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Alkenylation of C(sp³)—H Bonds by Zincation/Copper-Catalyzed Cross-Coupling with Iodonium Salts

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Abstract

α -Vinylolation of phosphonates, phosphine oxides, sulfones, sulfonamides, and sulfoxides has been achieved by selective C–H zincation and copper-catalyzed C(sp³)–C(sp²) cross-coupling reaction using vinylphenyliodonium salts. The vinylolation transformation proceeds in high efficiency and stereospecificity under mild reaction conditions. This zincative cross-coupling reaction represents a general alkenylation strategy, which is also applicable for α -alkenylation of esters, amides, and nitriles in the synthesis of β , γ -unsaturated carbonyl compounds.

Graphical Abstract

C(sp³)–H-Funktionalisierung Iodoniumsalze Kupferkatalyse Vinylisierung **General vinylolation**

strategy: α -Vinylolation of phosphonates, phosphine oxides, sulfones, sulfonamides, sulfoxides, and carbonyl derivatives has been achieved effectively by a one-pot C–H zincation and copper-catalyzed C(sp³)–C(sp²) cross-coupling reaction using vinylphenyliodonium salts under mild conditions. ■■ picture had to be simplified ■■

Universelle Vinylierungsstrategie: Die α -Vinylolierung von Phosphonaten, Phosphinoxiden, Sulfonen, Sulfonamiden, Sulfoxiden und Carbonylderivaten gelingt durch eine Ein-Topf-Reaktion aus C-H-Zinkierung und Kupfer-katalysierter C-(sp³)-C(sp²)-Kreuzkupplung unter Verwendung von Vinylphenyliodoniumsalzen unter milden Bedingungen.

Keywords

copper catalysis; iodonium salt; C(sp³)–H functionalization; vinylolation

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Conflict of interest

The authors declare no conflict of interest.

Alkene-containing molecules are ubiquitously desirable targets. Olefins are one of the most important functional groups and have rich and robust chemistry that is integral to organic synthesis and chemical science.^[1] Therefore, the development of effective methods for incorporating this functional group is an important goal. Toward this, great attention has been focused on developing C(sp³)–C(sp²) bond-formation reactions, such as the reactions of alkyl halides,^[2] alkyl organometallic compounds,^[3] carbonyl and imines,^[4] and carboxylic acids.^[5] On the other hand, vinylation of C(sp³)–H bonds represents an appealing direct approach. For example, palladium-catalyzed β-C–H olefination of amides has been achieved by a sophisticated directing-group assisted strategy (Scheme 1a).^[6] An elegant copper-catalyzed α-alkenylation of aldehydes has been reported via the synergy with amine catalysis (Scheme 1b).^[7,8] Alternatively, a deprotonative/transition metal-catalyzed vinylation approach has been elegantly developed via in situ formed carbanion nucleophiles. Examples include α-vinylation of ketones,^[9] nitromethane,^[10] and pyridylmethyl ethers^[11] (Scheme 1c). This deprotonative strategy is attractive without the requirement of directing groups, yet has received success only for relatively acidic C(sp³)–H bonds aforementioned. Nevertheless, in comparison to related arylation reactions, vinylation reactions of C(sp³)–H bonds are underexplored.^[12] With olefins as one of the most useful functional groups, a general and effective alkenylation strategy is greatly desired and valuable.

Here, we report an efficient α-vinylation method for phosphonate, sulfone, sulfoxide, and carbonyl derivatives by a modular C–H zincative/copper-catalyzed C(sp³)–C(sp²) cross-coupling reaction using vinylphenyliodonium salts (Scheme 1d). This approach utilizes Zn(tmp)Cl-mediated selective zincation of various C(sp³)–H bonds, from which the resulting nucleophilic organozinc intermediates could undergo a copper-catalyzed C(sp³)–C(sp²) cross-coupling reaction with vinylphenyliodonium salts. Vinylphenyliodonium salts are an attractive electrophilic vinylation reagent^[7b,8,13] due to their low toxicity, air- and moisture-stability, and high reactivity, despite being less explored than analogous diaryliodonium salts.^[14] In this work, we demonstrate that such a zincative vinylation approach is modular and remarkably effective for a wide scope of C(sp³)–H bonds under mild conditions. The use of chiral zinc base has been explored toward the development of asymmetric vinylation reactions.

We initially chose ethyldiphenylphosphine oxide (**1a**) and *trans*-strenylphenyl iodonium salt (**2a**) as model substrates to attempt the vinylation of C(sp³)–H bond (Table 1). First, several commonly used bases were tested to promote deprotonative/copper-catalyzed vinylation with CuOTf·1/2PhMe catalyst in THF at room temperature, in all of which **1a** was recovered with no vinylation product formed (Table 1, entries 1–5). A series of tetramethylpiperidine (tmp)-derived bases^[15,16] were next examined, including Mg(tmp)Cl·LiCl, Zn(tmp)₂·(LiCl)₂ and Zn(tmp)Cl·LiCl (entries 6–8). Encouragingly, all afforded desired product **3a**, with Zn(tmp)Cl·LiCl most effective (entry 8). Among different copper catalysts (entries 9–13), Cu(OTf)₂ proved to be most effective to form **3a** in 86% isolated yield (entry 13). Furthermore, the formation of **3a** was improved by increasing the reaction temperature to 50°C (entry 14), which was chosen as the standard conditions for subsequent studies. Note that only trace amounts of desired product **3a** were observed in the absence of a copper catalyst (entry 15).^[17]

With standard conditions established, the α -vinylation reactions of phosphine oxide **1** was examined using different vinylphenyliodonium salts (Scheme 2). Note that diphenylphosphine oxides bearing one or no α -substituent group were found compatible to afford vinylation products **3a** and **3b** in excellent yields, while α -disubstituted phosphine oxide failed to undergo zincation. When the reactions of **1a** were explored with vinylodonium salts bearing different substituents on the phenyl group, such as 4-position electron-withdrawing chloride and electron-donating methoxy group, both readily formed the desired products **3c** and **3d**. Alkyl substituted vinylodonium salts were well tolerated, such as benzyl, methyl and propyl groups that were demonstrated in the formation of **3e**, **3f**, and **3g**, respectively. It is worth noting that halogens are tolerated to give vinylation products **3h** and **3i**, thus allowing further functionalization by transition-metal catalyzed cross-couplings.

We also examined the vinylation reactions of phosphonates, a related class of important compounds having wide applications from agriculture to medicine^[18] (Scheme 3). In the reactions with vinylphenyliodonium salt **2a**, diethyl phosphonates **4a–4d** all formed **5a–5d** efficiently. Particularly, the reaction with cyclopropyl-substituted phosphonate **4d** did not result in the formation of any ring-opening byproducts, indicating the vinylation step does not involve a radical intermediate. On the other hand, different alkenylphenyliodonium salts are also viable under standard conditions, providing desired phosphonates **5e–5i** bearing different alkenyl groups at the α -position.

Using this zincative/cross-coupling approach, we next looked into α -vinylation of sulfone derivatives as a direct entry to allylic sulfones, which are highly valuable with its utilities as versatile building blocks and known biological activities^[19] (Scheme 4). Upon further optimization, CuBr was chosen as the catalyst for the vinylation reactions of sulfones and sulfonamides at room temperature.^[20] The vinylation reaction is applicable to a variety of sulfones, such as those bearing α -methyl, fluoro, or bromo group in the formation of **7a–7d**. Sulfonamides also participated in the vinylation smoothly to give the desired products **7e–7f**. Different vinylphenyliodonium salt partners are compatible for the successful formation benzyl- and proparyl-substituted vinyl sulfones **7g** and **7h**, respectively.

The applicability of this zincative/vinylation strategy was investigated among other types of C(sp³)–H bonds (Scheme 5). Under standard conditions, sulfoxide **8a** provided the α -vinylation product **9a** in 65% yield. α -Vinylation of nitrile derivatives were successful for the formation of **9b** and **9c**. α -Vinylation of *tert*-butyl acetate and *N,N*-dimethylacetamide were also effective, forming ester **9d** and amide **9e** in good yields. Note α -vinylation of ketones were ineffective under standard conditions. Overall, the generality of this copper-catalyzed vinylation demonstrated on a variety of C(sp³)–H bonds suggests its potential in constructing a wide range of vinyl–alkyl bonds.

In our attempt to use chiral ligands to explore asymmetric versions of the vinylation reaction, our initial investigations remained unsuccessful. Alternatively, we examined the use of chiral zinc bases for stereoselective control of vinylation in the vinylation reaction of phosphine oxide **1a** and sulfone **6a** (Scheme 6). Moderate stereoinduction was observed with commercially available (*R*)-bis((*R*)-1-phenylethyl)amine-derived zinc base. Although

the stereoselectivity at the current stage remains non-optimal, these initial results demonstrated the potential of developing an asymmetric vinylation reaction for the synthesis of optically active olefin-containing compounds.^[20] Further investigations of asymmetrical versions of the vinylation reaction and the synthesis of optically active alkenyl-containing molecules will be reported in the future.

To further demonstrate synthetic utility of this general vinylation strategy, representative vinyolated compounds were transformed into a broader range of functional molecules (Scheme 7). For example, phosphine oxide **3a** and phosphonate **5e** underwent Horner–Wadsworth–Emmons reactions to form *trans*-diene products **10** and **11**, respectively. The treatment of phosphonate **5b** with Lawesson’s reagent afforded thiophosphonate **12** in 86% yield, another useful class of molecules.^[21] Furthermore, subsequent α -alkylation of phosphonate **5b** led to the formation of phosphonate **13** containing fully substituted α -carbon atom, which offers a solution to the challenging α -disubstituted phosphonates under this zincative/vinylation transformation.

In summary, we have developed an efficient vinylation method for various $C(sp^3)$ –H bonds. This transformation was achieved by a one-pot C–H zincation and copper-catalyzed $C(sp^3)$ – $C(sp^2)$ bond formation using electrophilic vinylidonium salts. The developed transformation is not only valuable and useful for a rapid entry to alkene-containing compounds of importance in pharmaceuticals and functional materials, but also presents a general tactic for introducing diverse functional groups onto similar skeletons.

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(a) Pd-catalyzed direct-group assisted C–H alkenylation

(b) Cu-catalyzed alkenylation of aldehydes via amine catalysis

(c) Pd- or Ni-catalyzed alkenylation via deprotonation

(d) Cu-catalyzed alkenylation via a general C–H zincation (this work)

Scheme 1. Transition-metal-catalyzed alkenylation of C(sp³)–H bonds.

Scheme 2.

α-Vinylation reactions of phosphine oxides with different vinylphenyliodonium salts **2**.

Conditions: **1** (0.2 mmol), Zn(tmp)Cl·LiCl (0.3 mmol), **2** (0.24 mmol), Cu(OTf)₂ (0.02 mmol), THF (2 mL). Yields of isolated products.

Scheme 4.

α -Vinylation of sulfones and sulfonamides. Conditions: **6** (0.2 mmol), Zn(tmp)Cl·LiCl (0.3 mmol), **2** (0.3 mmol), CuBr (0.02 mmol), THF (2 mL). Yields of isolated products.

Scheme 5.

α -Vinylations reactions of sulfoxide, nitriles, ester and amide. Conditions: **8** (0.2 mmol), Zn(tmp)Cl·LiCl (0.3 mmol), **2a** (0.24 mmol), Cu(OTf)₂ (0.02 mmol), THF (2 mL). Yields of isolated products. [a] Reaction run at RT.

Scheme 6.

Synthesis of optically active α -vinylated phosphine oxide and sulfone. Yields of isolated products. The ee % values were determined by chiral HPLC analysis.

Scheme 7.

Representative transformations of vinylation phosphonates into diverse skeletons.

Table 1:

Condition optimization for α -vinylation of **1a**.^[d]

Entry	Base	Catalyst	3aa , Yield [%] ^[b]
1	KOH	CuOTf·1/2 PhMe	0
2	KOtBu	CuOTf·1/2 PhMe	0
3	NaOMe	CuOTf·1/2 PhMe	0
4	KHMDS	CuOTf·1/2 PhMe	0
5	<i>n</i> -BuLi	CuOTf·1/2 PhMe	0
6	Mg(tmp)Cl·LiCl	CuOTf·1/2 PhMe	47
7	Zn(tmp) ₂ ·(LiCl) ₂	CuOTf·1/2 PhMe	29
8	Zn(tmp)Cl·LiCl	CuOTf·1/2 PhMe	83
9	Zn(tmp)Cl·LiCl	CuCl	80
10	Zn(tmp)Cl·LiCl	CuBr	81
11	Zn(tmp)Cl·LiCl	Cu[CH ₃ CN] ₄ PF ₆	68
12	Zn(tmp)Cl·LiCl	Cu(OAc) ₂	66
13	Zn(tmp)Cl·LiCl	Cu(OTf) ₂	92 (86) ^[c]
14 ^[d]	Zn(tmp)Cl·LiCl	Cu(OTf)₂	(87) ^[c]
15	Zn(tmp)Cl·LiCl	-	trace

^[a] Conditions: **1a** (0.2 mmol), base (0.3 mmol), **2a** (0.24 mmol), catalyst (10 mol%), THF (2 mL), RT.

^[b] Yields determined by ¹H-NMR with CH₂Br₂ as an internal standard.

^[c] Yields of isolated products.

^[d] Reaction run at 50°C.