts gave quite similar results (entries 12–14). We were not able to improve the catalytic conditions by varying the temperature (entries 15 and 16). Under the same conditions, the reaction performed in air gave the desired product with lower stereospecificity and yield (entry 17). Extension of reaction time did not lead to enhanced results (entries 18 and 19).

The results that we obtained encouraged us to investigate the scope of application of this catalytic system as summarized in Table 2. Couplings of (*E*)-β-bromostyrene with different imidazoles gave good yields and *Z*/*E* ratios, although substituents showed a clear influence on the catalysis (Table 2, entries 1–4). Vinyl bromides with donor groups (such as methyl or methoxy groups) at their aromatic rings led to decreased yields but higher *Z*/*E* ratios (entries 5–9). Excitingly, we even discovered two examples of catalytic reactions yielding only the (*Z*)-isomer products in 60% yield and 50% yield, respectively (entries 8 and 9). In these cases, the other isomer was not observed. For example, a Cl-substituent on the ring of the vinyl bromide gave better yields of the corresponding products (entries 10–12), while an F-substituent in the vinyl bromide gave better *Z*/*E* ratios of the desired products (entries 13 and 14). In addition, it is noteworthy that we were able to get the (*Z*)-*N*-(1-alkenyl)imidazoles as the only product (entries 8 and 9 and 13 and 14).

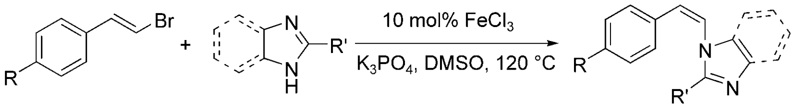
Using the optimized reaction conditions, we explored the *N*-arylation of imidazole with other vinyl bromides (*Z*/*E* = 5:7) (Scheme 1). Initial results showed that the coupling product (*Z*/*E* = 75:25) was obtained in 98% yield. In order to explore whether this protocol was generally selective for (*Z*)-type products, pure (*Z*)-β-bromostyrene was employed as the substrate: the corresponding (*Z*)-product (*Z*/*E* = 84:16) was acquired with 90% yield. Therefore, the selectivity rules in this protocol are clearly different from those of CuI catalytic systems.[5,6] Therefore, $FeCl_3$ and CuI catalysts may be complementary for getting desired products in different isomers.

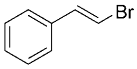
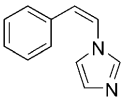
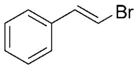
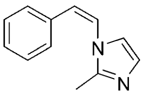
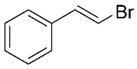
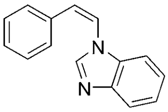
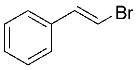
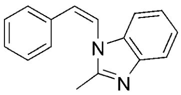
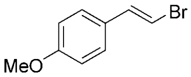
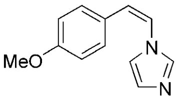
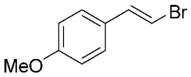
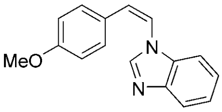
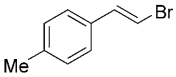
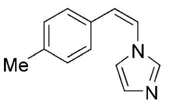
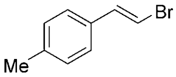
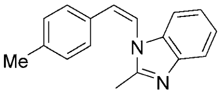
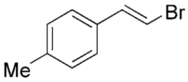
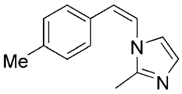
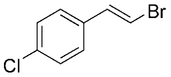
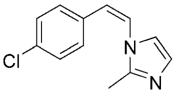
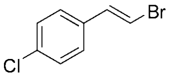
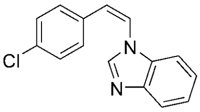
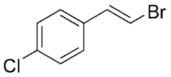
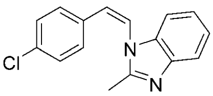
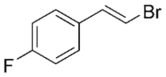
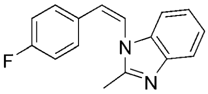
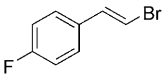
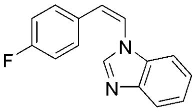
Under similar conditions, coupling reactions of nitrogen-containing heterocycles and vinyl chlorides afforded lower yields than those of vinyl bromides (Table 3). However, it was suprising to find that the (*E*)-products were obtained predominantly (Table 3, entry 1). In order to improve our initial result, we performed the reaction with a longer time (36 h). However, neither yield nor *E*/*Z* ratio of the product changed significantly (entry 2 *vs.* entry 1). In contrast, when the coupling of (*E*)-vinyl chloride was performed at a higher temperature (130 °C), a higher yield was obtained at the expense of the *E*/*Z* ratio (entry 3). Other imidazoles derivatives did not afford a better yield than imidazole itself using our protocol



Scheme 1.

Table 2. Catalytic *N*-vinylation of imidazoles with (*E*)-vinyl bromides by $FeCl_3$.[a]



Entry	Vinyl bromide	Product	*Z/E*	Yield [%][b]
1			80:20	>99
2			90:10	91
3			71:29	90
4			90:10	63
5			92:8	88
6			85:15	40
7			88:12	76
8			>99:1	60
9			>99:1	50
10			86:14	83
11			60:40	>99
12			73:27	72
13			>99:1	68
14			>99:1	35

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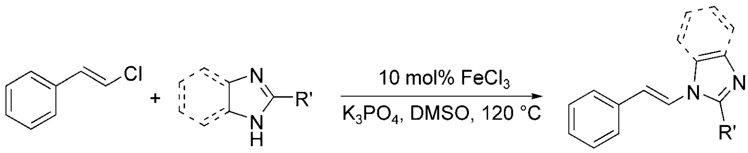
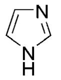
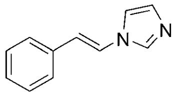
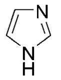
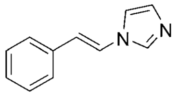
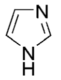
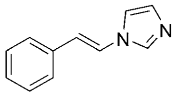
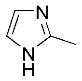
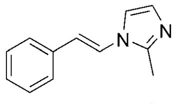
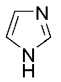
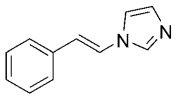
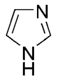
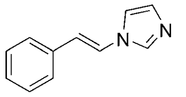
[a] $FeCl_3$ (0.05 mmol), vinyl bromide (0.5 mmol), nitrogen-containing heterocycle (0.6 mmol), K_3PO_4 (1.0 mmol), DMSO (2 mL), 120 °C, 24 h, under an argon atmosphere.

[b] Isolated yield based on vinyl bromides (average of two runs).

Table 3. Catalytic *N*-vinylation of imidazoles with (*E*)-vinyl chlorides by $FeCl_3$.[a]



Entry	Het-NH	Product	*Z/E*	Yield [%][b]
1			12:88	67
2[c]			18:82	53
3[d]			32:68	73
4			50:50	52
5[e]			10:90	56
6[f]			17:83	87

[a] All the reactions were processed in DMSO under argon atmosphere at 120 °C for 24 h. $FeCl_3$ (0.05 mmol), vinyl chloride (0.5 mmol), nitrogen-containing heterocycle (0.6 mmol), K_3PO_4 (1.0 mmol).

[b] Isolated yield based on vinyl chlorides (average of two runs).

[c] For 36 h.

[d] At 130 °C.

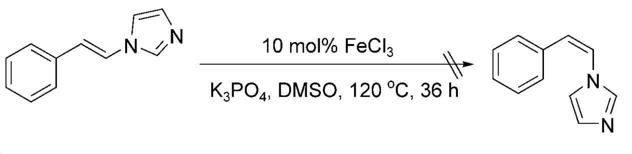
[e] 10 mol% CuI as additive.

[f] 20 mol% $FeCl_3$.

(entry 4). Using 10% of CuI as the additivie, the desired product ($Z/E=10/90$) was obtained in lower yield (entry 5). It is noteworthy that double-loading of $FeCl_3$ gave a better result (87% yield) (entry 6).

To ensure of the peculiarity and specificity of our catalytic system, we checked that (*E*)-*N*-vinylimidazole could not be transformed into (*Z*)-*N*-vinylimidazole (Scheme 2). We speculate from our results that the geometry of the double bond of the product was determined in the reaction process between the two substrates.

Since this is an example of ligand-free coupling, it is possible that the nitrogen-containing heterocycles may serve not only as the substrate but also as the ligand: during the catalytic reaction the double bond from the vinyl halide and both of the nitrogen atoms from the heterocycle compounds could participate in the iron coordination. We further speculate that the stereogenic configuration of the product may be ascribed to the substituent effect of the substrates and the difficulty of leaving group (X = Br, Cl).



Scheme 2.

In summary, we have shown that a highly effective coupling of nitrogen-containing heterocycles with (*E*)-vinyl bromides or chlorides can be carried out by using readily available iron catalysts under ligand-free, copper-free and Pd-free conditions. We found that the coupling of (*E*)-vinyl bromides led to (*Z*)-products predominantly, while the reactions of (*E*)-vinyl chlorides afforded (*E*)-isomers as the major products. Thus, this could provide a facile means to satisfy the demand for *N*-(1-alkenyl)imidazoles in different isomers. It has not escaped our attention that our catalytic system is low-cost, benign and easily available, which makes this catalytic method very attractive for scale-up towards practicably and industrial application.

Experimental Section

General Procedure

$FeCl_3$ (0.1 equiv.), K_3PO_4 (2.0 equiv.) were added to a screw-capped test tube. The tube was then evacuated and backfilled with argon (3 cycles). DMSO (2 mL), heterocycles (1.2 equiv.) (if liquid) and vinyl halide (if liquid) (1.0 equiv.) were added by syringe at room temperature. The tube was again evacuated and backfilled with argon (3 cycles). The mixture was heated to 120 °C and stirred for 24 h. After cooling to room temperature, the mixture was diluted with water, and the combined aqueous phases were extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated to yield the crude product, which was further purified by silica gel chromatography, using petroleum ether and ethyl acetate as eluents to provide the desired product. The identity and purity or *Z*/*E* of the product were confirmed by ^1H, ^{13}C NMR and HR-mass spectroscopic analysis.

Acknowledgements

We are grateful to the grants from the National Natural Science Foundation of China (No. 20802046) and the Key Laboratory of Organic Synthesis of Jiangsu Province for financial support. We thank Dr. Marc Creus of University of Basel, Switzerland for helpful discussions.

References

[1] For selected examples, see: a) K. Kurdaziel, T. Glowiak, *J. Coord. Chem.* **2002**, *55*, 327; b) D. Branowska, *Synthesis* **2003**, 2096; c) V. K. Aggarwal, J. De. Vicente, R. V. Bonnert, *J. Org. Chem.* **2003**, *68*, 5119; d) N. Mano, H. H. Kim, Y. Zhang, A. Heller, *J. Am. Chem. Soc.* **2002**, *124*, 6480; e) T. Morita, Y. Nozawa, *Nippon Ishinkin Gakkai Zasshi* **1990**, *31*, 363.

[2] a) M. W. Briscoe, R. D. Chambers, S. J. Mullins, T. Nakamura, J. F. S. Vaughan, *J. Chem. Soc. Perkin Trans. 1* **1994**, *21*, 3119; b) A. E. Feiring, E. R. Wonchoba, *J. Org. Chem.* **1992**, *57*, 7014; c) *Comprehensive Polymer Science*, (Eds.: G. Allen), Pergamon Press, New York, **1989**, Vol. 3; d) O. E. O. Hormi, W. L. Hirvel, *Tetrahedron Lett.* **1993**, *34*, 6463; e) Y. Hamada, S. Shinomoto, I. Yamada, H. Koike, European Patent EP 162359, **1985**; f) W. J. Ross, W. B. Jamieson, M. C. McCowen, *J. Med. Chem.* **1973**, *16*, 347; g) S. J. Barker, R. C. Storr, *J. Chem. Soc. Perkin Trans. 1* **1990**, 485.

[3] a) B. J. J. Aiscar, J. Henkelmann, T. Preiss, P. Knochel, D. Tzalis, C. Koradin, European Patent EP 1055653, **2000**; b) J. Henkelmann, M. Heider, T. Ruehl, European Patent EP 752422, **1997**.

[4] a) D. Tzalis, J. Henkelmann, M. Heider, *Tetrahedron Lett.* **1999**, *40*, 6193; b) S. Hayat, A. Rahman, M. I. Choudhary, K. M. Khan, W. Schumann, E. Bayer, *Tetrahedron* **2001**, *57*, 9951; c) P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon, P. K. Jadhav, *Tetrahedron Lett.* **2001**, *42*, 3415; d) G. Cooper, W. J. Irwin, *J. Chem. Soc. Perkin Trans. 1* **1975**, 798; e) G. Cooper, W. J. Irwin, *J. Chem. Soc. Perkin Trans. 1* **1976**, 545.

[5] a) A. Y. Lebedev, V. V. Izmer, D. N. Kazyul'kin, I. P. Beletskaya, A. Z. Voskoboynikov, *Org. Lett.* **2002**, *4*, 623; b) M. Taillefer, A. Ouali, B. Renard, J.-F. Spindler, *Chem. Eur. J.* **2006**, *12*, 5301; c) Z. Wang, W. Bao, Y. Jiang, *Chem. Commun.* **2005**, 2849; d) G. Shen, X. Lv, W. Qiu, W. Bao, *Tetrahedron Lett.* **2008**, *49*, 4556; e) W. Bao, Y. Liu, X. Lv, *Synthesis* **2008**, 1911.

[6] J. Mao, Q. Hua, J. Guo, D. Shi, S. Ji, *Synlett* **2008**, 2011.

[7] Recently we reported an example of highly effective ligand-free iron/copper cocatalyzed alkynylation coupling reactions, see: J. Mao, G. Xie, M. Wu, J. Guo, S. Ji, *Adv. Synth. Catal.* **2008**, *350*, 2477.

[8] For general reviews, see: a) C. Bolm, J. Legros, J. L. Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; b) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624.

[9] M. Taillefer, N. Xia, A. Oualli, *Angew. Chem.* **2007**, *119*, 952; *Angew. Chem. Int. Ed.* **2007**, ***46***, 934.

[10] V. H. Jadhav, D. K. Dumbre, V. B. Phapale, H. B. Borate, R. D. Wakharkar, *Catal. Commun.* **2007**, *8*, 65.

[11] a) A. Correa, C. Bolm, *Angew. Chem.* **2007**, *119*, 9018; *Angew. Chem. Int. Ed.* **2007**, *46*, 8862; b) A. Correa, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 391; c) A. Correa, S. Elmore, C. Bolm, *Chem. Eur. J.* **2008**, *14*, 3527.

[12] D. Guo, H. Huang, J. Xu, H. Jiang, H. Liu, *Org. Lett.* **2008**, *10*, 4513.

[13] (*E*)-Vinyl halides were synthesized according to: a) S. Chowdhury, S. Roy, *J. Org. Chem.* **1997**, *62*, 199; (*Z*)-vinyl halides were synthesized according to: b) C. Kuang, H. Senboku, M. Tokuda, *Tetrahedron Lett.* **2001**, *42*, 3893; c) C. Kuang, Q. Yang, H. Senboku, M. Tokuda, *Tetrahedron* **2005**, *61*, 4043.