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Synthetic Methods

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

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Abstract: The stereoselective synthesis of trisubstituted alkenes is challenging. Here, we show that an iron-catalyzed *anti*-selective carbozincation of terminal alkynes can be combined with a base-metal-catalyzed cross-coupling to prepare trisubstituted alkenes in a one-pot reaction and with high regio- and stereocontrol. Cu-, Ni-, and Co-based catalytic systems are developed for the coupling of sp-, sp^2-, and sp^3-hybridized carbon electrophiles, respectively. The method encompasses a 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 a distinct stereoselectivity.

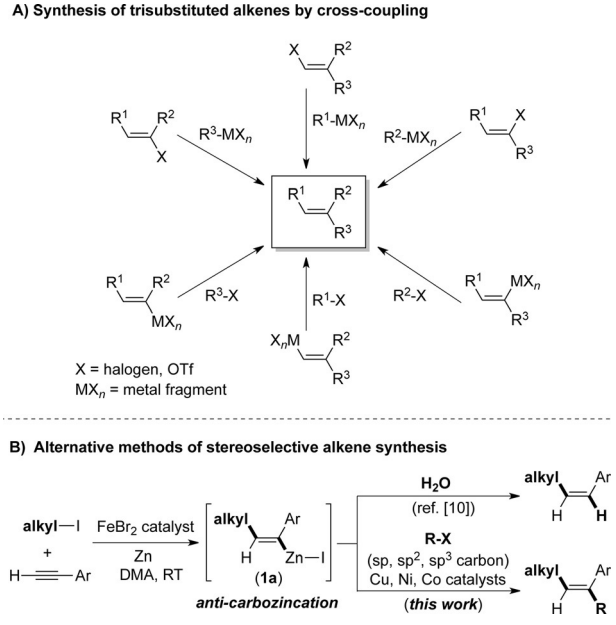
Introduction

The stereoselective synthesis of substituted alkenes is a long-standing 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 by using direct metal insertion or halogen/metal exchange.[3h,5] Alternatively, they can be prepared from alkynes by transition-metal-catalyzed carbozincation of alkynes by using organozinc reagents[1,6] or hydrozincation by using hydride sources.[7]

The carbozincation[1,6] and hydrozincation[7] of alkynes are usually *syn*-selective. The *anti*-carbozincation of alkynes is rarely reported and in limited cases, is achieved by 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 regiocontrol relies on the use of symmetric alkynes or directing groups.[6–8]

We recently reported an iron-catalyzed *Z*-selective olefin synthesis through the reductive coupling of alkyl halides with terminal aryl alkynes by using zinc as reductant (Scheme 1 B).[10] A mechanistic study suggested that the alkenylzinc intermediate **1 a** was formed through Fe-catalyzed *anti*-selective carbozinca-



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

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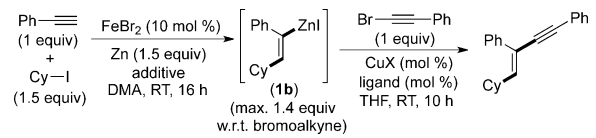
tion of the alkyne with alkyl halides. Herein, we show that by using suitable base metal catalysts (Cu, Ni, Co), such in-situ-formed alkenylzinc intermediates can be coupled to a wide range of sp-, sp^2-, and sp^3-hybridized carbon electrophiles to afford an array of trisubstituted alkenes[11] with high stereochemical control (Scheme 1B).

Results and Discussion

The cross-coupling of *Z*-alkenylzinc intermediates with bromoalkynes was first studied.[12] Initially, the alkenylzinc reagent **1b** was prepared by using the procedure optimized for *Z*-olefin synthesis.[10] Because Cu was used as a catalyst in the cross-coupling reactions of cyclic alkenylzinc reagents with bromoalkynes,[13,14] we have chosen a Cu catalyst for the analogous coupling of acyclic alkenylzinc reagents. In the presence of CuCl (20 mol%) and the 2,2′-dibypridyl ligand (bipy, 20 mol%), compound **1b** (in excess, up to 1.4 equiv assuming a 100% yield for the carbozincation) reacted with (bromoethynyl)benzene in tetrahydrofuran at room temperature to give the (*E*)-enyne product in 49% GC yield (Table 1, entry 1). The ligand bipy was superior than other nitrogen- and phosphine-type ligands (Table 1, entries 2–4). When iodotrimethylsilane (TMSI, 10 mol%) instead of iodine (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 the CuCl could be lowered to 15 mol% without a diminishment of the 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).

Table 1. Optimization of the sequential Fe-catalyzed *anti*-carbozincation of alkynes and the Cu-catalyzed alkenyl–alkynyl Negishi coupling.[a]



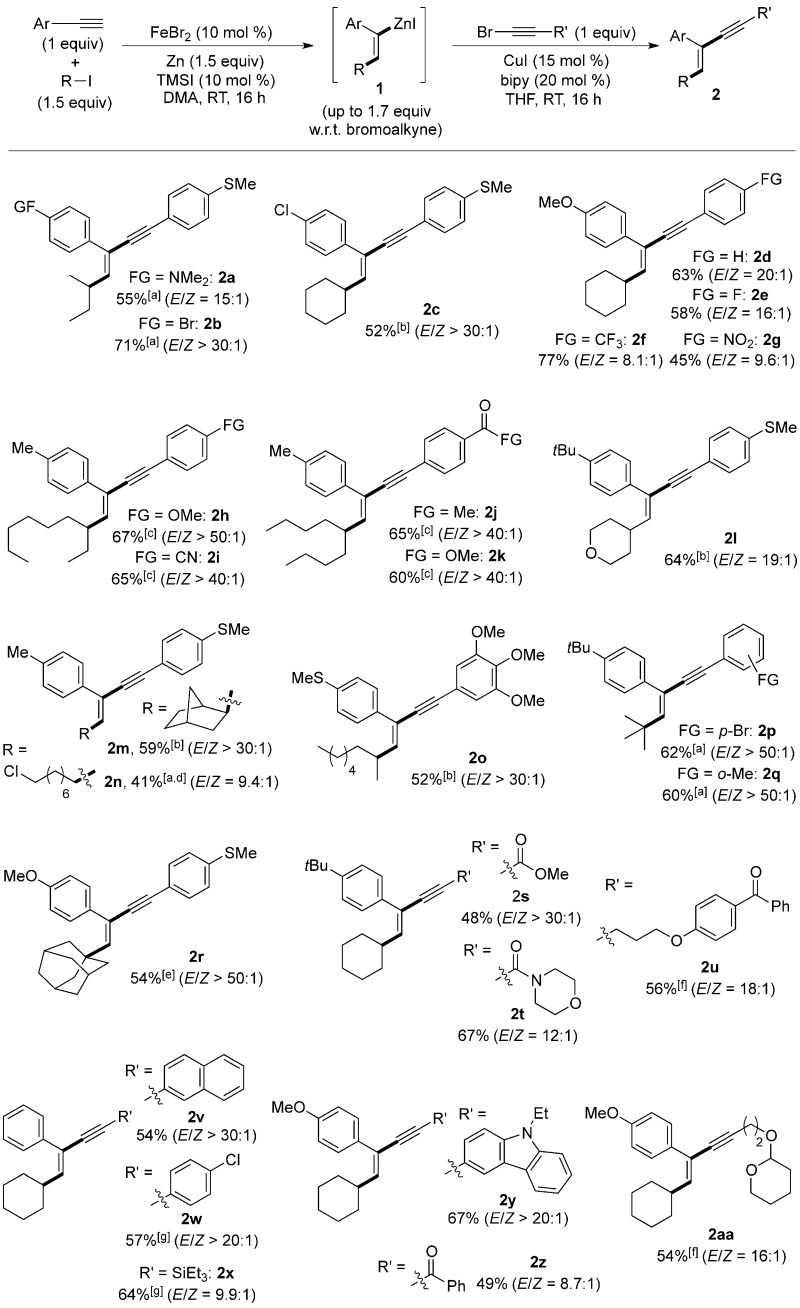
Entry	Additive ([mol%])	CuX ([mol%])	Ligand ([mol%])	GC yield [%]
1	I_2 (2)	CuCl (20)	bipy (20)	49
2	I_2 (2)	CuCl (20)	phenanthroline (20)	46
3	I_2 (2)	CuCl (20)	TMEDA (20)	48
4	I_2 (2)	CuCl (20)	dppe[b] (20)	28
5	TMSI (10)	CuCl (20)	bipy (20)	87
6	TMSI (10)	CuCl (15)	bipy (20)	91
7	TMSI (10)	CuI (15)	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] The reaction was based on 0.1 mmol of bromoalkyne. The GC yield was determined by using *n*-dodecane as an internal standard. [b] Dppe = 1,2-bis(diphenylphosphino)ethane.

However, the yields dropped significantly when a lower loading of the bipy ligand (15 mol%) or CuI (10 mol%) was used (Table 1, entries 11 and 12). Without CuI, the yield was much lower (Table 1, entry 13).

The optimized conditions given in Table 1 were then applied for the cross-coupling of a large number of alkenylzinc reagents with bromoalkynes (Scheme 2).[16] Terminal aryl alkynes containing electron-rich aryl groups, that is, compounds **2a**, **2d**, **2h**, **2l**, **2o**, and **2q**, electron-deficient aryl groups, that is compounds **2b** and **2c** and electron-neutral aryl groups, that is, compounds **2v–2x**, could be used to generate the corresponding alkenylzinc reagents for subsequent coupling processes. Acyclic (i.e., compounds **2a**, **2h**, **2j**, and **2o**) and cyclic secondary alkyl iodides (compounds **2c**, **2l**, and **2m**), as well as tertiary alkyl iodides (compounds **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 the enyne (compound **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 groups, that is, compounds **2a**, **2h**, **2o** and **2q**, and electron-withdrawing groups, that is, compounds **2b**, **2e–2g**, **2i–2k**, and **2p**, at different positions could be coupled in good yields. Moreover, the coupling reactions tolerated propiolate (compound **2s**), propiolamide (compound **2t**), phenylpropynone moieties (compound **2z**), as well as functionalized alkyl (compounds **2u** and **2aa**) and carbazole groups (compound **2y**). Base-sensitive groups, including nitro (compound **2g**), nitrile (compound **2i**), keto (compounds **2j**, **2u**, and **2z**), ester (compounds **2k** and **2s**) and amide groups (compound **2t**), were tolerated as well. Significantly, the stereoselectivity of the products was high to excellent ($E/Z \geq 9{:}1$ to $E/Z > 50{:}1$). To the best of our knowledge, the 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.

The cross-coupling of alkenylzinc reagents with aryl halides was then studied by using ethyl 4-bromobenzoate as a test substrate (Table 2).[12] As Ni catalysts were commonly utilized in the Negishi couplings of arylzinc reagents with aryl and alkenyl halides,[3i,18] we have chosen a Ni catalyst for the analogous coupling of the 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 compound **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 compound **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} pre-catalysts (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).

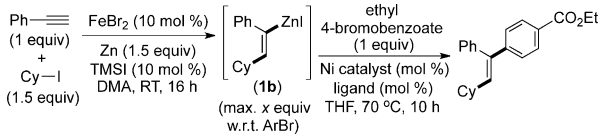


Scheme 2. Scope of the Cu-catalyzed alkenyl–alkynyl Negishi coupling of alkenylzinc reagents generated in situ from the Fe-catalyzed anti-carbozincation of terminal alkynes. The conditions were described in detail in the the Supporting Information. The yields of the isolated product are shown. [a] Alkyl 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] The 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), and TMSI (30 mol%) were used in the first step. [f] CuI (25 mol%), bipy (35 mol%). [g] CuI (20 mol%), bipy (30 mol%). DMA = *N*,*N*-dimethylacetamide, cod = 1,5-cyclooctadiene, Cy = cyclohexyl, Ac = acetyl, *t*Bu = *tert*-butyl.

The scope of this Ni-catalyzed alkenyl–aryl Negishi coupling was studied by using the optimized conditions (Scheme 3).[16] Both aryl bromides and iodides with varying electronics reacted smoothly to give the corresponding α-arylated styrenes in high yields (compounds **2a–2c**, **3e–3i**, and **3k**). Heteroaryl bromides, including bromothiophenes (compounds **3d** and **3j**), bromopyridines (compound **3m**) and bromoquionlines (compound **3n**), as well as aryl triflate (compound **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 (compounds **3o–3r**). Moreover, the coupling protocol could be applied for acylation. Thus, carbamyl (compound **3t**) and aroyl chlorides (compounds **3u–3w**) reacted at room temperature to generate the corresponding enone derivatives. Notably, a variety of base-sensitive functional groups, including ester (compounds **3a**, **3c**, **3d**, and **3k**), amide (compounds **3f** and **3t**), nitrile (compound **3g**) and keto groups (compounds **3h**, **3l**, **3s**, and **3u–3w**), were tolerated under the reaction conditions. The coupling of the alkenylzinc reagents with sp^2-hybridized carbon halides was stereospecific and only single stereoisomers were formed. As a result, compound **3l**, which exhibits an *anti*-proliferative activity toward a number of tumor cell lines,[20] was readily prepared by using this protocol, without the problem of separation from a mixture of isomeric products as previously described.

Finally, the cross-coupling of the alkenylzinc reagents with alkyl halides was also studied.[12] As a Co catalyst was applied in the cross-coupling reactions of arylzinc reagents with alkyl halides,[21,22] we have chosen a Co catalyst for the analogous coupling of the alkenylzinc reagents. The use of $CoBr_2$ (30 mol%) in conjunction with two equivalents of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was found to promote the reaction of compound **1b** with the secondary alkyl iodide 2-iodooctane, affording α-2-octyl-β-cyclohexylstyrene in 57% GC yield (Table 3, entry 1). In contrast, the use of derivatives of TMEDA, that is, *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA) and *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (TEEDA), led to significant drops in the yield (Table 3, entries 2 and 3). The same yield (i.e., 57%) was obtained when

Table 2. Optimization of the sequential Fe-catalyzed *anti*-carbozincation of alkynes and the Ni-catalyzed Negishi coupling with sp^2-hybridized carbon electrophiles.[a]

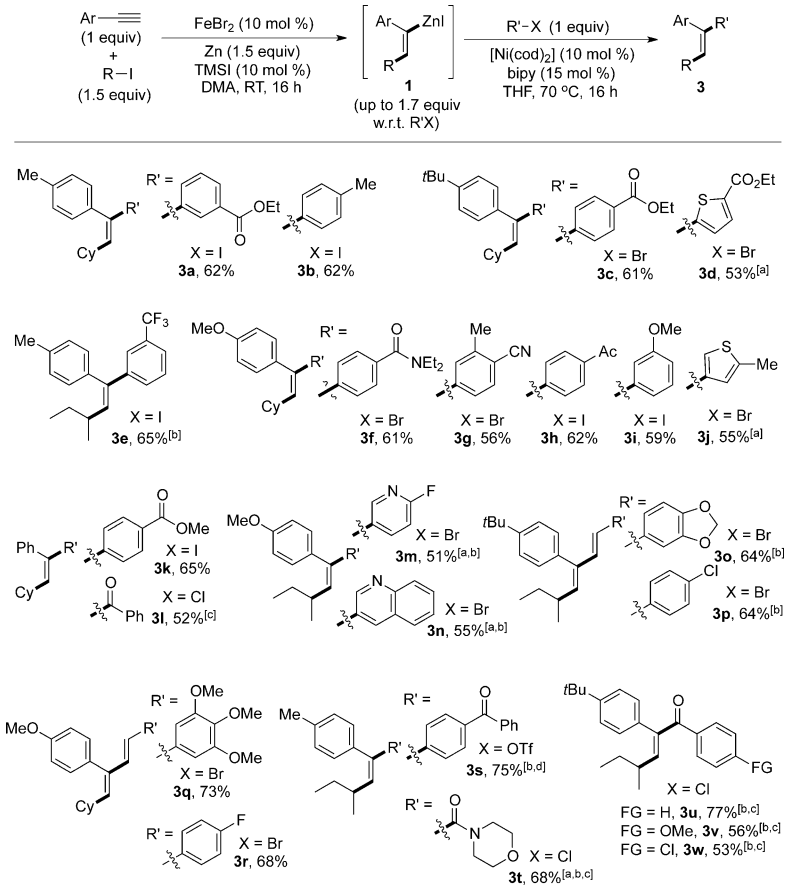


Entry	Alkenyl-ZnI [equiv]	Ni catalyst ([mol%])	Ligand ([mol%])	GC yield [%]
1	1.25	$[Ni(cod)_2]$ (20)	dppe (20)	9
2	1.25	$[Ni(cod)_2]$ (20)	dppf[b] (20)	16
3	1.25	$[Ni(cod)_2]$ (20)	PPh_3 (80)	22
4	1.25	$[Ni(cod)_2]$ (20)	xantphos (20)	11
5	1.25	$[Ni(cod)_2]$ (20)	bipy (20)	64
6	1.25	$[Ni(cod)_2]$ (20)	phen[c] (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	$[NiBr_2(diglyme)]$[d] (10)	bipy (10)	27
13	1.4	$[Ni(cod)_2]$ (0)	bipy (15)	18

[a] The reaction was based on 0.1 mmol of bromoalkyne. The GC yield was determined by using *n*-dodecane as an internal standard. [b] Dppf = 1,1′-bis(diphenylphosphino)ferrocene. [c] Phen = 1,10-phenantroline. [d] Diglyme = bis(2-methoxyethyl) ether.

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 to be beneficial, giving the product in 67% yield (Table 3, entry 8). By increasing the loading of compound **1b** to 1.7 equivalents with respect to 2-iodooctane, a yield of 76% was obtained (Table 3, entry 9). Under these conditions, a primary alkyl iodide, that is, 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).

The scope of this alkenyl–alkyl coupling was then explored (Scheme 4). A variety of acyclic and cyclic, non-activated secondary alkyl iodides could be coupled in reasonable yields (compounds **4a–4c**, **4g**, and **4h**). An activated secondary benzyl bromide, that is, 1-bromo-1-phenylethane, also reacted to give the desired product (compound **4d**). Primary alkyl iodides bearing both hydrocarbon skeletons (compounds **4e** and **4k**) and functional groups such as chloro (compound **4f**), olefin (compound **4i**) and ester groups (compound **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 (compounds **4l** and **4m**), suggesting a radical pathway for the alkyl iodide cleavage process.[3e] High isomeric ratios ($Z/E \geq 7:1$) were generally observed in the couplings with alkyl halides. Although there is room for improvement in the yields, this protocol represents, to the best of our knowledge, the first Co-catalyzed coupling of alkenylzinc reagents with non-activated alkyl halides.[21]

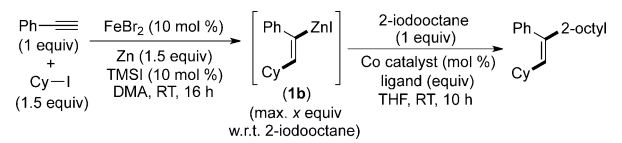


Scheme 3. Scope of Ni-catalyzed Negishi coupling of sp^2-carbon electrophiles with *in-situ* formed alkenylzinc reagents. The conditions were described in detail in the SI. Isolated yields were shown. In all products, the ratios of major to minor isomer were more than 50:1. [a] $Ni(cod)_2$ (15 mol%), 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.

Conclusion

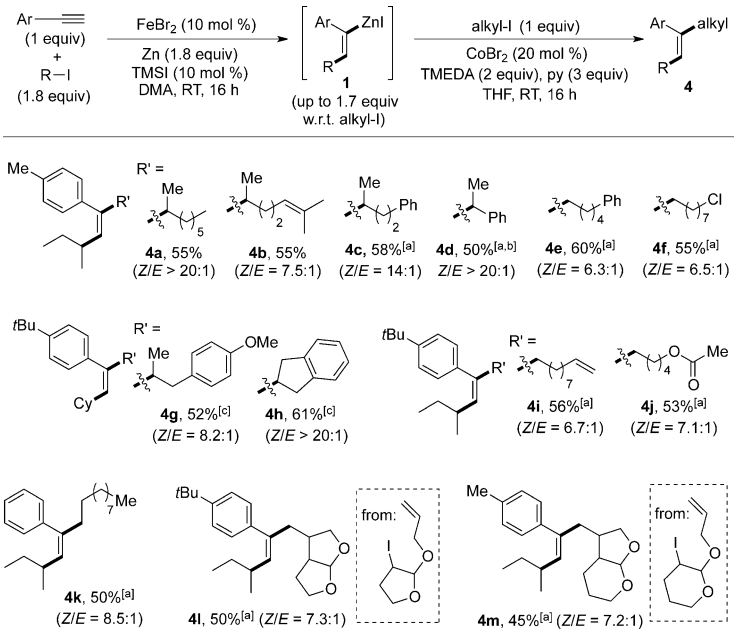
In conclusion, by combining Fe-catalyzed *anti*-carbozincation of alkynes with base-metal-catalyzed Neigishi coupling, we have developed an alternative and general method for the stereoselective synthesis of trisubstituted alkenes.[23] The method employs catalysts made of base metals and readily available reagents, avoiding pre-made organometallic reagents that are used in con-

Table 3. Optimization of the sequential Fe-catalyzed *anti*-carbozincation of alkynes and the Co-catalyzed Negishi-alkyl coupling.[a]



Entry	Alkenyl-ZnI ([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[e] (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] The reaction was based on 0.1 mmol of bromoalkyne. The GC yield was determined by using *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. [e] Py = pyridine.



Scheme 4. Scope of the Co-catalyzed alkenyl–alkyl Negishi coupling. The conditions were described in detail in the Supporting Information. Yields of the isolated products are shown. [a] Approximately 1.5 equivalents of the alkenylzinc reagent were 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.

ventional carbometalation reactions. The method has a large substrate scope and a high group tolerance. The high stereoselectivity and stereospecifity, as well as an unusual *anti*-selectivity for the carbozincation, would make the method an attractive tool for stereoselective organic synthesis.

Keywords: carbozincation · catalysis · cross-coupling · iron · olefin synthesis · stereoselective

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