Stereoselective Synthesis of Trisubstituted Alkenes via Sequential Iron-Catalyzed Reductive *anti*-Carbozincation of Terminal Alkynes and Base-Metal-Catalyzed Negishi Cross-Coupling

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Abstract: Stereoselective synthesis of trisubstituted alkenes is challenging. Here, we show that iron-catalyzed *anti*-selective carbozincation of terminal alkynes can be combined with base-metal-catalyzed cross-coupling to prepare trisubstituted alkenes in one-pot and with high regio- and stereo-control. Cu-, Ni-, and Co-based catalytic systems are developed for the coupling of *sp*-, sp^2-, and sp^3-carbon electrophiles, respectively. The method encompasses large substrate scope, as various alkynyl, aryl, alkenyl, acyl, and alkyl halides are suitable coupling partners. Compared with conventional carbometalation reactions of alkynes, the current method avoids pre-made organometallic reagents and has distinct stereoselectiviy.

Introduction

Stereoselective synthesis of substituted alkenes is a longstanding goal in organic synthesis.[1] In recent years, transition metal-catalyzed cross-coupling has emerged as a straightforward and versatile method for olefin synthesis.[2,3] This method is stereospecific; thus, to synthesize stereoselective trisubstituted alkenes, the corresponding cross-coupling partners, namely the alkenyl (pseudo)halides or organometallic reagents, need to have the appropriate stereo-configurations (Scheme 1, A).[2,3] However, stereoselective synthesis of these coupling partners can be difficult.[4]

Organozinc reagents are compatible with a large number of sensitive functional groups, which makes them attractive reagents in organic synthesis.[5] Alkenylzinc reagents are generally prepared from alkenyl halides via direct metal insertion or halogen/metal exchange.[3h,5] Alternatively they can be prepared from alkynes by transition-metal-catalyzed carbozincation of alkynes using organozinc reagents[1,6] or hydrozincation using hydride sources.[7]

The carbozincation[1,6] and hydrozincation[7] of alkynes are usually *syn*-selective. *anti*-Carbozincation of alkynes is rarely

reported, and in limited cases, is achieved using alkynes bearing directing groups such as carbonyl groups.[8,9] Moreover, the regioselectivity of the carbozincation of alkynes can be poor,[1b] and consequently, the regio-control relies on the use of symmetric alkynes or directing groups.[6-8]

We recently reported iron-catalyzed *Z*-selective olefin synthesis via the reductive coupling of alkyl halides with terminal arylalkynes using zinc as reductant (Scheme 1, B).[10] Mechanistic study suggested that an alkenylzinc intermediate (**1a**) was formed via Fe-catalyzed *anti*-selective carbozincation of alkyne with alkyl halides. Herein, we show that by using suitable base metal catalysts (Cu, Ni, Co), such *in-situ* formed alkenylzinc intermediates can be coupled to a wide range of *sp*, sp^2, and sp^3 carbon electrophiles to afford an array of trisubstituted alkenes[11] with high stereochemical control (Scheme 1, B).

(A) Synthesis of trisubstituted alkenes by cross-coupling
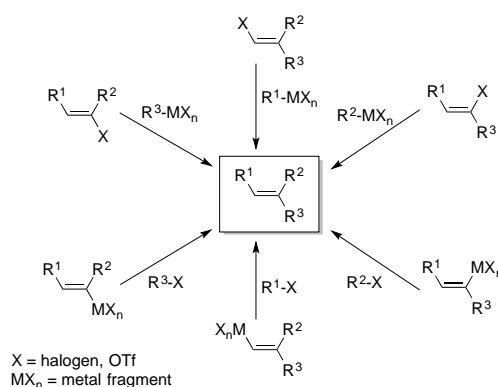
(B) Alternative methods of stereoselective alkene synthesis
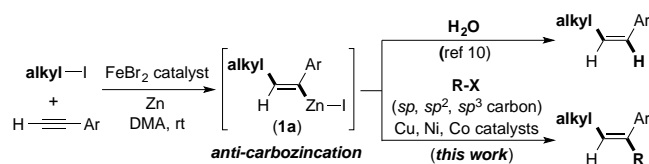
Scheme 1. (A): Synthesis of trisubstitued alkenes using cross-coupling methods. (B): Synthesis of trisubstituted alkenes by sequential iron-catalyzed *anti*-carbozincation of terminal alkynes and base-metal-catalyzed cross-coupling.

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Results and Discussion

The cross-coupling of *Z*-alkenylzinc intermediates with bromoalkynes was first studied.[12] Initially, the alkenylzinc reagent (**1b**) was prepared using the procedure optimized for *Z*-olefin synthesis.[10] Since Cu was used as a catalyst in the cross-coupling reactions of cyclic alkenylzinc reagents with bromoalkynes,[13,14] we chose Cu catalyst for the analogous coupling of acyclic alkenylzinc reagents. In the presence of CuCl (20 mol %) and 2,2'-dibypridyl ligand (bipy, 20 mol %), **1b** (in excess, up to 1.4 equiv assuming a 100% yield for carbozincation) reacted with (bromoethynyl)benzene in tetrahydrofuran (THF) at room temperature to give the (*E*)-enyne product in 49% GC yield (Table 1, entry 1). Bipy was superior than other nitogen- and phosphine-type ligands (Table 1, entries 2-4). When iodotrimethylsilane (TMSI, 10 mol %) instead of iodine (I₂, 2 mol%) was used as the Zn-activating reagent, the coupling yield was improved to 87% (Table 1, entry 5). Presumably, TMSI readily reacted with the residual water in the solvent, preserving the alkenylzinc reagent for cross-coupling.[15] The loading of CuCl could be lowered to 15 mol % without the diminishment in yield (Table 1, entry 6). Various Cu catalysts were also screened (Table 1, entries 7-10), and CuI was found to be the optimal catalyst to promote the highest yield (95%, Table 1, entry 7). However, the yields dropped significantly when a lower loading of bipy ligand (15 mol %) or CuI (10 mol %) was used instead (Table 1, entries 11 and 12). Without CuI, the yield was much lower (Table 1, entry 13).

coupling processes. Acyclic (**2a**, **2h**, **2j**, **2o**) and cyclic secondary alkyl iodides (**2c**, **2l**, **2m**), as well as tertiary alkyl iodides (**2p-2r**), served as suitable reaction partners for the *in-situ* synthesis of alkenylzinc reagents, leading to trisubstituted enynes in synthetically useful yields after the Negishi coupling. The use of primary iodide, however, only led to a modest yield of enyne (**2n**), likely due to the inefficient generation of the alkenylzinc reagent in the Fe-catalyzed carbozincation step.[10] The scope of bromoalkynes is also large. Functionalized (bromoethynyl)benzenes bearing both electron-donating (**2a**, **2h**, **2o**, **2q**) and electron-withdrawing groups (**2b**, **2e-g**, **2i-k**, **2p**) at different positions could be coupled in good yields. Moreover, the coupling reactions tolerated propiolate (**2s**), propiolamide (**2t**), phenylpropynone moieties (**2z**), as well as functionalized alkyl (**2u**, **2aa**) and carbazole groups (**2y**). Base-sensitive groups, including nitro (**2g**), nitrile (**2i**), keto (**2j**, **2u**, **2z**), ester (**2k**, **2s**), and amide groups (**2t**), were tolerated as well. Significantly, the stereoselectivity of the products were high to excellent (*E*:*Z*≥9:1 to *E*:*Z*>50:1). To our knowledge, synthesis of functionalized *E*-enynes is rarely reported.[17] This protocol would provide a general method to prepare a variety of stereoselective *E*-enynes from readily available alkenylzinc reagents and haloalkynes.
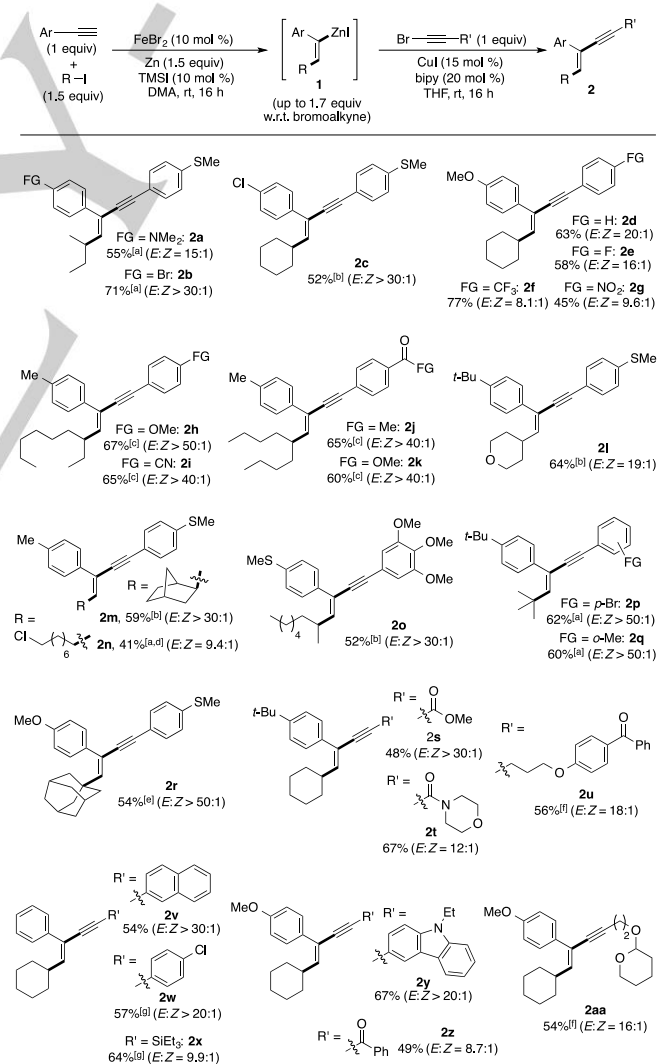
Table 1. Optimization of Sequential Fe-Catalyzed *anti*-Carbozincation of Alkyne and Cu-Catalyzed Alkenyl-Alkynyl Negishi Coupling[a]

entry	additive (mol %)	CuX (mol %)	ligand (mol %)	GC yield (%)
1	I₂ (2)	CuCl (20)	bipy (20)	49
2	I₂ (2)	CuCl (20)	phenanthroline (20)	46
3	I₂ (2)	CuCl (20)	TMEDA (20)	48
4	I₂ (2)	CuCl (20)	dppe (20)	28
5	TMSI (10)	CuCl (20)	bipy (20)	87
6	TMSI (10)	CuCl (15)	bipy (20)	91
7	TMSI (10)	CuI (15)	bipy (20)	95
8	TMSI (10)	CuBr (15)	bipy (20)	83
9	TMSI (10)	CuSCN (15)	bipy (20)	87
10	TMSI (10)	CuCN (15)	bipy (20)	89
11	TMSI (10)	CuI (15)	bipy (15)	79
12	TMSI (10)	CuI (10)	bipy (20)	83
13	TMSI (10)	CuI (0)	bipy (20)	41

[a] Reaction was based on 0.1 mmol of bromoalkyne; GC yield was determined *n*-dodecane as an internal standard.

The optimized conditions in Table 1 were then applied for the cross-coupling of a large number of alkenylzinc reagents with bromoalkynes (Figure 1).[16] Terminal arylalkynes containing electron-rich (**2a**, **2d**, **2h**, **2l**, **2o**, **2q**), electron-deficient (**2b**, **2c**), and electron-neutral aryl groups (**2v-2x**) could be used to generate the corresponding alkenylzinc reagents for subsequent

Figure 1. Scope of Cu-catalyzed alkenyl-alkynyl Negishi coupling of alkenylzinc reagents generated *in-situ* from Fe-catalyzed anti-carbozincation of terminal alkynes. The conditions were described in detail in the SI. Isolated yields were shown. [a] Alkyl iodide (3 equiv), Zn (3 equiv), and TMSI (20 mol %) were used in the first step. [b] Alkyl iodide (2 equiv) and Zn (2 equiv) were used in the first step. [c] Alkenylzinc reagent (~1.6 equiv) was used. [d] CuBr$_2$ (10 mol %) was added in the first step. [e] Alkyl iodide (5 equiv), Zn (5 equiv), TMSI (30 mol %) were used in the first step. [f] CuI (25 mol %), bipy (35 mol %). [g] CuI (20 mol %), bipy (30 mol %).

The cross-coupling of alkenylzinc reagents with aryl halides was then studied using ethyl 4-bromobenzoate as a test substrate (Table 2).[12] Since Ni catalysts were commonly utilized in the Negishi couplings of arylzinc reagents with aryl and alkenyl halides,[3i,18] we chose Ni catalyst for the analogous coupling of alkenylzinc reagents. With Ni(cod)$_2$ (20 mol %) as the Ni precursor, bipy (20 mol %) was the best ligand among many nitrogen- and phosphine-based mono- and bidentate ligands for the reaction of **1b** (1.25 equiv) with 4-bromobenzoate (1 equiv) (Table 2, entries 1-7), giving the *α*-arylated styrene in 64% GC yield (Table 2, entry 5). When a higher loading of **1b** (1.4 equiv) was used, the loadings of Ni(cod)$_2$ and bipy could be reduced to 10 and 15 mol %, respectively, giving the product in 76% yield (Table 2, entry 9). Ni(cod)$_2$ was a better Ni precursor than other Ni(II) precatalysts (Table 2, entries 8 and 12; entries 9 and 11).[19] Without a Ni catalyst, only a low yield was obtained (Table 2, entry 13).

Table 2. Optimization of Sequential Fe-Catalyzed *anti*-Carbozincation of Alkyne and Ni-Catalyzed Negishi Coupling with sp^2-Carbon Electrophiles[a]

entry	alkenyl-ZnI (x equiv)	Ni catalyst (mol %)	ligand (mol %)	GC yield (%)
1	1.25	Ni(cod)$_2$ (20)	dppe (20)	9
2	1.25	Ni(cod)$_2$ (20)	dppf (20)	16
3	1.25	Ni(cod)$_2$ (20)	PPh$_3$ (80)	22
4	1.25	Ni(cod)$_2$ (20)	Xantphos (20)	11
5	1.25	Ni(cod)$_2$ (20)	bipy (20)	64
6	1.25	Ni(cod)$_2$ (20)	phen (20)	18
7	1.25	Ni(cod)$_2$ (20)	2,2'-bis(oxazoline) (20)	28
8	1.25	Ni(cod)$_2$ (10)	bipy (10)	42
9	1.4	Ni(cod)$_2$ (10)	bipy (15)	76
10	1.4	Ni(cod)$_2$ (15)	bipy (15)	62
11	1.4	Ni(TMEDA)(2-tolyl)Cl (10)	bipy (15)	68
12	1.25	NiBr$_2$(diglyme) (10)	bipy (10)	27
13	1.4	Ni(cod)$_2$ (0)	bipy (15)	18

[a] Reaction was based on 0.1 mmol of bromoalkyne; GC yield was determined *n*-dodecane as an internal standard.

The scope of this Ni-catalyzed alkenyl-aryl Negishi coupling was studied using the optimized conditions (Figure 2).[16] Both aryl bromides and iodides with varying electronics reacted smoothly to give the corresponding *α*-arylated styrenes in high yields (**2a-c**, **3e-i**, **3k**). Heteroaryl bromides, including bromothiophenes (**3d**, **3j**), bromopyridines (**3m**), and bromoquionlines (**3n**), as well as aryl triflate (**3s**), reacted

equally well at slightly higher loadings of Ni(cod)$_2$ (15 mol %) and bipy (25 mol %). Furthermore, alkenyl bromides also reacted to give the *α*-alkenylated styrenes in high yields (**3o-r**). Moreover, the coupling protocol could be applied for acylation. Thus, carbamyl (**3t**) and aroyl chlorides (**3u-w**) reacted at room temperature to generate the corresponding enone derivatives. Notably, a variety of base-sensitive functional groups, including ester (**3a**, **3c**, **3d**, **3k**), amide (**3f**, **3t**), nitrile (**3g**), and keto groups (**3h**, **3l**, **3s**, **3u-w**), were tolerated under the reaction conditions. The coupling of alkenylzinc reagents with sp^2-carbon halides was stereospecific and only single stereoisomers were formed. As a result, **3l**, which exhibits an *anti*-proliferative activity toward a number of tumor cell lines,[20] was readily prepared using this protocol, without the problem of separation from a mixture of isomeric products as previously described.
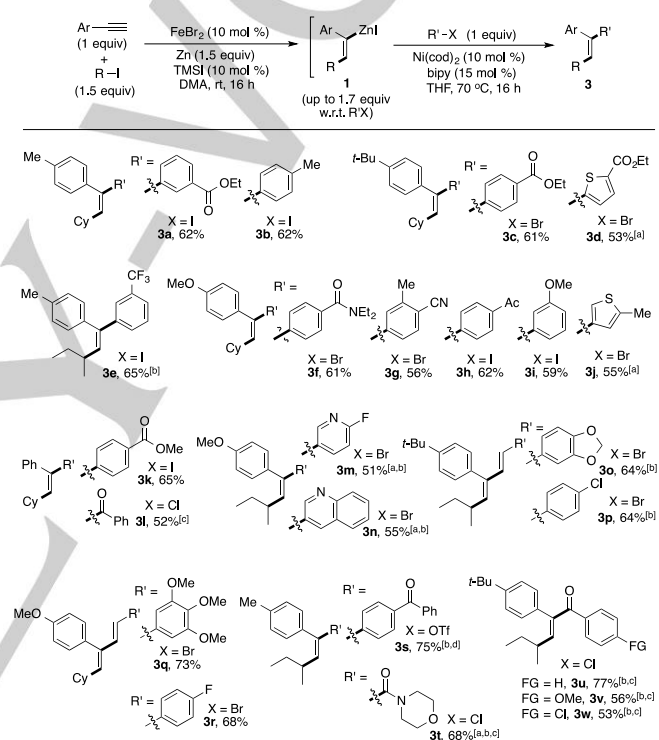
Figure 2. Scope of Ni-catalyzed Negishi coupling of sp^2-carbon electrophiles with *in-situ* formed alkenylzinc reagents. The conditions were described in detail in the SI. Isolated yields were shown. In all products, the ratios of major to minor isomer were more than 50:1. [a] Ni(cod)$_2$ (15 mol %), bipy (25 mol %). [b] Alkyl iodide (1.8 equiv) and Zn (1.8 equiv) were used in the first step. [c] rt. [d] Ni(cod)$_2$ (20 mol %), bipy (30 mol %), 80 °C.

Finally, the cross-coupling of alkenylzinc reagents with alkyl halides was also studied.[12] As Co catalyst was applied in the cross-coupling reactions of arylzinc reagents with alkyl halides,[21,22] we chose Co catalyst for the analogous coupling of alkenylzinc reagents. The use of CoBr$_2$ (30 mol %) in conjunction with 2 equiv of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was found to promote the reaction of **1b** with a secondary alkyl iodide, 2-iodooctane, affording *α*-2-octyl-*β*-cyclohexylstyrene in 57% GC yield (Table 3, entry 1). In contrast, the use of the derivatives of TMEDA, *N,N,N',N'*-tetramethyl-1,3-propanediamine (TMPDA) and *N,N,N',N'*-tetraethylethylenediamine (TEEDA), led to the

significant drops in yields (Table 3, entries 2 and 3). The same yield (57%) was obtained when the loading of CoBr$_2$ was lowered to 20 mol % (Table 3, entry 4). Co-additives were then screened (Table 3, entries 6-8), and the additional use of pyridine (3 equiv) was found beneficial, giving the product in 67% yield (Table 3, entry 8). By increasing the loading of **1b** to 1.7 equiv with respect to 2-iodooctane, a 76% yield was obtained (Table 3, entry 9). Under these conditions, a primary alkyl iodide, 1-iodooctane, reacted equally well to give α-1-octyl-β-cyclohexylstyrene in 76% yield (Table 3, entry 9). Without CoBr$_2$, only a trace amount of product was formed (Table 3, entry 10).

Table 3. Optimization of Sequential Fe-Catalyzed *anti*-Carbozincation of Alkyne and Co-Catalyzed Negishi-alkyl Coupling[a]
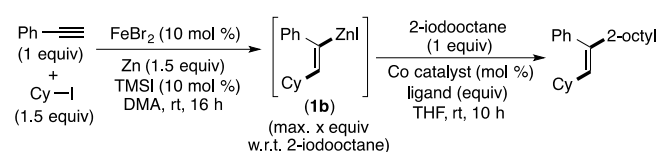
entry	alkenyl-ZnI (x equiv)	Co catalyst (mol %)	ligand(s) (equiv)	GC yield (%)
1	1.4	CoBr$_2$ (30)	TMEDA (2)	57
2	1.4	CoBr$_2$ (30)	TMPDA (2)[b]	26
3	1.4	CoBr$_2$ (30)	TEEDA (2)[c]	37
4	1.4	CoBr$_2$ (20)	TMEDA (2)	57
5	1.4	CoBr$_2$ (10)	TMEDA (2)	47
6	1.4 (+ 1.4 equiv LiCl)	CoBr$_2$ (20)	TMEDA (2)	49
7	1.4	CoBr$_2$·2LiCl (30)	TMEDA (2)	22
8	1.4	CoBr$_2$ (20)	TMEDA (2), py (3)	67
9	1.7	CoBr$_2$ (20)	TMEDA (2), py (3)	76 (76)[d]
10	1.7	CoBr$_2$ (0)	TMEDA (2), py (3)	<5 (<1)[d]

[a] Reaction was based on 0.1 mmol of bromoalkyne; GC yield was determined *n*-dodecane as an internal standard. [b] TMPDA = *N,N,N',N'*-tetramethyl-1,3-propanediamine. [c] TEEDA = *N,N,N',N'*-tetraethylethylenediamine. [d] 1-Iodooctane was used instead of 2-iodooctane.

The scope of this alkenyl-alkyl coupling was then explored (Figure 3). A variety of acyclic and cyclic, non-activated secondary alkyl iodides could be coupled in reasonable yields (**4a-c, 4g, 4h**). An activated secondary benzyl bromide, 1-bromo-1-phenylethane, also reacted to give the desired product (**4d**). Primary alkyl iodides bearing both hydrocarbon skeletons (**4e, 4k**) and functional groups such as chloro (**4f**), olefin (**4i**), and ester groups (**4j**) all reacted smoothly to afford the α-alkylated-styrene products. 2-(Allyloxy)-3-iodotetrahydrofuran and 2-(allyloxy)-3-iodotetrahydro-2*H*-pyran reacted to form the products containing the bicyclic groups (**4l, 4m**), suggesting a radical pathway for the alkyl-iodide cleavage process.[3e] High isomeric ratios (*Z:E*≥7:1) were generally observed in the couplings with alkyl halides. While there is room for improvement in the yields, this protocol represents, to our knowledge, the first Co-catalyzed coupling of alkenylzinc reagents with non-activated alkyl halides.[21]
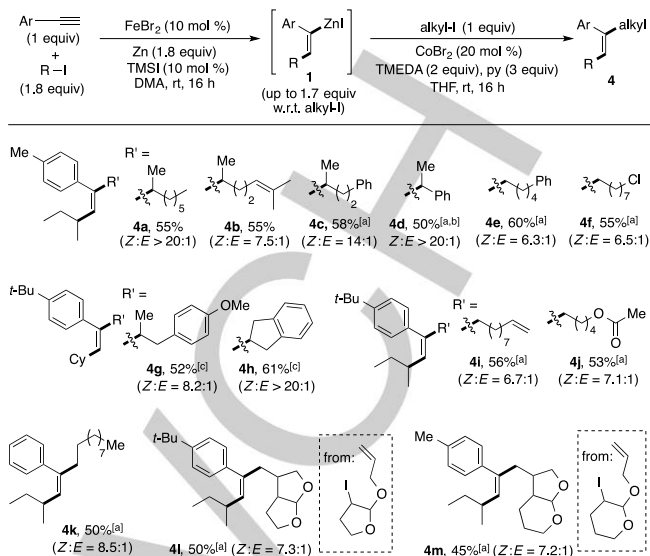

Figure 3. Scope of Co-catalyzed alkenyl-alkyl Negishi coupling. The conditions were described in detail in the SI. Isolated yields were shown. [a] ~1.5 equiv of alkenylzinc reagent was used. [b] 1-Bromo-1-phenyethane was used in the second step. [c] Alkyl iodide (1.5 equiv) and Zn (1.5 equiv) were used in the first step.

Conclusions

In conclusion, by combining Fe-catalyzed *anti*-carbozincation of alkynes with base-metal-catalyzed Neigishi coupling, we have developed an alternative and general method for stereoselective synthesis of trisubstituted alkenes.[23] The method employs catalysts made of base metals and readily available reagents, avoiding pre-made organometallic reagents that are used in conventional carbometallation reactions. The method has large substrate scope and high group tolerance. The high stereoselectivity and stereospecificity, as well as the unusual *anti*-selectivity for carbozincation, would make the method an attractive tool for stereoselective organic synthesis.

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[16] Initial studies showed that the use of 1.4 equiv of alkenylzinc reagents with respect to organohalide in the second reaction step gave the trisubsituted products in less than 50% isolated yields. Therefore, we increased the loading of alkenylzinc reagents to 1.7 equiv in the substrate scope study.

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[18] Recent examples of Ni-catalyzed C-C cross-coupling reactions: a) A. S. Dudnik, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 10693. b) C.-Y. Huang, A. G. Doyle, *J. Am. Chem. Soc.* **2012**, *134*, 9541. c) P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280. d) S. L. Zultanski, G. C. Fu, *J. Am. Chem. Soc.,* **2013**, *135*, 624. e) M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 3303. f) K. L. Jensen, E. A. Standley, T. F. Jamison, *J. Am. Chem. Soc.* **2014**, *136*, 11145.

[19] A new, air-stable Ni(II) precatalyst, Ni(TMEDA)(2-tolyl)Cl, has been developed for various cross-coupling reactions. See: a) J. D. Shields, E. E. Gray, A. G. Doyle, *Org. Lett.* **2015**, *17*, 2166. b) J. Magano, S. Monfette, *ACS Catal.* **2015**, *5*, 3120.

[20] I. Karpaviciene, I. Cikotiene, J. M. Padrón, *Eur. J. Med.Chem.* **2013**, *70*, 568.

[21] An example of Co-catalyzed coupling of arylzinc reagents with non-activated alkyl halides has been reported. See: see: J. M. Hammann, D. Haas, D. P. Knochel, *Angew. Chem.* **2015**, *127*, 4560; *Angew. Chem. Int. Ed.* **2015**, *54*, 4478.

[22] Recent examples of Co-catalyzed C-C cross-coupling reactions: a) S.-F. Hsu, C.-W. Ko, Y.-T. Wu, *Adv. Synth. Catal.* **2011**, *353*, 1756. b) T. Iwasaki, H. Takagawa, S. P. Singh, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2013**, *135*, 9604. c) O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher, P. Knochel, *Angew. Chem.* **2013**, *125*, 5045; *Angew. Chem. Int. Ed.* **2013**, *52*, 4945. d) M. Corpet, X.-Z. Bai, C. Gosminia, *Adv. Synth. Catal.* **2014**, *356*, 2937. e) R. Frlan, M. Sova, S. Gobec, G. Stavber, Z. Časar, *J. Org. Chem.* **2015**, *80*, 7803. f) L. Gonnard, A. Guérinot, J. Cossy, *Chem. Eur. J.* **2015**, *21*, 12797.

[23] We have also studied the cross-couplings of *in-situ* formed alkenylzinc reagents with other sp-, sp^2-, and sp^3-carbon electrophiles as shown in Figures S1, S2, and S3 in the Supporting Information. The yields were generally lower than that shown in the main text. Notably, the cross-coupling of alkyl-substituted bromoalkynes generally gave lower product yields. The cross-couplings of other functionalized primary and secondary alkyl iodides generally gave lower product yields.

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FULL PAPER

A wide range of trisubstituted olefins can be stereoselectively prepared via sequential iron-catalyzed *anti*-carbozincation of terminal arylalkynes with alkyl iodides followed by copper-, nickel-, and cobalt-catalyzed cross-couplings with various *sp*-, *sp*^{2}-, and *sp*^{3}-carbon electrophiles, respectively.
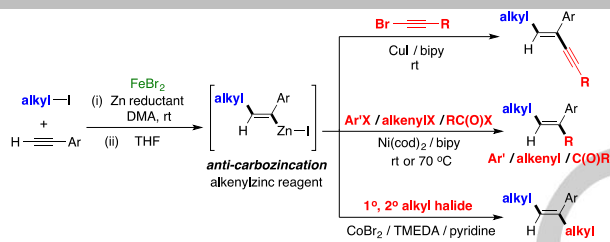
Chi Wai Cheung and Xile Hu*

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Stereoselective Synthesis of Trisubstituted Alkenes via Sequential Iron-Catalyzed Reductive *anti*-Carbozincation of Terminal Alkynes and Base-Metal-Catalyzed Negishi Cross-Coupling