

Nickel-Catalyzed Three-Component Domino Reactions of Aryl Grignard Reagents, Alkynes, and Aryl Halides Producing Tetrasubstituted Alkenes

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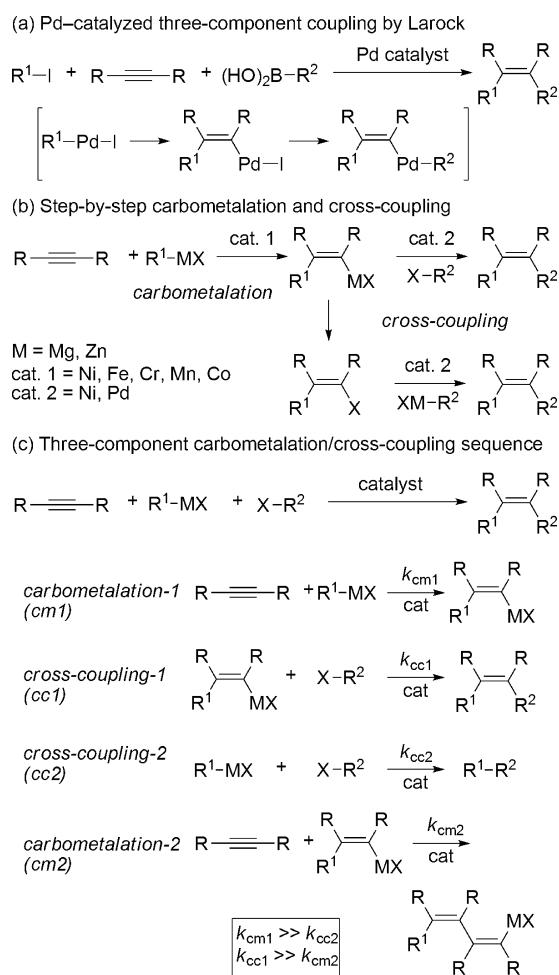
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S Supporting Information

ABSTRACT: Three-component reaction of aryl Grignard reagents, alkynes, and aryl halides in the presence of 1 mol % of NiCl₂ proceeded sequentially through carbomagnesiation of the alkyne followed by cross-coupling of the resulting alkenyl Grignard reagent with aryl halide to give tetrasubstituted alkenes in high yields.

Transition-metal-catalyzed multicomponent domino and tandem reactions have been powerful tools for constructing complex molecules in a single flask.¹ One representative reaction is the Pd-catalyzed three-component reaction, reported by Larock, of internal alkynes, aryl iodides, and arylboronic acids producing tetrasubstituted alkenes.^{2,3} The reaction proceeds through an alkenylpalladium species as a key intermediate, which is formed by oxidative addition of aryl iodide to Pd(0) followed by arylpalladation of alkyne. It reacts with arylboronic acid to give the tetrasubstituted alkene through reductive elimination (Scheme 1a).^{4,5} Another synthesis scheme to produce tetrasubstituted alkenes from alkynes, aryl halides, and arylmetal reagents can be via alkenyl metals generated by carbometalation of alkynes. There have been several reports on the addition of organomagnesium⁶ or -zinc⁷ reagents to unfunctionalized alkynes forming the corresponding alkenyl metals, catalyzed by transition metal salts or complexes, and these have been subjected to further reactions to produce tetrasubstituted alkenes by taking advantage of their high reactivity.⁸ Scheme 1b illustrates some reactions where the alkenyl metal reagents were used for the next step. Alkenyl Grignard reagents generated by Fe- or Cr-catalyzed carbomagnesiation of alkynes are mixed with organic halides in the presence of a Ni or Pd complex that catalyzes the cross-coupling to give tetrasubstituted alkenes.^{6e,g} Alternatively, the alkenyl metal reagents are converted first into alkenyl iodides and then they are subjected to Ni- or Pd-catalyzed cross-coupling with organometallic reagents.^{7a,f,9} To our knowledge, there have been no reports on the reactions where a mixture of alkyne, organometallic reagent, and organic halide produces a tetrasubstituted alkene by the carbometalation/cross-coupling sequence⁸ (Scheme 1c). The three-component reaction should consist of two sequential reactions: carbometalation generating alkenyl metal species (*cm1*) and its cross-coupling with organic halide (*cc1*). One serious problem in a three-component reaction would be a possible side reaction where R¹-MX reacts with organic halide X-R² (*cc2*) before the reaction

Scheme 1. Three-Component Reactions of Organometallics, Alkynes, and Aryl Halides Producing Tetrasubstituted Alkenes



with alkyne. Another problem is the carbometalation of alkyne with the alkenyl metal generating dienyln metal species (*cm2*). To realize the three-component reaction, *cm1* must be much faster

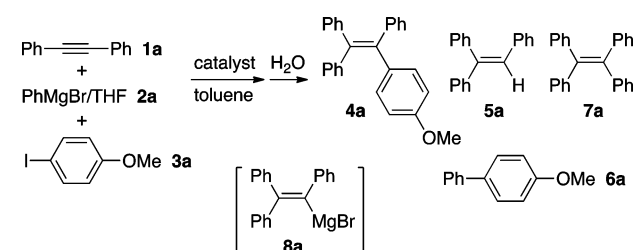
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than the unfavorable competing cross-coupling (*cc2*), and *cc1* must be much faster than *cm2*.

During our studies on the NiCl₂-catalyzed arylmagnesiumation of arylalkynes generating alkenylmagnesium reagents,^{6b} we found that the three-component domino reaction of aryl Grignard reagents, alkynes, and aryl halides is also efficiently catalyzed by NiCl₂. Table 1 summarizes the results obtained for the reaction

Table 1. Three-Component Reaction of Diphenylacetylene (1a), Phenylmagnesium Bromide (2a), and 4-Iodoanisole (3a)^a



entry	catalyst	yield 4a	reconvd 1a	yield 5a	yield 6a ^b	yield 7a
1	NiCl ₂	82	0	5	11	5
2 ^c	NiCl ₂	51	0	12	17	9
3 ^d	NiCl ₂	77	0	8	13	7
4 ^e	NiCl ₂	0	98	<1	0	0
5 ^f	NiCl ₂	82	0	6	12	3
6	NiCl ₂ ·6H ₂ O	81	0	7	11	5
7	Ni(acac) ₂	75	0	8	15	3
8	Ni(OAc) ₂ ·4H ₂ O	62	0	15	27	3
9	NiCl ₂ (PPh ₃) ₂	33	25	18	53	9
10 ^c	NiCl ₂ (PPh ₃) ₂	32	55	2	55	0
11	NiCl ₂ (dppe)	30	10	55	15	3
12	PdCl ₂ (PPh ₃) ₂	0	88	9	70	0
13 ^g	Fe(acac) ₃ /IPr ^h	0	40	38	3	2
14 ⁱ	MnCl ₂	5	52	33	5	2
15 ^j	NiCl ₂	81	0	5	15	6

^aTo a mixture of **1a** (0.50 mmol), **3a** (0.60 mmol), and catalyst (0.005 mmol, 1 mol %) in toluene (2.0 mL) was added PhMgBr (**2a**: 1.0 M in THF, 0.60 mL, 0.60 mmol), and the mixture was stirred under N₂ at 30 °C for 2 h. Values given are percent isolated yield. ^bBased on the amount of **3a** used. ^cPhMgBr (**2a**: 1.0 M in THF, 0.60 mL) + THF (2.0 mL). ^dPhMgBr (**2a**: 1.0 M in THF, 0.60 mL) + Et₂O (2.0 mL). ^ePhMgBr (**2a**: 1.0 M in Et₂O, 0.60 mL) + toluene (2.0 mL). ^fPhMgBr (**2a**: 1.5 M in Et₂O, 0.40 mL) + toluene (2.0 mL) + THF (0.20 mL). ^gFe(acac)₃ (5 mol %) and IPr (20 mol %) at 60 °C for 16 h. ^hIPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. ⁱMnCl₂ (10 mol %) at 100 °C for 16 h. ^jThe reaction was scaled up 10-fold.

of diphenylacetylene (**1a**) with phenylmagnesium bromide (**2a**) and 4-iodoanisole (**3a**) in the presence of transition metal salts and complexes that have been reported to catalyze the carbomagnesiumation and/or cross-coupling reactions. The highest selectivity in forming the tetrasubstituted alkene was obtained with NiCl₂ as a catalyst in a THF/toluene mixed solvent. Thus, to a mixture of **1a** (0.50 mmol), **3a** (0.60 mmol), and NiCl₂ (0.005 mmol, 1 mol %) in toluene (2.0 mL), was added PhMgBr/THF (**2a**, 0.60 mL of 1.0 M THF solution, 0.60 mmol), and the mixture was stirred at 30 °C for 2 h (entry 1). Aqueous workup gave 82% yield of the three-component coupling product **4a**. Formation of a minor amount of triphenylethene (**5a**, 5%) and tetraphenylethene (**7a**, 5%), together with biaryl **6a** (11%), was also observed. It is likely that **5a** is formed by hydrolysis of **8a** and

that **7a** is formed by cross-coupling of **8a** with phenyl iodide that is generated by the Mg/I exchange reaction.¹⁰ No 1,3-dienes, which would be formed by the addition of **8a** to **1a**, were detected.¹¹

The toluene/THF mixed-solvent system is important for high selectivity of **4a**. Using all THF gave **4a** in only 51% yield, with a greater amount of the side products (entry 2). The yield of **4a** was 77% using diethyl ether in place of toluene as a diluting solvent (entry 3). Interestingly, arylmagnesiumation or cross-coupling did not take place with **2a** in diethyl ether, with starting **1a** being recovered intact (entry 4). Addition of a small amount of THF to the toluene/diethyl ether mixed-solvent system gave essentially the same result as that of toluene/THF (entry 5). NiCl₂·6H₂O catalyzed the three-component reaction as well as NiCl₂ to give **4a** in a comparable yield (81%, entry 6). Because of its easy handling, NiCl₂·6H₂O was used as one of the standard conditions for the present study (vide infra). Other Ni salts, Ni(acac)₂ and Ni(OAc)₂·4H₂O, also catalyzed the reaction, but the yield of **4a** was a little lower (entries 7 and 8). NiCl₂(PPh₃)₂, known to catalyze both cross-coupling of Grignard reagents¹² and arylmagnesiumation of alkynes,^{6a} gave **6a** as a main product together with a minor amount of three-component coupling product **4a** in both THF/toluene and Et₂O/toluene (entries 9 and 10). PdCl₂(PPh₃)₂ did not catalyze the formation of 3-component coupling product **4a** at all, whereas **6a** was formed at a high yield (70%, entry 12). Reactions in the presence of Fe(acac)₃/IPr (entry 13) and MnCl₂ (entry 14), both of which have been reported to catalyze arylmagnesiumation,^{6c,e} either did not produce **4a** at all or gave **4a** in a very low yield, respectively, although phenylmagnesiumation proceeded to some extent. The present system can be scaled up 10-fold without difficulty (entry 15, **4a** in 81% yield).

By monitoring the reaction progress of **1a**, **2a**, and **3a** in the presence of 1 mol % NiCl₂ (Table 1, entry 1), we gained substantial information on the reaction mechanism (Figure 1). The most significant feature is that phenylmagnesiumation of **1a** to form **8a** is very fast. Within 10 min, more than 70% of **1a** is converted into **8a**, and in 20 min all **1a** is consumed. Second, the cross-coupling of **8a** with **3a**, giving final product **4a**, is slow

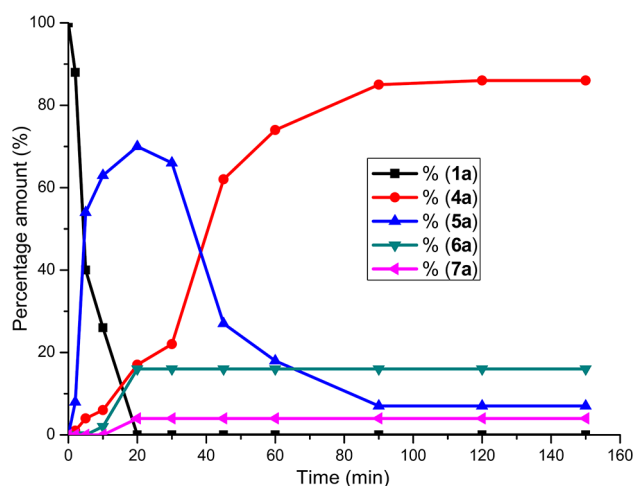
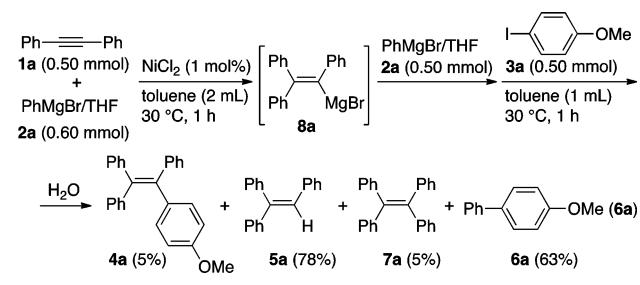


Figure 1. Time-dependent percentage of **1a**, **4a**, **5a**, **6a**, and **7a** in the reaction of **1a** (0.50 mmol), **2a** (0.60 mmol), and **3a** (0.60 mmol) in the presence of NiCl₂ (1 mol %) in toluene (2.0 mL) at 30 °C (Table 1, entry 1). Reaction was quenched by addition of H₂O, and organic layer was analyzed by GC-MS using hexadecane as an internal standard. The amount of **5a** should correspond to that of alkenylmagnesium **8a**.

compared with phenylmagnesium of **1a**. We observed that **8a** was gradually converted into cross-coupling product **4a** over 90 min. Third, the cross-coupling of **2a** with **3a** giving **6a** took place in an initial stage. The yield of **6a** was 16% at 20 min and remained thus until the end of the reaction. This is ascribed to the fast consumption (<20 min) of all of **2a**, mainly by the phenylmagnesium of **1a** and partly by the cross-coupling with **3a**. Furthermore, **7a** formed between **8a** and phenyl iodide (vide supra) can be detected after 20 min, and the yield of **7a** remained 5% over the course of the reaction.

A competition reaction (Scheme 2) demonstrates that **2a** is more reactive than **8a** toward the Ni-catalyzed cross-coupling

Scheme 2. Competition between Alkenylmagnesium **8a** and PhMgBr (**2a**) in NiCl₂-Catalyzed Cross-Coupling



with **3a** under the present conditions. Thus, to the solution of **8a** generated by the NiCl₂-catalyzed phenylmagnesium of **1a**, an equivalent amount of PhMgBr/THF **2a** was added, and the resulting mixture of **8a** and **2a**, containing the Ni catalyst, was allowed to react with **3a**. Aqueous workup gave 78% yield of **5a** and 63% of **6a** with a minor amount (5%) of **4a** and **7a**.

The high selectivity in giving the three-component arylmagnesium/cross-coupling product is mainly ascribed to the very fast arylmagnesium of **1a** with **2a** in the presence of NiCl₂ catalyst (Scheme 1, *cm1*). Although the cross-coupling of the resulting alkenylmagnesium reagent **8a** with **3a** to form **4a** (*cc1*) is slower than the cross-coupling of **2a** with aryl iodide (*cc2*), most of **2a** is first consumed by the phenylmagnesium of **1a**; as a result, only a small amount of the unreacted **2a** participates in the cross-coupling with **3a**. Under the present conditions, the carbomagnesium of **1a** with **8a** which would generate dienyilmagnesium species (*cm2*) is not observed.

The scope of the diarylacetylenes **1**, arylmagnesium bromides **2**, and aryl halides **3** in the three-component domino reaction is summarized in Table 2. This method applies well to **2** and **3** with an electron-donating or -withdrawing group on the phenyl ring at different positions. The aryl iodides with a substituent in the para position gave higher yields than those in the ortho or meta position (entries 1–5). The electron-donating substituent on the aryl iodides gave a higher yield of **4** than an electron-withdrawing substituent (entries 3 and 4). Similar electronic and steric effects were also observed for aryl Grignards. Aryl Grignard with a methyl group in the para position gave as high as 83% yield (entry 8), but the *ortho*-methyl gave **4** in 60% yield at higher temperature (entry 10). Diarylacetylenes with an electron-rich substituent in the meta or para position produced tetrasubstituted olefin only after longer reaction time (16 h, entries 11–12). The reaction also works well with aryl bromides at an elevated temperature and after a longer reaction time (entries 13–14). High *Z* selectivity was observed in entries 15 and 16, which demonstrates that the cross-coupling of alkenylmagnesium with aryl iodides proceeds with retention of

Table 2. Reaction of Diarylacetylenes with Aryl Iodides and the Grignard Reagents^a

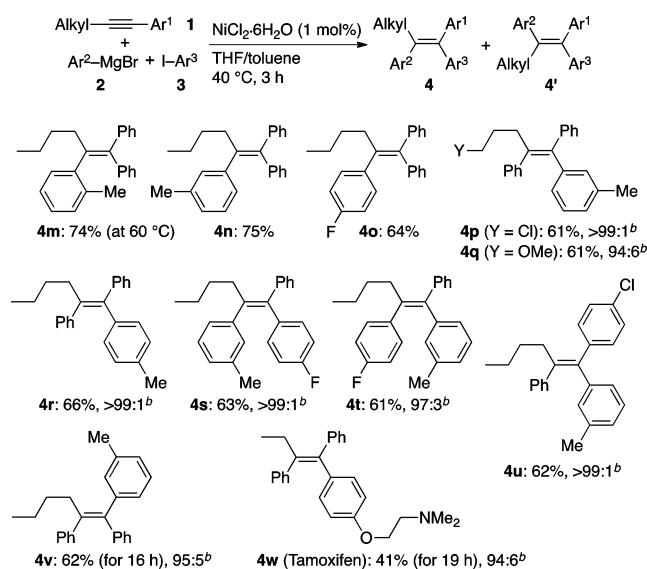
$\text{Ar}^1\text{—C}\equiv\text{C—Ar}^2 + \text{Ar}^3\text{—MgBr} + \text{X—Ar}^3 \xrightarrow[\text{THF/toluene, 30 }^\circ\text{C, 2 h}]{\text{NiCl}_2\cdot 6\text{H}_2\text{O (1 mol\%)}}$				$\text{Ar}^1\text{—C}=\text{C—Ar}^3$
entry	Ar ¹	Ar ²	Ar ³ -X	yield (%) ^b
1	Ph	Ph	Ph-I	77 (4b)
2	Ph	Ph	3-MeC ₆ H ₄ -I	71 (4c)
3	Ph	Ph	4-MeC ₆ H ₄ -I	78 (4d)
4	Ph	Ph	4-FC ₆ H ₄ -I	64 (4e)
5	Ph	Ph	1-naphthyl-I	65 (4f)
6	Ph	4-MeOC ₆ H ₄	Ph-I	64 (4a)
7	Ph	3-MeC ₆ H ₄	Ph-I	64 (4c)
8	Ph	4-MeC ₆ H ₄	Ph-I	83 (4d)
9 ^c	Ph	4-FC ₆ H ₄	Ph-I	62 (4e)
10 ^d	Ph	2-MeC ₆ H ₄	Ph-I	60 (4g)
11 ^e	3-MeC ₆ H ₄	Ph	3-MeC ₆ H ₄ -I	70 (4h)
12 ^e	4-MeC ₆ H ₄	Ph	4-MeC ₆ H ₄ -I	64 (4i)
13 ^{d,e}	Ph	Ph	Ph-Br	62 (4b)
14 ^{d,e}	Ph	Ph	4-MeC ₆ H ₄ -Br	61 (4d)
15 ^f	Ph	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄ -I	73 ^g (4j)
16	Ph	4-FC ₆ H ₄	4-MeOC ₆ H ₄ -I	66 ^h (4k)
17 ^{c,d}	2-MeC ₆ H ₄ , Ph	2-MeC ₆ H ₄	Ph-I	51 ⁱ (4l)

^aAll reactions were carried out with diarylacetylene (0.50 mmol), Ar² MgBr/THF (0.60 mmol), Ar³X (0.60 mmol), and NiCl₂·6H₂O (0.005 mmol) in toluene (2.0 mL) under N₂ at 30 °C for 2 h. ^bIsolated yield. ^cFor 6 h. ^dAt 60 °C. ^eFor 16 h. ^fAt 40 °C. ^g*Z*/*E* = 93:7. ^h*Z*/*E* = 88:12. ⁱMixture of three isomers in a ratio of 70:25:5; 2-MeC₆H₄MgBr (2.0 M in Et₂O, 0.30 mL) + toluene (2.0 mL) + THF (0.30 mL).

olefin geometry. In the reaction of unsymmetrically substituted diarylacetylene (entry 17), the arylmagnesium step is not highly regioselective to give a mixture of isomers.

The domino reaction of alkyl(aryl)acetylenes also proceeded successfully (Scheme 3). The regiochemistry is consistent with

Scheme 3. Reaction of Alkyl(aryl)acetylenes with Aryl Iodides and the Grignard Reagents^a



^aAlkyl(aryl)acetylene **1** (0.50 mmol), Ar² MgBr/THF **2** (0.60 mmol), Ar³I **3** (0.60 mmol), and NiCl₂·6H₂O (0.005 mmol) in toluene (2.0 mL). ^bRatio of **4**/**4'**

our previous work on the arylmagnesium where magnesium attaches the aryl-substituted carbon.^{6b} An array of arylmagnesium bromides with electron-rich or -poor substituents reacted with 1-phenyl-1-hexyne and iodobenzene to give tetrasubstituted alkenes **4m,n,o** with exclusive regioselectivity. The aryl iodides with electron-rich and -deficient groups at para or meta position gave corresponding olefins **4r,s,t** with highly stereo- and regioselectivity. The olefin products bearing a chloroalkyl (**4p**) or -aryl (**4u**), methyl ether (**4q**), and an amino group (**4w**, Tamoxifen)¹³ were prepared by the present domino reaction. The molecular structures of **4m,r,t,v** were determined by X-ray single crystal diffraction.

We have studied a three-component domino coupling of internal alkynes with aryl Grignard reagents and aryl iodides, which is catalyzed by a simple Ni salt, NiCl₂. Monitoring the reaction progress revealed that the arylmagnesium of alkyne generating alkenylmagnesium species is extremely fast, which realizes the selective three-component coupling with a minimal amount of side products. This Ni-catalyzed reaction provides us with a new operationally simple method of synthesizing tetrasubstituted alkenes with high stereo- and regioselectivity.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, spectra, and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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