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Preparation of Organozinc Reagents via Catalyst Controlled Three-Component Coupling between Alkyne, Iodoarene, and Bis(iodozincio)methane

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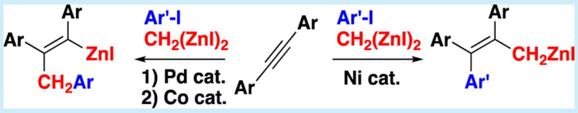
Ⓢ *Supporting Information*

ABSTRACT: Three-component coupling between an alkyne, iodoarene, and bis(iodozincio)methane yields allylic zinc with a tetrasubstituted alkene moiety in the presence of a nickel catalyst. The reaction proceeds via aryl nickelation of the alkyne and subsequent cross-coupling with bis(iodozincio)methane. Meanwhile, the same combination in the presence of a palladium and cobalt catalyst gives tetrasubstituted alkenylzinc. The reaction proceeds via a palladium-catalyzed cross-coupling of iodoarene with bis(iodozincio)methane followed by a cobalt-catalyzed benzylzincation of alkyne.

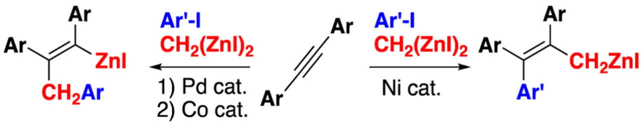


Although an organozinc reagent was the first practical carbanion equivalent, today Grignard reagent is more commonly used to add a C-nucleophile into a carbonyl compound.[1] Regardless, organozinc has been studied for certain highly selective molecular transformations because it possesses a high chemoselectivity in the reaction as well as a high functional group tolerability.[2] One example is asymmetric inductions such as the Soai reaction.[3]

Because highly functionalized organozinc reagents are still useful, an efficient method for their preparation is still being investigated. The presence of LiCl dramatically improves the classical reduction of organic halides with zinc metal from the viewpoint of efficiency and functional group tolerability;[4] higher order zincates are also good reagents to afford highly functionalized arylzinc.[5] The transition metal catalyzed carbo- and hydrozincation of alkynes gives the alkenylzinc species via a C−C bond forming reaction.[6] We have also developed a new homologation strategy with chemoselectivity to prepare functionalized allyl-, homoallyl-, and arylmethylzinc species by the cross-coupling of bis(iodozincio)methane (**1**) with the corresponding organic halides.[7]

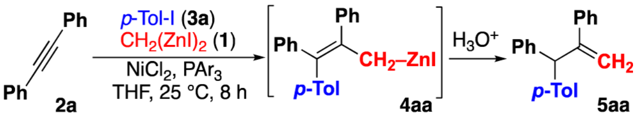
In this paper, we show a novel method to prepare organozinc species by a three-component coupling of alkyne, iodoarene, and **1** in the presence of a transition-metal catalyst.[8] As shown in Scheme 1, the reaction in the presence of a nickel catalyst gives allylic zinc; the predominant reactions are arylnickelation of alkyne followed by cross-coupling with **1**.[9] Employing a palladium catalyst instead of a nickel one results in the cross-coupling between iodoarene and **1** to afford arylmethylzinc iodide,[7c] which can perform arenylmethylmetalation to alkynes in the presence of a cobalt catalyst.[10]

Scheme 1. Catalyst Controlling of Alkyne/Aryl Iodide/Bis(iodozincio)methane Coupling



As shown in Table 1, various combinations of NiCl$_2$ and arylphosphine ligands were examined for the three-component coupling between diphenylacetylene (**2a**), *p*-iodotoluene (**3a**), and **1**. The formed allylic zinc **4aa** *in situ* is protonated by 1 M HClaq and isolated as 2,3-diphenyl-3-(*p*-tolyl)-1-propene **5aa**.

Table 1. Ligand for Nickel-Catalyzed Diphenyl Acetylene/*p*-Iodotoluene/Bis(iodozincio)methane Coupling[a]



entry	Ar−I	NiCl$_2$ (mol %)	PAr$_3$ (mol %)	product[b] %
1	2.0	10	PPh$_3$ (20)	9
2	2.0	10	P(p-MeOC$_6$H$_4$)$_3$ (20)	5
3	2.0	10	P(p-ClOC$_6$H$_4$)$_3$ (20)	37
4	2.0	10	P(2-furyl)$_3$ (20)	70
5	2.0	10	P(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_3$ (20)	65
6	1.4	10	P(2-furyl)$_3$ (20)	26
7	1.4	10	P(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_3$ (20)	93
8	1.4	5	P(2-furyl)$_3$ (10)	46
9	1.4	5	P(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_3$ (10)	75
10[c]	2.2	2	P(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_3$ (3)	98

[a] **2a** (0.5 mmol) and **1** (0.6 mmol) were used. [b] Isolated yields. [c] 2.0 equiv of **1** (1.0 mmol) were used.

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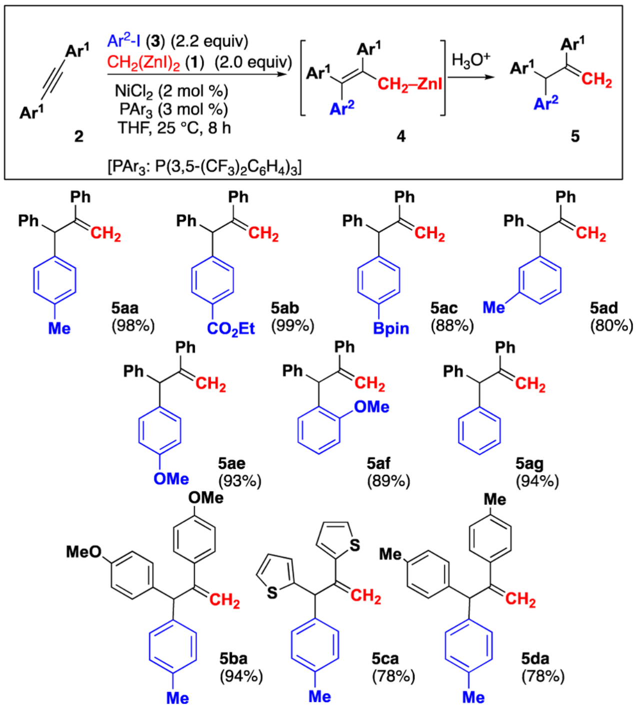
Electron-deficient phosphines give better yields (entries 1−5) for **5aa**. After optimization, using 2 mol % of nickel dichloride and 3 mol % of tris[3,5-bis(trifluoromethyl)phenyl]phosphine yields **5aa** quantitatively (entry10).

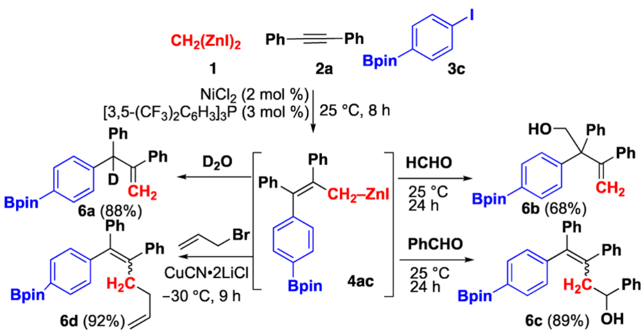
Scheme 2 shows the various allylic zinc species prepared using the nickel-catalyzed three-component coupling. The applicability of various iodoarenes demonstrates the functional group tolerability. For example, ester, Bpin, and methoxy groups remain intact during the transformation.

Scheme 2. Various Allylic Zinc Formation by Nickel-Catalyzed Alkyne/Aryl Iodide/Bis(iodozincio)methane Coupling



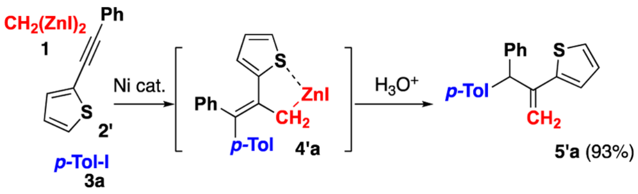
The reaction of the obtained allylic zinc species with various electrophiles was also examined. Allylic zinc **4ac** prepared from diphenyl acetylene (**2a**), p-BpinC$_6$H$_4$I (**3c**), and the dizinc **1** can be treated with various electrophiles (Scheme 3). Treatment of **4ac** with paraformaldehyde gives γ-adduct **6b**, while that with benzaldehyde affords α-adduct **6c**. The regioselective formation of **6b** implies that the σ-metal species **4ac** reacts with formaldehyde at the γ-position to produce the kinetically favored product. The regioselective formation of product **5** in Scheme 2 is also explainable in the same way. The α-adduct **6c** is formed by the isomerization of the γ-adduct that has the more serious steric hindrance compare to **6b** via retro-allylation.[11] The copper-mediated coupling reaction with allyl bromide gives **6d** with α-selectivity. Products **6c** and **6d** are obtained as an E/Z-mixture. These chemoselective processes make the preparation of highly functionalized arylboronic acids possible.

Scheme 3. Reactions of Allylic Zinc with the Bpin Group



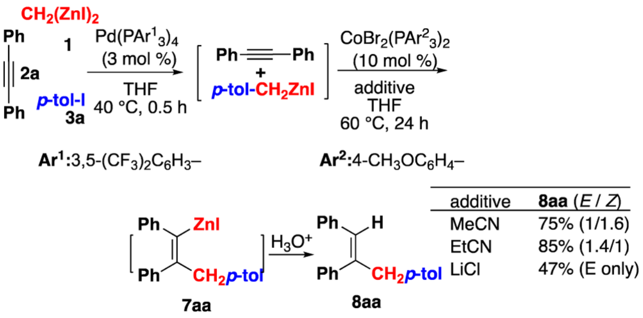
The regioselectivity in the case of unsymmetrical alkynes is low. For example, treatment of p-anisyl 4-trifluoromethyl acetylene and p-iodotoluene (**3a**) with **1** in the presence of a nickel catalyst affords a mixture of regioisomers. Exceptionally, the reaction using 2-(phenylethylnyl)thiophene (**2′**) as the alkyne and **3a** gives corresponding alkene **5′a** selectively. It may be the result of the preferential formation of allylic zinc **4′a**, which is stabilized by the coordination of thiophene to zinc intramolecularly (Scheme 4).[12]

Scheme 4. Regioselective Formation of Allylic Zinc from Unsymmetrical Alkyne 2′



Cross-coupling between iodoarene **3** and **1** proceeds preferentially, even in the presence of alkynes, when employing a palladium catalyst instead of a nickel one, affording arenylmethylzinc as reported previously[7c] (Scheme 5). The addition of a Co catalyst in the presence of a coordinative additive prompts carbozincation to the alkyne to give the alkenylzinc species.[9] The addition of LiCl produces alkenylzinc **7aa** with a high stereoselectivity.

Scheme 5. Additive for the Palladium/Cobalt-Catalyzed Reaction

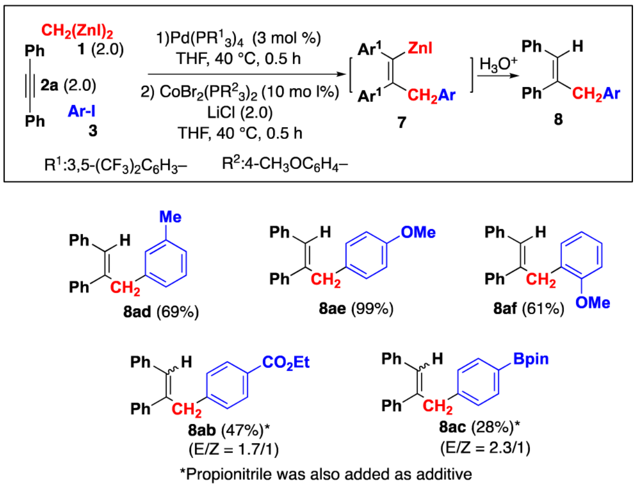


additive	8aa (*E*/*Z*)
MeCN	75% (1/1.6)
EtCN	85% (1.4/1)
LiCl	47% (E only)

Alkenylzinc formation from dizinc **1**, diphenylacetylene (**2a**), and various iodoarenes was examined using the Pd/Ni/LiCl system (Scheme 6). Iodoarenes with an electron-donating substituent such as methyl and methoxy give the corresponding E-alkenylzinc selectively with good yields, while those carrying electron-withdrawing groups retard the Co-catalyzed step. To obtain the products in these cases, EtCN was added as an additive, resulting in a loss of stereoselectivity.

Thus, the three-component coupling between alkyne, aryl iodide, and bis(iodozincio)methane can be sorted based on the catalyst. This method yields various allylzinc and alkenyl zinc products.

Scheme 6. Various Alkenylzinc Formation by Palladium/Cobalt-Catalyzed Reaction



*Propionitrile was also added as additive

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00917.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) Selective reaction of bis(iodozincio)methane (**1**) as a zinciomethylation reagent in the presence of organomonozinc species such as allylic or benzylic zinc might be explained by the higher nucleophlicity of **1**, which benefits to the transmetalation step with the transition metal intermediate.

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(12) The use of aryl alkyne acetylene also gives the adduct **5** as a mixture of regioisomers. The reaction with the terminal alkyne does not proceed.