Iron-Catalyzed Alkenylzincation of Internal Alkynes

Wei-Na Wang\textsuperscript{1}, Qiang Huang\textsuperscript{1}, Ye Jin\textsuperscript{1}, Qi-Lin Zhou\textsuperscript{1}, and Shoufei Zhu\textsuperscript{1}

\textsuperscript{1}Nankai University

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Abstract

The alkenylzincation of internal alkynes is an effective method for the synthesis of multi-substituted conjugated dienes; however, the current catalytic systems for this reaction are limited in terms of substrate scope and selectivity control, which restricts its practical applications. Herein, we report the first iron-catalyzed alkenylzincation of internal alkynes, which features mild conditions, simple operation, broad substrate scope (including aryl/alkyl, diaryl, and dialkyl acetylenes), excellent functional group tolerance (tolerating highly active functional groups such as ester, methylthio, amide, sulfonyl, cyano, etc), and high activity (with a turnover number of up to 11500, the highest record for carbometallation reactions). Notably, the catalytic system described in this article also realized the highly selective vinylzincation of unfunctionalized internal alkynes as well as the alkenylzincation of unsymmetrical diarylacetylenes and dialkyl acetylenes, which have not been achieved with other catalytic systems reported in the literatures. The current study provides a highly selective access to synthetically important multi-substituted conjugated dienes.

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\textsuperscript{a}Frontiers Science Center for New Organic Matter, State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China

Keywords

Iron catalysis | Internal alkynes | Vinylzincation | Conjugated dienes

Comprehensive Summary

The alkenylzincation of internal alkynes is an effective method for the synthesis of multi-substituted conjugated dienes; however, the current catalytic systems for this reaction are limited in terms of substrate scope and selectivity control, which restricts its practical applications. Herein, we report the first iron-catalyzed alkenylzincation of internal alkynes, which features mild conditions, simple operation, broad substrate scope (including aryl/alkyl, diaryl, and dialkyl acetylenes), excellent functional group tolerance (tolerating highly active functional groups such as ester, methylthio, amide, sulfonyl, cyano, etc), and high activity (with a turnover number of up to 11500, the highest record for carbometallation reactions). Notably, the catalytic system described in this article also realized the highly selective vinylzincation of unfunctionalized internal alkynes as well as the alkenylzincation of unsymmetrical diarylacetylenes and dialkyl acetylenes, which have not been achieved with other catalytic systems reported in the literatures. The current study provides a highly selective access to synthetically important multi-substituted conjugated dienes.

Background and Originality Content

Conjugated dienes possess unique electronic structures and exhibit rich reactivity,

which make them important building blocks in fields of pharmaceuticals, optical materials, and polymer chemistry. Moreover, many natural products contain structural units of conjugated olefins. Therefore, the synthesis of conjugated dienes has been of great interest. However, the synthesis of multi-substituted conjugated olefins is highly challenging due to the difficulty in controlling the \( Z / E \) selectivity.

The alkenylzincation of alkynes represents a powerful strategy for the synthesis of conjugated dienes. This reaction enables facile control over the stereo- and regioselectivity of the newly formed olefins, making it a
highly advantageous method. While alkenylzincation of terminal alkynes has been well established recently,[8] the corresponding reactions with internal alkynes remains underdeveloped, as evidenced by only two reported examples with significant limitations in substrate scope and selectivity control (Scheme 1A). In 2009, Lam and co-workers[9] developed a directed carbozincation of ynamides using Rh(cod)(acac) as the catalyst, where the zinc group is selectively added to the proximal side of the amide. One example of vinylzincation was achieved, leading to the synthesis of functionalized conjugated diene in moderate yield (66%) and regioselectivity (7:1). In 2016, Yoshikai and co-workers[10] used CoF$_2$/Bu-Xantphos as a catalyst for the alkenylzincation of unactivated internal alkynes and obtained corresponding conjugated dienyl zinc products with moderate to good yields (34–95%). However, the reaction suffered from competing 1,4-cobalt migration, which led to uncontrollable regio- and chemoselectivity. Furthermore, this Co catalyst system was not effective for vinylzincation, probably due to the high reactivity of the vinylzinc reagent towards undergoing its own addition reaction in the presence of the catalyst.[11] In view of these challenges in substrate scope and selectivity control, the development of efficient new catalysts for alkenylzincation of internal alkynes is highly desired.

Scheme 1 Catalytic alkenylzincation of internal alkynes

As our continuous efforts on the development of iron catalysis,[12] we herein report an iron-catalyzed alkenylzincation of internal alkynes that exhibits exceptional reaction activity (up to 11500 turnover numbers), high stereo- and regioselectivity ($E/Z > 95:5$; regioisomeric ratios, $r_r > 95:5$), and a wide range of substrate applicability (Scheme 1B). Notably, the reaction also shows excellent functional group tolerance, and enables for the first time the highly selective vinylzincation of unfunctionalized internal alkynes as well as carbozincation of unsymmetrical diarylacetylenes and dialkyl acetylenes. This reaction provides a competitive approach to the synthesis of structurally diverse multi-substituted conjugated dienes.

Results and Discussion

We began by the reaction of 4-methoxyphenylacetylene 1aa with divinylzinc reagent in THF at room temperature (Table 1). Initially, the catalysts reported in literature for carbozincation of internal alkynes were investigated,[13] but none of them provided satisfactory results (entries 1–7). Subsequently, we systematically evaluated iron complexes bearing various types of ligands. The tridentate phenanthroline-imine iron complexes L1-FeCl$_2$ and L2-FeCl$_2$, with the 9-position of the ligand substituted with 2,4,6-triisopropylphenyl, exhibited high activity and complete conversion of the alkyne was achieved (entries 8 and 9). The tridentate pyridine-diimine iron complexes also showed high catalytic activity, and the catalysts L3-FeCl$_2$, L4-FeCl$_2$, and L5-FeCl$_2$ produced the conjugated diene product 2aa in high yield and with exclusive selectivity (entries 10–12). Although iron complexes bearing bidentate phenanthroline ligands (L6-FeCl$_2$ and L7-FeCl$_2$) showed good activity, reactions catalyzed by these complexes gave moderate regioselective and stereoselective (entries 13 and 14). Furthermore, other iron/bidentate nitrogen complexes with different backbones showed poor reaction results (entries 15–17). When the bidentate α-diimine iron complex L9-FeCl$_2$ was evaluated, the results showed 22% of the desired carbozincation product and 30% of the secondary carbozincation product 4,4’-((1E,3E)-2,4-dimethylhexa-1,3,5-triene-1,3-diyli)bis(methoxybenzene) (entry 16), which was due to the excessively high activity of the catalyst towards the secondary carbozincation of product 2aa. Other bidentate nitrogen ligands, tridentate nitrogen ligands and diphosphine ligands, were also evaluated but showed no significant improvement in activity or selectivity (see Table S1 for details). After comprehensive consideration, L3-FeCl$_2$ was selected as the optimal catalyst for the following studies. Control experiments demonstrated that the reaction did not occur when FeCl$_2$ was used as the catalyst or when only the L3 ligand was added (entries 18, 19). Furthermore, the purity of the complexes L3-FeCl$_2$ and L5-FeCl$_2$ were analyzed and a series of control experiments were carried out to exclude the influence of impurities on the reaction. Replacement of the central iron atom by other metals resulted in no reaction (see Tables S2 and S3 for details).

After obtaining the optimal reaction conditions (Table 1, entry 10), we investigated substrate scope of aryl-alkyl acetylenes (Scheme 2). First, we examined the effect of substituents on the benzene ring of the alkynes. The electronic effects of substituents on the phenyl ring had a small effect on the yield.
When the phenyl ring was substituted with electron-donating groups, methoxy (2aa) or dimethylamino (2ad) at the para-position, the corresponding conjugated diene products were obtained in 91% and 96% yields, respectively. When the phenyl rings of the alkynes substituted with electron-withdrawing groups, the corresponding vinylzincation products (2ah – 2aq) were obtained with satisfactory yields and selectivity under standard conditions, albeit those containing ester (2ah) and cyano (2aj) groups exhibited slightly reduced stereoselectivities with unidentified reasons. In addition, steric effects of substituent on the phenyl ring of the alkyne slightly affect the reaction. The alkynes having ortho- or meta-substituted phenyl rings gave high yield and selectivity (2ao, 2as, 2au). In addition to phenyl, the aryl group of the alkynes 1 could also be benzodioxole (2ba), naphthalene (2bb) and heteroaromatics (benzofuran 2bc, indole 2bd, thiophene 2be, furan 2bf, pyridine 2bg). Note that the reaction exhibited excellent functional group tolerance, as methoxy (2aa), silyl (2ac), amino (2ad), methylthio (2ae), ester (2ah), amide (2ai), cyano (2aj), sulfonyl (2ak), acetal (2al), trifluoromethyl (2am), halogen (2an – 2aq, 2as, 2au), and hydroxy (2cg) groups were all tolerated.

Table 1 Catalytic vinylzincation of an internal alkyne1aa: optimizing reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conv. (%)</th>
<th>Yield 2aa (%)</th>
<th>Yield 3aa (%)</th>
<th>Yield 4aa (%)</th>
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<tr>
<td>1</td>
<td>Cu(OTf)2</td>
<td>&lt; 5</td>
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<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>Ni(cod)2</td>
<td>&lt; 5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Ni(acac)2</td>
<td>&lt; 5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>Ti(OiPr)4</td>
<td>10</td>
<td>trace</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Rh(cod)(acac)</td>
<td>10</td>
<td>trace</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>CoBr2/bpy</td>
<td>&lt; 5</td>
<td>trace</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>CoF2/4BuXantphos</td>
<td>&lt; 5</td>
<td>trace</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>L1-FeCl2</td>
<td>&gt; 95</td>
<td>88(69)</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>L2-FeCl2</td>
<td>&gt; 95</td>
<td>93</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>L3-FeCl2</td>
<td>&gt; 95</td>
<td>93(91)</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>L4-FeCl2</td>
<td>&gt; 95</td>
<td>90</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>12</td>
<td>L5-FeCl2</td>
<td>&gt; 95</td>
<td>94</td>
<td>trace</td>
<td>trace</td>
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<td>13</td>
<td>L6-FeCl2</td>
<td>&gt; 95</td>
<td>82(76)</td>
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<tr>
<td>14</td>
<td>L7-FeCl2</td>
<td>91</td>
<td>56</td>
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<td>6</td>
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<tr>
<td>15</td>
<td>L8-FeCl2</td>
<td>38</td>
<td>24</td>
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<td>trace</td>
</tr>
<tr>
<td>16b</td>
<td>L9-FeCl2</td>
<td>&gt; 95</td>
<td>22</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>17</td>
<td>L10-FeCl2</td>
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<tr>
<td>18</td>
<td>FeCl2</td>
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<td>ND</td>
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<tr>
<td>19</td>
<td>L3</td>
<td>&lt; 5</td>
<td>trace</td>
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</table>

*a Reaction conditions: 1aa (0.3 mmol), divinylzinc (0.33 mmol), catalyst (3 mol %), THF (2.5 mL), rt, 10 h. Determined by 1H NMR using 1,3,5-trimethoxybenzene as an internal standard. The data in parentheses is the isolated yield. The iron catalysts used in this study are all preprepared. ND = Not detected. b 30% 4,4’-((1E,3E)-2,4-dimethylhexa-1,3,5-triene-1,3-diyl)bis(methoxybenzene) was isolated.

Subsequently, we investigated the effect of alkyl moieties of the aryl-alkyl acetylenes (Scheme 2). The reactions with the alkynes having primary alkyl groups, a benzyl group, and secondary alkyl groups all afforded the corresponding cis-addition products (2ca – 2ch) in good to excellent yields (85–99%), indicating that the catalytic system was not sensitive to properties of the alkyl moiety of the alkyne substrates.

Scheme 2 Iron-catalyzed vinylzincation of aryl-alkyl acetylenes

*a Reaction conditions: 1 (0.5 mmol), divinylzinc (0.55 mmol), L3-FeCl2 (3 mol %) in THF (4.5 mL) at rt
for 3 h, the reaction mixture was quenched with water (150 μL) unless otherwise noted. All of the reactions exhibited full conversion of internal alkynes. Isolated yields were given. $E/Z$ and regioisomeric ratios (rr) of all the products were determined by $^1$H NMR. $^b$ The reaction was conducted at 40 °C. $^c$ The reaction was conducted at 35 °C, 0.3 mmol scale.

Additionally, we successfully extended the catalytic system to the vinylzincation of diarylacetylenes (Scheme 3A). Symmetrical diarylacetylenes could be selectively converted to the desired products (2da –2dc ) with moderate to good yields and high stereoselectivity. Notably, we achieved the first example of directed alkenylzincation of an unsymmetrical diarylacetylene containing a pyridine moiety (2dd ). Unfortunately, the regioselectivity was poor for the reaction of a diarylacetylene with one phenyl group bearing an electron-donating substituent and the other with an electron-withdrawing substituent, and 1:1 mixture of products2de and 2df were obtained.

The regioselectivity of vinylzincation of unsymmetrical dialkyl acetylenes is a remarkable challenge because the two substituents of the alkyne have similar electron and steric properties. In deed, the carbozincation of unsymmetrical dialkyl acetylenes could only obtained a poor regioselectivity (rr = 55:45) in the literature.$^{[13c]}$ To our delight, the iron-catalyzed vinylzincation reactions of unsymmetrical dialkyl acetylenes exhibited unprecedented high regioselectivities (Scheme 3B). The reactions of phenylpropyl propyne, benzyl propyne, substituted benzyl propyne, and cyclohexyl propyne afforded the single regioisomers in good to excellent yields (2ea –2ed ).

Next, we also investigated the reactions of different types of alkenylzinc reagents (Scheme 3C). It was found that β-alkyl-substituted alkenylzinc reagents could undergo the reaction smoothly, affording multi-substituted conjugated dienes with excellent yields (2fa ,2fb ). Furthermore, when L8-FeCl$_2$ was used as the catalyst, the substrate scope could be extended to α-alkyl-substituted alkenylzinc reagent, leading to the formation of a single syn-addition product 2fc in 69% yield.

**Scheme 3** Iron-catalyzed alkenylation of internal alkyne: substrate scope

$a$ Reaction conditions: 1 (0.5 mmol), divinylzinc (0.55 mmol), L3-FeCl$_2$ (3 mol %) in THF (4.5 mL) at rt for 3 h, the reaction mixture was quenched with water (150 μL) unless otherwise noted. $^b$ The reaction was conducted at 50 °C. $^c$ 0.3 mmol. $^d$ NMR yield. $^e$ Used 3 mol % L5-FeCl$_2$ as catalyst. $^f$ Used 3 mol %L8-FeCl$_2$ as catalyst.

The activity of the current reaction is high, and the reaction proceeds smoothly even when the substrate/catalyst ratio (S/C) is increased to 12500, resulting in a 92% isolated yield (turnover number, TON = 11500) of 4.05 g of conjugated diene product 2ag (Scheme 4A). To the best of our knowledge, this is the highest TON record for carbometallation reactions.$^{[14]}$ In order to demonstrate the potential applications of this method in synthesis, we carried out various transformations on the conjugated dienyl zinc product 2aa’ (Scheme 4B). When organozinc intermediate was trapped with D$_2$O, deuterated conjugated diene T1 was obtained. The conjugated dienyl zinc product2aa’ smoothly underwent Negishi coupling reactions with iodomethane, 4-nitroiodobenzene, and vinyl bromide, affording conjugated dienes T2 – T4 with well retention of configuration in 90%, 69%, and 90% isolated yields, respectively. Transformation of zinc group of 2aa’ to allyl group mediated by copper salt ran smoothly to afford functionalized conjugated olefins T5 in 97% yield. The intermediate 2aa’ could also undergo addition reactions with isocyanate, affording the mono-configurational amide-conjugated diene T6 in 90% yield. Thus, by combining the iron-catalyzed alkenylation of internal alkynes with rich transformations of the C(sp$^2$)-Zn bond, we have developed a new method for the selective synthesis of tetrasubstituted olefin-containing conjugated dienes from easily accessible alkynes. Note that the stereospecific synthesis of multi-substituted conjugated dienes has been a challenge task because the difficult stereoselective control.$^{[15]}$

**Scheme 4** Applications of iron-catalyzed alkenylation of internal alkynes

$a$ Reaction conditions: (a) D$_2$O, THF, rt, 0.5 h; (b) MeI, Pd(PPh$_3$)$_4$, THF, rt, 12 h; (c) 1-iodo-4-nitrobenzene, Pd(PPh$_3$)$_4$, THF, rt, 12 h; (d) vinyl bromide, Pd(PPh$_3$)$_4$, THF, rt, 12 h; (e) allyl bromide, CuCN, THF, rt,
4 h; (f) $p$-tolyl isocyanate, THF, 50 °C, 8 h.

Conclusions

In summary, we reported the first iron-catalyzed alkenylzincation of internal alkynes, which exhibited not only high reaction activity and selectivity, but also good functional group tolerance and broad substrate scope. The resulting products are amenable to a variety of transformations, enabling efficient synthesis of a range of multi-substituted conjugated dienes. This research provides a new catalytic system for alkenylzincation of internal alkynes, overcomes limitations of other catalysts on substrate type, catalytic activity, and selectivity, thereby demonstrating the significant potential of iron catalysts in organic synthesis.

Experimental

Preparation of alkenylzinc reagents: In an argon-filled glovebox, a vial (10 mL) was charged with anhydrous ZnBr$_2$ (1.0 equiv), anhydrous LiCl (1.0 equiv), anhydrous THF (10 mL per 1 mmol zinc bromide). Then, alkenylmagnesium bromide (0.5 M or 1.0 M, 2.0 equiv) was added slowly and the reaction mixture was stirred for another 10 minutes at rt. A slight yellow solution was formed and used without further titration.

General procedure for iron-catalyzed vinylzincation of internal alkynes: In an argon-filled glovebox, internal alkyne 1 (0.5 mmol) and catalyst (0.015 mmol) were added to the pre-prepared divinylzinc solution (0.55 mmol, 0.1 M in THF, 1.1 equiv) in sequence. After stirring for 3 h at rt, the reaction mixture was quenched with an electrophilic reagent and filtered over silica gel using ethyl acetate as an eluant. The combined organic phases were concentrated by rotary evaporation, and the product was isolated by column chromatography over silica gel.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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References


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The Authors

**Left to Right:** Top panel: Wei-Na Wang, Qiang Huang, Ye Jin Bottom panel: Qi-Lin Zhou, Shou-Fei Zhu

**Entry for the Table of Contents**

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