Synthesis of 3-Alkenyl- and 3-Arylalkyl-Δ^3-cephems by Use of Terpyridine- or Bipyridine-Ligated Organocopper Species

Hideo Tanaka, Shin-ichi Sumida, and Sigeru Torii*,†

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima-Naka, Okayama 700, Japan

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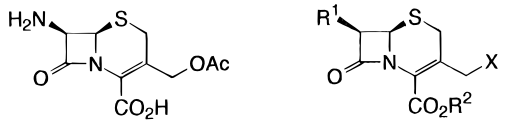
Introduction

Organocopper reagents have been widely used in modern organic synthesis.[1] The vast majority of the organocoppers are prepared by transmetalation of organometallic compounds with copper(I) salts. Organolithium and organomagnesium have been employed as the most common organometallic precursors for the formation of the organocopper reagents. Rieke[2] and Ebert[3] reported a straightforward approach to the organocoppers relying on the reaction of organic halides with a zerovalent copper species which was prepared by the reduction of copper(I) salt complexes, *e.g.*, CuI·PR_3 and CuCN·*n*LiX, with lithium naphthalenide at −100 °C. Tokuda[4] prepared allyl- and benzylcopper reagents by the reaction of allyl and benzyl halides with an activated zerovalent copper generated from electroreduction of copper(II) salts.

Recently, we,[5] Ghosal,[6] Piers,[7] Beddoes,[8] Takeda,[9] Allred,[10] and Nicolaou[11] performed various intra- and intermolecular Stille-type reactions by the aid of copper(I) salt without palladium catalysts, in which the transmetalation of organotins with copper(I) salt would occur to generate organocopper(I) species. Farina reported ^{119}Sn NMR studies on the formation of a vinylcopper(I) species by the transmetalation of tributylvinyltin with copper(I) iodide in *N*-methyl-2-pyrrolidinone (NMP).[12] More recently, Falck succeeded in copper(I)-catalyzed cross-coupling reaction of α-heteroatom-substituted alkyltributyltins with organic halides and proposed the formation of intramolecular stabilized organocopper species as an intermediate.[13]

Scheme 1



7-Aminocephalosporanic Acid (7-ACA) | 3-Halomethyl-Δ^3-cephems X = Cl, Br, I

Incidentally, β-lactam antibiotics possess high antibacterial activity against many infectious diseases and exceptionally low toxicity toward the host by exerting their toxic effects on only peptidoglycan metabolism of a bacterial cell wall.[14] A large number of potent cephalosporin antibiotics have been prepared by modifications of 3′- and/or 7-substituents of the cephalosporin framework. The chemical modifications of the 3′-substituent have mainly relied on the replacement of the acetoxy group of 7-aminocephalosporanic acid (7-ACA) or the halides of 3-(halomethyl)-Δ^3-cephems with heteroatom nucleophiles (Scheme 1).[15] However, only a few procedures for the substitution with carbon nucleophiles, *e.g.*, Stille-type reaction of 3-(chloromethyl)-Δ^3-cephem with organotins in the presence of a palladium catalyst and modified phosphine ligand,[16] reaction of 3-(bromomethyl)-Δ^3-cephem sulfoxide with organocuprates,[17] and others,[18−21] have been explored so far. Therefore, there still remains a great demand of more practical and versatile methods for the carbon−carbon bond formation at the 3′-position of cephalosporins.

In previous papers, we disclosed new synthetic methods of 3-alkenylcephems including the carbon−carbon bond formation by use of an alkenyltins/CuCl combination.[5] In this connection, we investigated reaction of 3-(chloromethyl)-Δ^3-cephem **1** with organotins in the presence of copper(I) chloride and the related copper(0)-promoted coupling reaction of **1** with or without allyl and

† Tel: +81-86-251-8072. Fax: +81-86-255-3424. E-mail: toriiken@cc.okayama-u.ac.jp.

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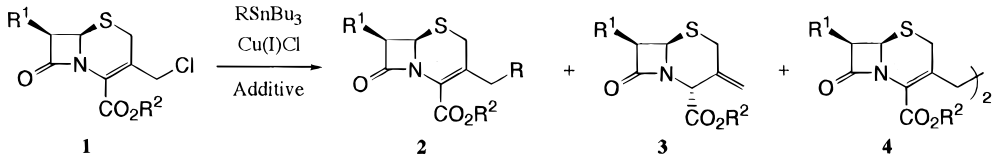
Scheme 2



R^1 = $PhCH_2CONH$
R^2 = *p*-$MeOC_6H_4CH_2$
R = alkenyl

Table 1. Copper(I)-Promoted Reaction of 3-(Chloromethyl)-Δ^3-cephem 1 with Tributylvinyltin in the Presence of Various Additives[a]

			isolated yield (%)			
entry	additive (mol amt)	time (h)	**2a**	**3**	**4**	**1**
1	none	3				62
2	terpyridine (1)	3.5	68		21	
3	bipyridine (1)	3	46	4	43	
4	1,10-phenanthroline (1)	5	25	15	48	
5	pyridine (2)	5				66
6	PPh_3 (2)	7.5				82

[a] All reactions were carried out with tributylvinyltin (1.5 mol amt), copper(I) chloride (1.0 mol amt), and additive in NMP at room temperature.

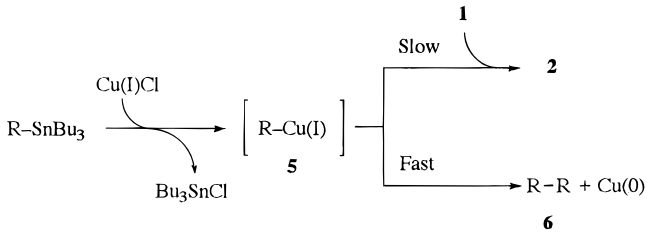
benzyl bromides. Consequently, we found that both the reactions could be achieved only in the presence of terpyridine (tpy) or bipyridine (bpy) as a ligand to afford 3-alkenyl- and 3-(arylalkyl)-Δ^3-cephems, respectively. Herein, we describe the synthesis of the C(3)-substituted Δ^3-cephems **2** and **4** relying on the substitution with coordinatively stabilized organocopper species generated either by transmetalation of organotins with copper(I) chloride or by reaction of **1** and/or allyl and benzyl bromides with copper powder.

Results and Discussion

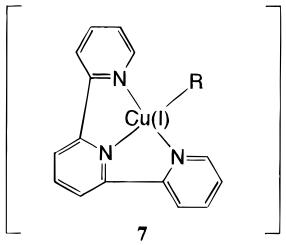
Copper(I)-Promoted Reaction of 3-(Chloromethyl)-Δ^3-cephem with Organotins (Scheme 2). First of all, the reaction of the 3-(chloromethyl)-Δ^3-cephem **1** with tributylvinyltin (1.5 mol amounts) in the presence of copper(I) chloride (1.0 mol amount) in NMP was attempted at room temperature for 3 h, but any detectable amount of 3-allyl-Δ^3-cephem **2a** (R = vinyl) could not be obtained, resulting in the recovery of **1** (62%) (Table 1, entry 1). The failure may be explained by assuming that a vinylcopper(I) species, generated from the transmetalation of tributylvinyltin with copper(I) chloride, is not stable enough to survive in the medium. Thus far generated vinylcopper(I) species **5** (R = vinyl) would mainly undergo disproportionation to give butadiene **6** (R = vinyl) together with copper(0) prior to the reaction with **1** leading to **2a** (Scheme 3).[22]

In order to avoid the undesired disproportionation (**5** → **6**), we surveyed various ligands to coordinatively stabilize the vinylcopper(I) species **5**. Thus, the reaction of **1** with tributylvinyltin and copper(I) chloride was carried out in the presence of various additives which were expected to work as tridentate, bidentate, and monodentate ligands (Table 1, entries 2−6). In the

Scheme 3



Scheme 4



presence of terpyridine, the desired reaction took place predominantly to afford the 3-allyl-Δ^3-cephem **2a** in 68% yield together with dimer **4** (21%) (entry 2). Bipyridine and 1,10-phenanthroline were also effective though the yields of **2a** were reduced to 46 and 25%, respectively (entries 3 and 4). In contrast, pyridine and triphenylphosphine could not effect the desired reaction, resulting in the recovery of **1** (66 and 82%) (entries 5 and 6).

The results suggest that the tridentate ligand, *i.e.*, terpyridine, would form coordinatively saturated vinylcopper(I) **7** (R = vinyl) (Scheme 4)[23] which is stable enough to survive in the reaction medium and undergoes the replacement of the 3′-chlorine atom of **1**.[24] Bipyridine and 1,10-phenanthroline would produce an unsaturated copper(I) species which is less stable than the terpyridine-ligated vinylcopper(I) complex **7** so as to less effectively eliminate the undesired disproportionation. The monodentate ligands, *i.e.*, pyridine and triphenylphosphine, do not seem to form such stabilized copper(I) complexes.

The copper(I)(tpy) complex-promoted reaction was successfully applied to the synthesis of the 3-alkenyl-Δ^3-cephems **2** as compiled in Table 2. The reaction of **1** with allenyltributyltin (1.5 mol amounts) in the presence of copper(I) chloride (1.0 mol amount) and terpyridine (1.0 mol amount) in NMP at room temperature afforded 3-(2,3-butadienyl)-Δ^3-cephem **2b** (α-substitution product)

(22) In the reaction of the 3-(chloromethyl)-Δ^3-cephem **1** (0.41 mmol) with styryltributyltin (1.5 M amounts) and copper(I) chloride (1.0 mol amount) in NMP (2 mL), 1,4-diphenyl-1,3-butadiene was afforded in 50% yield (based on styryltributyltin) and **1** was recovered in 72% yield.

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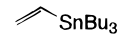
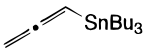
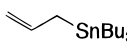
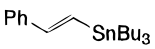
(24) It is also expected that the coordination of terpyridine would enhance the nucleophilicity of the *in situ* generated vinylcopper(I) species **5**.

Table 2. Copper(I)-Promoted Reaction of 3-(Chloromethyl)-Δ^3-cephem 1 with Organotins[a]

entry	$RSnBu_3$	Time (h)	Isolated Yield (%) (Product)	
			2	**4**
1		3.5	68 (**2a**)	21
2		2	84 (**2b**)	–
3		3	61 (**2c**)	14
4		3.5	50 (**2d**)	21
5[b]	Bu_4Sn	3	– (**2e**)	–
6[b]	$Bu_3SnSnBu_3$	3	– (**2f**)	–

[a] All reactions were carried out in NMP at room temperature. [b] Most of the 3-(chloromethyl)-Δ^3-cephem **1** and organotin compounds were recovered.

Scheme 5

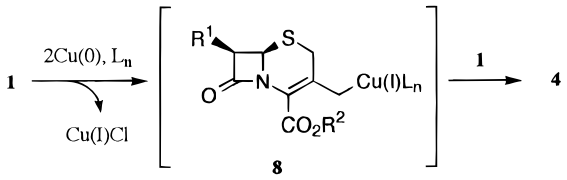


Table 3. Copper(0)-Promoted Homo-Coupling Reaction of 3-(Chloromethyl)-Δ^3-cephem 1[a]

entry	additive	temp (°C)	time (h)	isolated yield (%) **4**	**1**
1	terpyridine	50	1.5	41	
2[b]	bipyridine	r.t.	4	91	3
3	none	r.t.	5		91

[a] All reactions were carried out with copper powder (1.0 mol amt) and additive (1.0 mol amt) in NMP at room temperature. [b] The 3-*exo*-methylenecepham **3** was afforded in 3% yield.

in 84% yield (entry 2). Notably, the reaction proceeded in a regioselective manner; thus, any detectable amount of 3-(3-butynyl)-Δ^3-cephem (γ-substitution product) was not observed. Similarly, the reaction of **1** with allyl- or styryltributyltin afforded 3-(3-butenyl)-Δ^3-cephem **2c** (61%) and 3-cinnamyl-Δ^3-cephem **2d** (50%), respectively (entries 3 and 4). With tetrabutyltin and hexabutylditin, however, no appreciable reactions occurred and most of the organotin compounds remained intact (entries 5 and 6).

Copper(0)-Promoted Reaction of 3-(Chloromethyl)-Δ^3-cephem. In the reaction of the 3-(chloromethyl)-Δ^3-cephem **1** with organotins *vide supra*, a significant amount of the dimer **4** was occasionally produced. The formation of **4** can be rationalized by assuming that the copper(0), generated from the disproportionation of the organocoppers **5**, promotes a Wurtz-type dimerization of **1**. The consideration, in turn, encouraged us to investigate a homo-coupling reaction of **1** with copper powder (Scheme 5). Thus, the reaction of **1** with copper powder (200 mesh, 1.0 mol amount) and terpyridine (1.0 mol amount) in NMP at 50 °C afforded 41% yield of the dimer **4** (Table 3, entry 1). When bipyridine was used in place of terpyridine, the reaction proceeded smoothly even at room temperature to give **4** in 91% yield (entry 2). The significant change of the yields of **4** suggests that a

Scheme 6

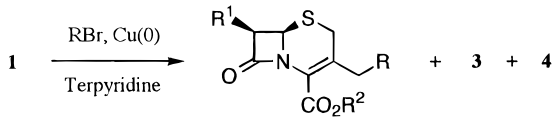


Table 4. Copper(0)-Promoted Allylation of 3-(Chloromethyl)-Δ^3-cephem 1 with Allyl Bromide[a]

entry	Cu (mol amt)	time (h)	isolated yield (%) **2c**	**4**
1[b]	4	5	59	20
2	4	1.5	72	4
3	1	8.0	45	18
4	2	3.5	51	11
5	3	1.75	64	10
6	5	1.25	72	7
7	6	1.2	68	10

[a] All reactions were carried out with allyl bromide (5.0 mol amt) and terpyridine (1.0 mol amt) in NMP at 50 °C unless otherwise noted. [b] The reaction was carried out with bipyridine (1.0 mol amt) at room temperature.

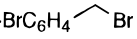
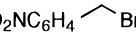
coordinatively saturated copper(I) species **8** (L_n = tpy) generated in a **1**/Cu(0)/terpyridine system would be stable and resist subsequent reaction in some extent, while bipyridine-ligated copper(I) complex **8** (L_n = bpy) is less stable so as to efficiently react with **1** leading to **4**. Notably, the presence of terpyridine or bipyridine is essential for the homo-coupling reaction of **1** since in the absence of the additive (L_n), no appreciable reaction occurred, resulting in the recovery of most of **1** (91%) (entry 3). It is likely that the stabilization of the *in situ* generated copper species with terpyridine or bipyridine may play an important role in facilitating the formation of the copper(I) species **8**.

The success in the above copper(0)-promoted homo-coupling reaction of the 3-(chloromethyl)-Δ^3-cephem **1** enabled us to investigate cross-coupling reaction of **1** with allyl and benzyl bromides (Scheme 6). The reaction of **1** with allyl bromide (5.0 mol amounts) and copper powder (4.0 mol amounts) in the presence of bipyridine (1.0 mol amount) in NMP at room temperature afforded 3-(3-butenyl)-Δ^3-cephem **2c** (R = allyl) (59%) together with the dimer **4** (20%) (Table 4, entry 1). A similar reaction in the presence of terpyridine resulted in increase of the yield of **2c** (72%) as well as decrease of the formation of **4** (4%) though higher temperature (50 °C) were required to complete the reaction (entry 2). The amount of copper powder used had a considerable influence on the yield of **2c** (Table 4, entries 3−7). Four molar amounts of copper powder was optimum for the formation of **2c**.

In a similar manner, synthesis of the 3-(arylalkyl)-Δ^3-cephems **2g**−**i** was performed (Table 5). The reaction of **1** with benzyl bromides (5.0 mol amounts), copper powder (4.0 mol amounts), and terpyridine (1.0 mol amount) in NMP at 50 °C proceeded smoothly to afford the cephems **2g**−**i** in 56−68% yields, respectively.

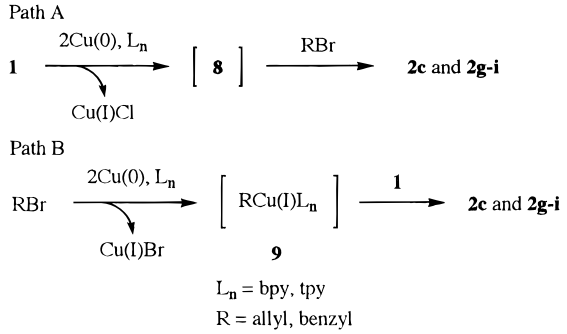
Plausible reaction pathways to the cross-coupling products **2c** and **2g**−**i** are shown in Scheme 7. One involves generation of the copper(I) species **8** by the reaction of **1** with copper powder and subsequent reaction of **8** with allyl and benzyl bromides leading to **2c** and **2g**−**i** (path A). The other consists of generation of allyl- and benzylcopper(I) species **9** by the reaction of allyl and benzyl bromides with copper powder followed by the reaction of **9** with **1** affording **2c** and **2g**−**i** (path B).[3] In

Table 5. Copper(0)-Promoted Cross-Coupling Reaction of 3-(Chloromethyl)-Δ³-cephem 1 with Allyl and Benzyl Bromides[a]

entry	RBr	Time (h)	Isolated Yield (%) (Product) 2	3	4
1		1.5	72 (**2c**)	–	4
2		2	65 (**2g**)	9	25
3		1.5	68 (**2h**)	9	23
4		1.25	56 (**2i**)	14	23

[a] All reactions were carried out with allyl or benzyl halides (5.0 mol amt) and terpyridine (1.0 mol amt) in NMP at room temperature.

Scheme 7



this concern, it should be remembered that in the reaction of **1** with 5 mol amounts of allyl bromide and 1 mol amount of copper powder, most of **1** was consumed. The result suggests that the cross-coupling reaction of **1** with allyl and benzyl bromides mainly proceeds through path a rather than path b. In fact, the reaction of benzyl bromide with copper powder (4 mol amounts) and bipyridine (1 mol amount) in NMP afforded no appreciable amount of the homo-coupling product (bibenzyl), resulting in the recovery of most of the benzyl bromide (57%).

Experimental Section

IR spectra were obtained on a Japan Spectroscopic Co. Ltd. JASCO FT/IR-5000 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer. The 3-(chloromethyl)-Δ³-cephem **1**[25] and organotins[26] were prepared according to the reported procedures in the literature. Copper powder (200 mesh) was activated according to the literature before use.[27] NMP was distilled from calcium hydride under reduced pressure and stored over 4A molecular sieves. All other reagents were available from commercial sources and used without further purification.

General Procedure for Copper(I)-Promoted Reaction of 3-(Chloromethyl)-Δ³-cephem with Organotins (Table 2). To a mixture of the 3-(chloromethyl)-Δ³-cephem **1** (50 mg, 0.10 mmol), copper(I) chloride (10 mg, 0.10 mmol), and terpyridine (24 mg, 0.10 mmol) in NMP (1 mL) was added organotin (0.15 mmol) at room temperature. After being stirred for 2−3.5 h, the reaction mixture was poured into ice-cold 5% HCl aqueous and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 8/1) to afford the 3-alkenyl-Δ³-cephems **2a**−**d**.

***p*-Methoxybenzyl 3-Allyl-7-(phenylacetamido)-Δ³-cephem-4-carboxylate (Entry 1, 2a).** According to the general procedure, the reaction of **1** with tributylvinyltin (48 mg, 0.15 mmol) was carried out for 3.5 h to give the 3-allyl-Δ³-cephem **2a** (33 mg, 68%) and the dimer **4** (10 mg, 21%).

2a: IR (KBr) 3412, 1783, 1721, 1682 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.88 (dd, *J* = 7.7, 14.3 Hz, 1H), 3.25 (d, *J* = 18.3 Hz, 1H), 3.36 (d, *J* = 18.3 Hz, 1H), 3.36 (dd, *J* = 7.7, 14.3 Hz, 1H), 3.61 (d, *J* = 16.2 Hz, 1H), 3.64 (d, *J* = 16.2 Hz, 1H), 3.79 (s, 3H), 4.90 (d, *J* = 4.8 Hz, 1H), 5.08, (d, *J* = 16.0 Hz, 1H), 5.09 (d, *J* = 10.7 Hz, 1H), 5.17 (s, 2H), 5.75 (m, 1H), 5.76 (dd, *J* = 4.8, 9.0 Hz, 1H), 6.16 (d, *J* = 9.0 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.21−7.42 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 37.6, 43.3, 55.2, 57.3, 59.0, 67.6, 113.9, 117.9, 123.3, 127.1, 127.7, 129.1, 129.4, 130.5, 131.3, 133.7, 133.9, 159.8, 161.7, 164.5, 171.1. Anal. Calcd for $C_{26}H_{26}N_2O_5S$: C, 65.25; H, 5.48; N, 5.85. Found: C, 64.95; H, 5.44; N, 5.66.

4: IR (KBr) 3265, 1779, 1717, 1662 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (t, *J* = 8.3 Hz, 2H), 2.91 (t, *J* = 8.3 Hz, 2H), 3.22 (d, *J* = 18.3 Hz, 2H), 3.28 (d, *J* = 18.3 Hz, 2H), 3.63 (s, 4H), 3.79 (s, 6H), 4.88 (d, *J* = 4.7 Hz, 2H), 5.16 (s, 4H), 5.75 (dd, *J* = 4.7, 9.2 Hz, 2H), 6.46 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 4H), 7.19−7.41 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.6, 32.5, 43.1, 55.2, 57.8, 58.9, 67.5, 113.9, 123.0, 126.8, 127.3, 128.7, 128.8, 129.0, 129.2, 130.5, 134.1, 135.7, 159.8, 161.7, 165.5, 171.4. Anal. Calcd for $C_{48}H_{46}N_4O_{10}S_2$: C, 63.84; H, 5.13; N, 6.20. Found: C, 63.75; H, 5.21; N, 6.21.

***p*-Methoxybenzyl 3-(2,3-Butadienyl)-7-(phenylacetamido)-Δ³-cephem-4-carboxylate (Entry 2, 2b).** According to the general procedure, the reaction of **1** with allenyltributyltin (49 mg, 0.15 mmol) was carried out for 2 h to give the 3-(2,3-butadienyl)-Δ³-cephem **2b** (42 mg, 84%): IR (KBr) 3299, 1953, 1775, 1719, 1671 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.87 (dd, *J* = 8.0, 13.8 Hz, 1H), 3.26 (m, 1H), 3.30 (d, *J* = 18.4 Hz, 1H), 3.41 (d, *J* = 18.4 Hz, 1H), 3.62 (d, *J* = 16.2 Hz, 1H), 3.63 (d, *J* = 16.2 Hz, 1H), 3.80 (s, 3H), 4.73 (dt, *J* = 2.8, 6.2 Hz, 2H), 4.90 (d, *J* = 4.7 Hz, 1H), 5.11 (m, 1H), 5.18 (s, 2H), 5.78 (dd, *J* = 4.7, 9.1 Hz, 1H), 6.02 (d, *J* = 9.1 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.19−7.40 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.1, 32.7, 43.2, 55.2, 57.2, 58.9, 67.6, 75.9, 86.7, 113.9, 123.0, 126.9, 127.6, 129.1, 129.4, 130.5, 131.5, 133.7, 159.7, 161.6, 164.5, 171.1, 209.3. Anal. Calcd for $C_{27}H_{26}N_2O_5S$: C, 66.10; H, 5.34; N, 5.71. Found: C, 66.32; H, 5.45; N, 5.55.

***p*-Methoxybenzyl 3-(3-Butenyl)-7-(phenylacetamido)-Δ³-cephem-4-carboxylate (Entry 3, 2c).** According to the general procedure, the reaction of **1** with allyltributyltin (50 mg, 0.15 mmol) was carried out for 3 h to give the 3-(3-butenyl)-Δ³-cephem **2c** (31 mg, 61%) and the dimer **4** (6 mg, 14%): IR (KBr) 3306, 1771, 1723, 1661 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.01−2.68 (m, 4H), 3.21 (d, *J* = 18.1 Hz, 1H), 3.39 (d, *J* = 18.1 Hz, 1H), 3.62 (s, 2H), 3.79 (s, 3H), 4.89 (d, *J* = 4.7 Hz, 1H), 4.96 (d, *J* = 9.8 Hz, 1H), 4.98 (d, *J* = 17.7 Hz, 1H), 5.17 (s, 2H), 5.73 (dd, *J* = 4.7, 8.9 Hz, 1H), 5.61−5.82 (m, 1H), 6.25 (d, *J* = 8.9 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 2H), 7.20−7.41 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.5, 32.3, 32.5, 42.8, 55.0, 57.5, 58.9, 67.2, 113.6, 115.5, 122.7, 126.8, 127.1, 128.1, 128.6, 129.1, 130.2, 133.9, 135.0, 136.6, 159.5, 161.6, 164.5, 171.3. Anal. Calcd for $C_{27}H_{28}N_2O_5S$: C, 65.83; H, 5.73; N, 5.69. Found: C, 65.69; H, 5.95; N, 5.41.

***p*-Methoxybenzyl 3-Cinnamyl-7-(phenylacetamido)-Δ³-cephem-4-carboxylate (Entry 4, 2d).** According to the general procedure, the reaction of **1** with styryltributyltin (59 mg, 0.15 mmol) was carried out for 3.5 h to give the 3-cinnamyl-Δ³-cephem **2d** (28 mg, 50%) and the dimer **4** (10 mg, 21%): IR (KBr) 3308, 1779, 1723, 1680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.97 (dd, *J* = 8.2, 14.4 Hz, 1H), 3.29 (d, *J* = 18.1 Hz, 1H), 3.40 (d, *J* = 18.1 Hz, 1H), 3.50 (dd, *J* = 5.1, 14.4 Hz, 1H), 3.61 (d, *J* = 16.2 Hz, 1H), 3.63 (d, *J* = 16.2 Hz, 1H), 3.78 (s, 3H), 4.91 (d, *J* = 4.8 Hz, 1H), 5.20 (s, 2H), 5.77 (dd, *J* = 4.8, 9.0 Hz, 1H), 6.16 (d, *J* = 9.0 Hz, 1H), 6.01−6.32 (m, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.86

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(d, J = 8.6 Hz, 2H), 7.18−7.40 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.0, 36.9, 43.3, 55.2, 57.3, 59.0, 67.7, 113.9, 123.3, 125.4, 126.2, 127.0, 127.6, 127.7, 128.5, 129.1, 129.4, 130.6, 131.1, 133.0, 133.6, 136.7, 159.8, 161.8, 164.5, 171.1. Anal. Calcd for $C_{32}H_{30}N_2O_5S$: C, 69.29; H, 5.45; N, 5.05. Found: C, 69.01; H, 5.28; N, 5.27.

Copper(0)-Promoted Homo-Coupling Reaction of 3-(Chloromethyl)-Δ^3-cephem (Table 3, Entry 2). A mixture of the 3-(chloromethyl)-Δ^3-cephem **1** (200 mg, 0.41 mmol), copper powder (26 mg, 0.41 mmol), and bipyridine (64 mg, 0.41 mmol) in NMP (2 mL) was stirred at room temperature for 4 h. The reaction mixture was poured into ice-cold 5% HCl aqueous and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 2/1) to afford the dimer **4** (168 mg, 91%), whose spectral and physical data were identical to those described above, **3** (6 mg, 3%), and **1** (6 mg, 3%).

***p*-Methoxybenzyl 3-*exo*-methylene-7-(phenylacetamido)-cepham-4-carboxylate (3)**: IR ($CDCl_3$) 3412, 3317, 1771, 1738, 1674 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.11 (d, J = 14.9 Hz, 1H), 3.57 (d, J = 14.9 Hz, 1H), 3.61 (s, 2H), 3.81 (s, 3H), 5.05 (s, 1H), 5.07 (d, J = 11.8 Hz, 1H), 5.11 (d, J = 11.8 Hz, 1H), 5.17 (s, 1H), 5.19 (s, 1H), 5.33 (d, J = 4.4 Hz, 1H), 5.65 (dd, J = 4.4, 9.3 Hz, 1H), 6.14 (d, J = 9.3 Hz, 1H), 6.88 (d, J = 8.0 Hz, 2H), 7.10−7.41 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.1, 43.1, 55.1, 56.3, 56.7, 59.2, 67.5, 113.9, 117.0, 126.7, 127.4, 128.9, 129.3, 130.0, 133.5, 133.8, 159.8, 165.5, 167.6, 170.9. Anal. Calcd for $C_{24}H_{24}N_2O_5S$: C, 63.70; H, 5.35; N, 6.19. Found: C, 63.94; H, 5.35; N, 6.10.

General Procedure for Copper(0)-Promoted Cross-Coupling Reaction of 3-(Chloromethyl)-Δ^3-cephem with Allyl and Benzyl Bromides (Table 5). To a mixture of copper powder (25 mg, 0.40 mmol) and terpyridine (24 mg, 0.10 mmol) in NMP (1 mL) were successively added the 3-(chloromethyl)-Δ^3-cephem **1** (50 mg, 0.10 mmol) and organobromide (0.50 mmol) at room temperature. After being stirred at 50 °C for 1.25−2 h, the reaction mixture was poured into ice-cold 5% HCl aqueous and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 8/1) to afford the 3-(3-butenyl)-Δ^3-cephem **2c** or the 3-arylalkyl-Δ^3-cephems **2g**−**i**.

***p*-Methoxybenzyl 3-(3-Butenyl)-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (Entry 1, 2c).** According to the general procedure, the reaction of **1** with allyl bromide (60 mg, 0.5 mmol) was carried out for 1.5 h to give the 3-(3-butenyl)-Δ^3-cephem **2c** (37 mg, 72%), whose spectral and physical data were identical to those described above, and **4** (2 mg, 4%).

***p*-Methoxybenzyl 3-Phenethyl-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (Entry 2, 2g).** According to the general procedure, the reaction of **1** with benzyl bromide (86 mg, 0.5 mmol) was carried out for 2 h to give the 3-phenethyl-Δ^3-cephem **2g** (36 mg, 65%), **3** (4 mg, 9%), and **4** (12 mg, 25%): IR (KBr) 3290, 1778, 1723, 1668 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42−2.90 (m, 4H), 3.10 (d, J = 18.1 Hz, 1H), 3.31 (d, J = 18.1 Hz, 1H), 3.61 (s, 2H), 3.77 (s, 3H), 4.85 (d, J = 4.7 Hz, 1H), 5.14 (d, J = 11.8 Hz, 1H), 5.17 (d, J = 11.8 Hz, 1H), 5.72 (dd, J = 4.7, 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.11−7.41 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.9, 34.8, 35.6, 43.1, 55.1, 57.3, 58.9, 67.5, 113.8, 123.0, 126.2, 126.9, 127.5, 128.2, 128.4, 129.0, 129.3, 130.5, 133.8, 134.3, 140.5, 159.7, 161.7, 164.5, 171.2. Anal. Calcd for $C_{31}H_{30}N_2O_5S$: C, 68.61; H, 5.57; N, 5.16. Found: C, 68.44; H, 5.75; N, 5.02.

***p*-Methoxybenzyl 3-[2-(*p*-Bromophenyl)ethyl]-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (Entry 3, 2h).** According to the general procedure, the reaction of **1** with *p*-bromobenzyl bromide (125 mg, 0.5 mmol) was carried out for 1.5 h to give the 3-((*p*-bromophenyl)ethyl)-Δ^3-cephem **2h** (43 mg, 68%), **3** (4 mg, 9%), and **4** (11 mg, 23%): IR (KBr) 3411, 3275, 1774, 1720, 1655 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.36−2.88 (m, 4H), 3.09 (d, J = 18.2 Hz, 1H), 3.35 (d, J = 18.2 Hz, 1H), 3.63 (d, J = 16.7 Hz, 1H), 3.64 (d, J = 16.7 Hz, 1H), 3.79 (s, 3H), 4.87 (d, J = 4.7 Hz, 1H), 5.14 (d, J = 11.8 Hz, 1H), 5.18 (d, J = 11.8 Hz, 1H), 5.75 (dd, J = 4.7, 9.0 Hz, 1H), 6.23 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 7.2 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 7.20−7.41 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.5, 34.9, 36.1, 43.9, 55.8, 58.0, 59.6, 68.2, 114.5, 120.6, 123.9, 127.5, 128.3, 129.7, 130.1, 130.7, 131.3, 132.1, 134.3, 140.1, 160.4, 162.3, 165.1, 171.8. Anal. Calcd for $C_{31}H_{29}BrN_2O_5S$: C, 59.91; H, 4.70; N, 4.51. Found: C, 59.88; H, 4.78; N, 4.39.

***p*-Methoxybenzyl 3-[2-(*p*-Nitrophenyl)ethyl]-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (Entry 4, 2i).** According to the general procedure, the reaction of **1** with *p*-nitrobenzyl bromide (108 mg, 0.5 mmol) was carried out for 1.25 h to give the 3-((*p*-nitrophenyl)ethyl)-Δ^3-cephem **2i** (34 mg, 56%), **3** (7 mg, 14%), and **4** (11 mg, 23%): IR (KBr) 3302, 1779, 1721, 1671, 1587, 1517, 1346, 852 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38−3.02 (m, 4H), 3.16 (d, J = 18.3 Hz, 1H), 3.41 (d, J = 18.3 Hz, 1H), 3.63 (s, 2H), 3.78 (s, 3H), 4.89 (d, J = 4.7 Hz, 1H), 5.14 (d, J = 12.5 Hz, 1H), 5.18 (d, J = 12.5 Hz, 1H), 5.75 (dd, J = 4.7, 8.9 Hz, 1H), 6.48 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.16−7.41 (m, 9H), 8.06 (d, J = 8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.7, 34.5, 35.0, 43.1, 55.1, 57.3, 59.0, 67.6, 113.8, 123.4, 123.5, 123.6, 126.7, 127.5, 129.0, 129.1, 129.2, 129.3, 130.4, 130.5, 133.0, 133.7, 146.4, 148.2, 159.7, 161.6, 164.5, 171.2. Anal. Calcd for $C_{31}H_{29}N_3O_7S$: C, 63.36; H, 4.97; N, 7.15. Found: C, 63.26; H, 5.21; N, 7.19.

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