DOI: 10.1002/adsc.200900123

Iron-Catalyzed Cross-Coupling Reactions of Terminal Alkynes with Vinyl Iodides

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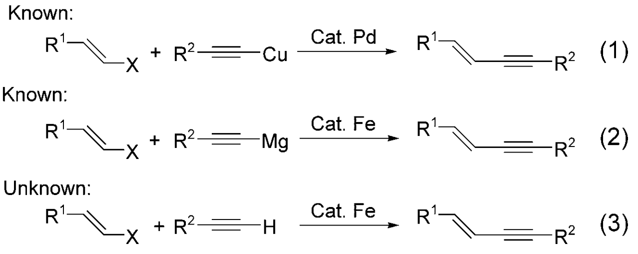
Received: February 21, 2009; Published online: May 28, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900123.

Abstract: A convenient iron-catalyzed cross-coupling reaction of terminal alkynes with vinyl iodides is reported. The reaction was applicable to various acetylenes and vinyl iodides. The present reaction provides an efficient, environmentally friendly protocol to afford conjugated enyne derivatives in good to excellent yields under mild conditions.

Keywords: C–C bond formation; cross-coupling; enynes; iron catalysis; vinyl iodides

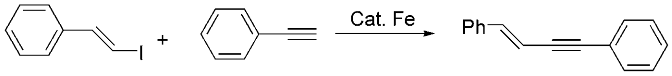
The development of sustainable, environmentally benign C–C bond forming procedures is one of the fundamental goals in organic chemistry. The coupling reaction between *sp*^{2} and *sp* carbon centers is one of the most utilized cross-coupling reactions for the construction of new C–C bonds.[1] It allows the straightforward synthesis of conjugated enynes and arylalkynes, which are interesting intermediates and building blocks for the synthesis of a variety of natural products and pharmaceuticals.[2] Typically, these kinds of cross-couplings involve the use of both palladium and copper as catalysts [Eq. (1)].[1] In recent years, some Pd-free variants were also reported.[3] Although significant progress has been made with the regard to the Pd/Cu-catalyzed protocols, the search for sustainable, environmentally friendly and less expensive catalysts to accomplish such processes is still highly desired. In this respect, iron could be the metal of choice for such purposes, because iron compounds are usually less toxic, low priced and easy to synthesize. There have been a lot of reports concerning the Fe-catalyzed coupling reactions with the use of Grignard reagents.[4] It is important to note that Nakamura and co-workers reported the Fe-catalyzed coupling between terminal alkynes and vinyl halides *via* the alkynyl-Grignard produced *in situ* [Eq. (2)],[5] this is the first example of an Fe-catalyzed coupling between terminal alkynes and vinyl halides with the assistance of Grignard reagents. In the past few years, Fe-catalyzed couplings without the utilization of Grignard reagents have also drawn considerable attention.[6] For example, Bolm et al. reported excellent work on ligand-assisted Fe-catalyzed C–N,[7] C–O[8] and C–S[9] cross-coupling reactions and C–C cross-coupling between aryl iodides and terminal alkynes to afford arylalkynes using a sealed tube technique.[10] However, no example of an Fe-catalyzed cross-coupling of vinyl halides and terminal alkynes to enynes has been reported to the best of our knowledge [Eq. (3)].



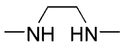
Herein, we would like to present efficient Fe-catalyzed enyne-forming reactions using vinyl iodides and terminal alkynes.

Initially, we examined the cross-coupling using (*E*)-1-(2-iodovinyl)benzene (**1a**) and phenylacetylene (**2a**) as the prototypical case to optimize the reaction conditions, the results are depicted in Table 1. Several kinds of heteroatom-containing compounds such as 1,3-dicarbonyl compounds, amino acids, amines and 1,10-phenanthroline were tested as ligands in the presence of $FeCl_3$ in toluene with different bases. Firstly, the reaction was carried out using 15 mol%

Table 1. Optimization of the reaction conditions for the formation of **3a**.



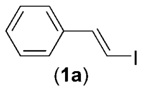
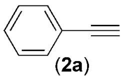
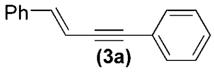
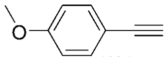
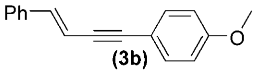
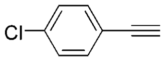
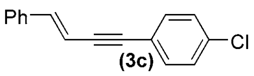
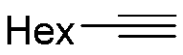
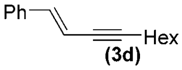
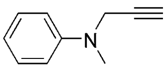
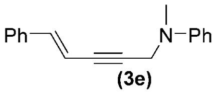
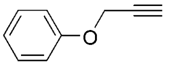
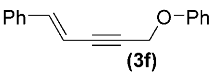
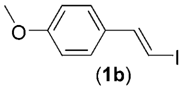
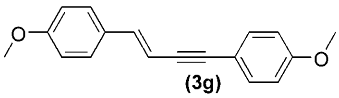
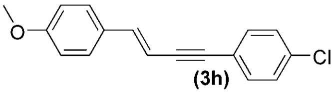
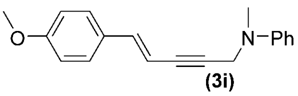
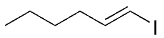
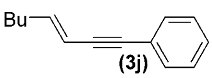
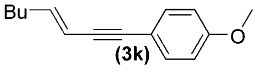
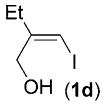
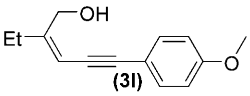
1a **2a** **3a**

Entry	Fe source (15mol%)	Ligand (30 mol%)	Base	Time [h]	Yield [%][a]
1	$FeCl_3$		Cs_2CO_3	48	25
2	$FeCl_3$	*Rac-trans-N,N'*-dimethyl-cyclohexane-1,2-diamine	Cs_2CO_3	24	6
3	$FeCl_3$	pentane-2,4-dione	Cs_2CO_3	24	0
4	$FeCl_3$	2-acetylcyclohexanone	Cs_2CO_3	24	0
5	$FeCl_3$	L-proline	Cs_2CO_3	24	0
6	$FeCl_3$	*N, N*-dimethylglycine hydrochloride	Cs_2CO_3	24	0
7	$FeCl_3$	aniline	Cs_2CO_3	24	0
8	$FeCl_3$	TMEDA	Cs_2CO_3	48	56 (42)
9	$FeCl_3$	1,10-phenanthroline (**L1**)	Cs_2CO_3	48	82 (69)
10	$FeCl_3$	**L1**	NaOH	24	0
11	$FeCl_3$	**L1**	Na_2CO_3	24	0
12	$FeCl_3$	**L1**	Et_3N	24	0
13	$FeCl_3$	**L1**	Cs_2CO_3	24	0[b]
14	$FeCl_2$	**L1**	Cs_2CO_3	24	0
15	$Fe(acac)_3$	**L1**	Cs_2CO_3	48	26
16	$FeCl_3$	**L1**	Cs_2CO_3	48	10[c]
17	$FeCl_3$	**L1**	Cs_2CO_3	48	50[d]
18	$FeCl_3$	**L1**	Cs_2CO_3	48	35[e]

[a] NMR yields, isolated yields are given in the parentheses. Unless noted, all the reactions were carried out using 1.0 equiv of **1a** and 1.0 equiv of **2a** with 3 equiv of base in toluene at 110 °C.
[b] DMF was used as solvent.
[c] 10 mol% of $FeCl_3$ and 10 mol% of **L1** were used.
[d] 10 mol% of $FeCl_3$ and 20 mol% of **L1** were used.
[e] 15 mol% of $FeCl_3$ and 15 mol% of **L1** were used.

$FeCl_3$ as the catalyst and 30 mol% *N,N'*-dimethylethane-1,2-diamine as as the ligand at 110 °C.[10] It was encouraging that the desired (*E*)-1,4-diphenylbut-1-en-3-yne (**3a**) was produced in 25% yield after 48 h (Table 1, entry 1). *rac-trans-N,N'*-Dimethylcyclohexane-1,2-diamine gave a similar result. When dicarbonyl compounds and amino acids were used, no desired product could be detected (Table 1, entries 3–6). Then we turned our attention back to amines. Aniline has no good effect on the coupling reaction, and *N,N,N',N'*-tetramethylethane-1,2-diamine (TMEDA) resulted in the formation of **3a** in 56% yield after 48 h (Table 1, entry 8). It is interesting to note that tertiary diamines gave better yields than primary and secondary amines. The best result was achieved when the reaction was performed in the presence of 1,10-phenanthroline (**L1**), affording the target enyne in 82% yield (Table 1, entry 9), along with *ca.* 2% of 1,4-diphenylbuta-1,3-diyne resulting from the homocoupling of phenylacetylene. It is noteworthy that the

Table 2. Preparation of enynes from 1-alkynes and vinyl iodides.

Entry	Vinyl Iodide	Alkyne	Time [h]	Product	Yield [%][a]
1	 (**1a**)	 (**2a**)	48	 **(3a)**	82 (69)
2	**1a**	 (**2b**)	48	 **(3b)**	83 (76)
3	**1a**	 (**2c**)	48	 **(3c)**	98 (90)
4	**1a**	 (**2d**)	36	 **(3d)**	90 (85)
5	**1a**	 (**2e**)	60	 **(3e)**	80 (57)
6	**1a**	 (**2f**)	60	 **(3f)**	60 (45)
7	 (**1b**)	**2b**	48	 **(3g)**	80 (69)
8	**1b**	**2c**	64	 **(3h)**	70 (58)
9	**1b**	**2e**	72	 **(3i)**	67 (56)
10	 (**1c**)	**2a**	60	 **(3j)**	70 (52)
11	**1c**	**2b**	60	 **(3k)**	70 (61)
12	 (**1d**)	**2b**	48	 **(3l)**	(25)[b]

[a] NMR yields, isolated yields are given in the parentheses.

[b] 1.5 equiv. of **1d** was used, 60% **2b** was recovered.

choice of Cs_2CO_3 as the base and toluene as the solvent was crucial for the enyne-forming reaction. When other bases like NaOH, Na_2CO_3, Et_3N and solvents such as DMF were employed, no desired enyne was observed (Table 1, entries 10–13). Decreasing the amount of $FeCl_3$ or ligand resulted in much lower yields (Table 1, entries 16–18). Controlled reactions in the absence of $FeCl_3$ and ligand led to no detection of the desired cross-coupling product. Other iron source such as $FeCl_2$ or $Fe(acac)_3$ failed to accomplish the coupling reaction or gave very low yields of the enynes, respectively (Table 1, entries 14 and 15). It was clear that the optimized reaction conditions was to use 15 mol% $FeCl_3$ as the catalyst and 30 mol%

1,10-phenanthroline as the ligand, Cs_2CO_3 as the base and toluene as the solvent.

Having established an effective iron-catalyzed system for the coupling reactions, we next explored the scope of the reaction by treating a variety of vinyl iodides with different acetylenes under the optimized reaction conditions. The representative results are shown in Table 2. The reaction was applicable to various acetylenes and vinyl iodides. The coupling of various alkenyl iodides with both electron-rich and electron-deficient acetylenes afforded the products in good to excellent yields. Acetylenes with an electron-donating (OMe) aryl group or an electron-withdrawing (Cl) aryl group coupled with (*E*)-1-(2-iodovinyl)-benzene (**1a**) to give rise to the corresponding enynes in 83% and 98% yields, respectively (Table 2, entries 2 and 3). Alkyl-substituted alkynes led to the desired product in 90% yield (Table 2, entry 4). It is noteworthy that propargylamine and propargyl ether are also compatible under the reaction conditions and furnishing products **3e** and **3f** in 80% and 60% yields, respectively, while the −NMePh and −OPh groups are well tolerated (Table 2, entries 5 and 6). When 4-methoxyphenylvinyl iodide (**1b**) was employed, it coupled with 4-methoxyphenylacetylene (**2b**), 4-chlorophenylacetylene (**2c**) and *N*-methyl-*N*-(prop-2-ynyl)-benzenamine (**2e**) to provide the corresponding enynes **3g**, **3h**, **3i** in high yields (Table 2, entries 7–9). Alkyl-substituted alkenyl iodide **1c** reacted with **2a** and **2b** to afford the expected products both in 70% yields (Table 2, entries 10 and 11). Interestingly, when a vinyl iodide bearing a propargyl alcohol moiety was employed, the desired coupling product could also be obtained in 25% yield.

In summary, we have developed an efficient, high-yielding iron-catalyzed coupling reaction between alkenyl iodides and terminal alkynes for the synthesis of conjugated enynes. The combination of $FeCl_3$, 1,10-phenanthroline, Cs_2CO_3 and toluene is crucial for the enyne forming reaction. Further studies of the reaction mechanism and applications of this novel iron-catalyzed C−C bond forming procedure to extend the scope and synthetic utility of the reaction are under progress in our group.

Experimental Section

Typical Procedure for the Fe-Catalyzed Formation of (*E*)-1-Chloro-4-[4-(4-methoxyphenyl)but-3-en-1-yn-yl]benzene (3h)

Iron(III) chloride (0.15 mmol), 5 mL toluene, 1,10-phenanthroline (0.3 mmol), 1-chloro-4-ethynylbenzene (1.0 mmol), (*E*)-1-(2-iodovinyl)-4-methoxybenzene (1.0 mmol) and cesium carbonate(3.0 mmol) was added in this order to a dry Schlenk tube under nitrogen, the mixture was stirred and heated at reflux for 64 h. Then it was cooled to room temperature and quenched with water and extracted with ether (3×20 mL). The extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel to afford a light-yellow solid of enyne derivative **3h**; yield: 156 mg (58%); mp 139–140 °C. ^{1}H NMR ($CDCl_3$, Me_4Si): $\delta = 3.72$ (s, 3H), 6.13 (d, $J = 16.0$ Hz, 1H,), 6.78 (d, $J = 8.0$ Hz, 2H), 6.91 (d, $J = 16.0$ Hz, 1H), 7.16–7.30 (m, 6H); ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 55.29$, 89.80, 90.26, 105.32, 114.20, 122.14, 127.71, 128.63, 129.05, 132.58, 133.90, 141.27, 160.20; HR-MS: $m/z = 268.0659$, calcd for $C_{17}H_{13}ClO$: 268.0655.

Supporting Information

Experimental details and spectroscopic characterization of all new compounds are given in the Supporting Information file.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 20572025 and 20872037) for financial support. We also thank the Lab of Organic Functional Molecules and the Sino-French Institute of ECNU for support.

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