Reductive Cross-Coupling of 3-Substituted Δ^3-Cephems with Alkenyl Halides in an Al/$PbBr_2$/$NiBr_2$(bpy) Triplemetal Redox System. Synthesis of 3-Alkenyl-Δ^3-cephems

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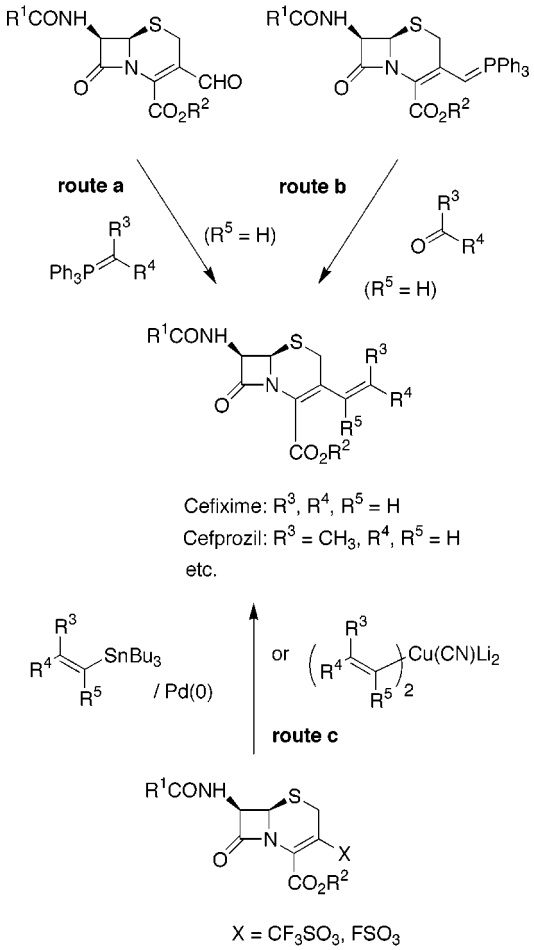
Synthesis of 3-alkenyl-Δ^3-cephems was performed successfully by cross-coupling 3-(trifluoromethylsulfonyloxy or chloro)-Δ^3-cephem with alkenyl halides, e.g., vinyl bromide, *trans*-1-bromo-1-propene, and *trans*-*β*-bromostyrene in an Al/cat·$PbBr_2$/cat·$NiBr_2$(bpy)/NMP (or DMF) system. Reduction of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem into norcephalosporin was also achieved by a similar reaction in the presence of 5 molar equiv of water. Scope and a plausible mechanism of the Al/Pb/Ni triplemetal-redox promoted reactions are discussed.

Introduction

β-Lactam antibiotics represent the most widely prescribed drugs in medicine because of their high antibacterial activities against many pathogenic bacteria as well as exceptionally low toxicity toward hosts by exerting their toxic effects on only peptidoglycan metabolism of a bacterial cell wall.[1] A wide variety of prominent cephalosporin antibiotics have been developed by chemical modification of the (C)3-substituent as well as (C)7-amido moiety of naturally occurring cephalosporins.[2] Among these, 3-alkenyl-Δ^3-cephems, e.g., 3-vinyl-Δ^3-cephem (Cefixime) and 3-(*Z*)-propenyl-Δ^3-cephem (Cefprozil), have met a great success particularly as potent orally active drugs in antibacterial chemotherapy (Scheme 1).[3]

Convenient general methodologies for the synthesis of cephems bearing C(3)-alkenyl substituents are not available, thereby hindering progress in this medicinally important area. The hitherto disclosed procedures for introduction of the C(3)-alkenyl substituents mainly rely on Wittig reaction of 3-formyl-Δ^3-cephems with phosphoranes (route a) or 3-[(triphenylphosphoranylidene)methyl]-Δ^3-cephems with aldehydes (route b), which, however, invariably produces an *E*/*Z* mixture.[4] Stereoselective construction of the C(3)-alkenyl moieties has been achieved by the reaction of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem and its analogues with organotins in the presence of a palladium catalyst[5] and/or with organocuprate[6] (route c). The scope of the reaction is rather limited and the 3-alkenyl-Δ^3-cephems isolated are often contaminated with the undesired Δ^2-isomers, and we need tedious operations to prepare the required organotins or the organocuprates before the reaction. Although other approaches to 3-alkenyl-Δ^3-cephems have been reported,[7] the methods explored so far are not always satisfactory in term of selectivity, versatility, yield, operational simplicity, and manufacturing cost. Indeed, there still remains a great demand for development of newly

Scheme 1



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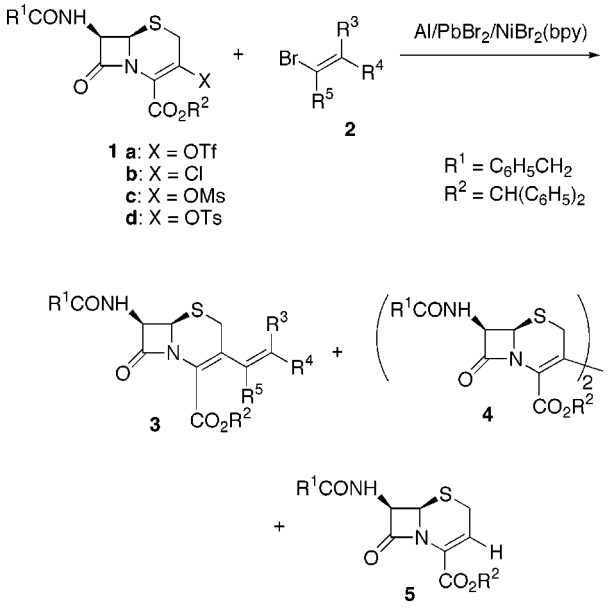
devised procedures for the introduction of the C(3)-alkenyl substituents to fulfill the requirements in the synthesis of the highly sophisticated cephalosporin antibiotics.

Incidentally, aluminum is an ideal reducing reagent because it is cheap, easy to handle, and able to release enough electrons ($3e^-$/atom). However, aluminum is not frequently used in modern organic chemistry owing to the lack of efficient electron transfer between aluminum metal and organic substrates. Recently, various combinations of aluminum metal and a catalytic amount of metal salts have been developed and used as a powerful reduction system for various synthetic purposes, wherein aluminum acts as an electron pool (electron source) and the metal salts work as an electron-transfer catalyst.[8] The chemical behavior of the multimetal redox systems is highly dependent on the nature of the metal salts employed. In this connection, we developed an Al/$PbBr_2$/$NiBr_2$(bpy) triplemetal redox system (bpy: 2,2′-bipyridine) that could efficiently promote homocoupling reactions of alkenyl and aryl halides through disproportionation of in situ generated alkenyl- and aryl-Ni(II) complexes.[9]

Scheme 2



In our continuing studies on the Al/$PbBr_2$/$NiBr_2$(bpy) redox system, we found that the cross-coupling reaction of 3-(trifluoromethylsulfonyloxy or chloro)-Δ^3-cephem **1** (X = OTf or Cl) with alkenyl bromides **2** was performed successfully in the Al/$PbBr_2$/$NiBr_2$(bpy) redox system to afford the corresponding 3-alkenyl-Δ^3-cephems **3** (Scheme 2). This procedure could be operated successfully under ambient conditions without use of any organometal reagents, offering a new straightforward route to 3-alkenyl−Δ^3-cephems **3**. Herein, we describe the new access to 3-alkenyl-Δ^3-cephems **3** through alkenylation of 3-substituted Δ^3-cephems **1** with alkenyl bromides **2** in the Al/$PbBr_2$/$NiBr_2$(bpy) system and several attempts to utilize the triplemetal redox system to synthesis of the Δ^3-cephems **3** baring carbon-based C(3)-substituents as well as norcephalosporin **5**.

Results and Discussion

Preparation of 3-(Trifluoromethylsulfonyloxy)- and 3-Chloro-Δ^3-cephems. 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** was prepared by treatment of 3-hydroxy-Δ^3-cephem[10] with trifluoromethanesulfonic anhydride in dichloromethane containing diisopropylethylamine at −78 °C for 0.5 h. 3-Chloro-Δ^3-cephem **1b** was prepared through several steps starting from readily available penicillin G according to the procedure reported previously.[11] Preparation of 3-chloro-Δ^3-cephem **1b** was also achieved successfully by treatment of **1a** with LiCl in THF at room temperature for 24 h.

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with Vinyl Bromide 2a in an Al/$PbBr_2$/$NiBr_2$(bpy) System. The cross-coupling reaction of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (X = OTf) with vinyl bromide **2a** (R^3, R^4, R^5 = H, 5 molar equiv) was carried out in *N*-methyl-2-pyrrolidinone (NMP) in the presence of aluminum (7.5 molar equiv) and catalytic

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Table 1. Coupling of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem and Vinyl Bromide[a]

entry	Al[c] (equiv)	$PbBr_2$[c] (equiv)	$NiBr_2$(bpy)	solvent	time (h)	yield[b] (%) 3a	4	5	1a
1	7.5	0.1	0.3	NMP	0.7	85	10	4	
2	–	0.1	0.3	NMP	6				83
3	7.5	–	0.3	NMP	6				80
4	7.5	0.1	–	NMP	6				59
5	7.5	0.1	0.3	DMF	0.3	78	15	6	
6	7.5	0.1	0.3	THF	1				85
7	7.5	0.1	0.3	CH_3CN	1				78
8	7.5	0.1	0.3	wet DMF[d]	3	2	–	75	

[a] Carried out at room temperature with **1a** (0.2 mmol) and **2a** (1.0 mmol) in the solvent (2 mL) indicated in the table. [b] Determined by HPLC. [c] Molar equivalent(s) based on **1a**. [d] Containing 1 mmol (5 molar equiv) of water.

Table 2. Coupling of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem and Vinyl Bromide in M/M′X_n/$NiBr_2$(bpy) Systems[a]

entry	M	MX_n	time (h)	yield[b] (%) 3a	4	5	1a
1	Al	$PbBr_2$	0.3	78	15	6	
2	Al	$PbCl_2$	0.3	69	17		2
3	Al	$BiCl_3$	1	40	20	20	
4	Al	$SnCl_2$	1	16		27	51
5	Al	$CrCl_2$	1				88
6	Sn	$PbBr_2$	0.3				80
7	Zn	$PbBr_2$	0.3	18	27	45	5
8	Pb	$PbBr_2$	1	15		27	7
9	Mn	$PbBr_2$	0.1	60	11	22	
10[c]	Mg	$PbBr_2$	0.3				

[a] Carried out with **1a** (0.2 mmol) and **2a** (1.0 mmol) in DMF (2 mL) in the presence of M (1.5 mmol), MX_n (0.02 mmol), and $NiBr_2$(bpy) (0.06 mmol) at room temperature. [b] Determined by HPLC. [c] A complex mixture without detectable amounts of **1a**, **3a**, **4**, and **5** was obtained.

amounts of $PbBr_2$ (0.1 molar equiv) and $NiBr_2$(bpy) (0.3 molar equiv) at room temperature. After the mixture was stirred for 0.7 h, workup of the mixture afforded 3-vinyl-Δ^3-cephem **3a** (85%) together with small amounts of homocoupling product **4** (10%) and norcephalosporin **5** (4%) (Table 1, entry 1). The presence of aluminum, $PbBr_2$ and $NiBr_2$(bpy) is indispensable for the cross-coupling, since a lack of any component of the combination resulted in the recovery of **1a** (59−83%) without formation of any detectable amounts of **3a** (Table 1, entries 2−4). Proper choice of the solvent is also important; DMF could be used without significant change of the products, affording the desired product **3a** (78%) together with **4** (15%) and **5** (6%) (entry 5), while in THF and acetonitrile (entries 6 and 7), no appreciable reaction occurred, resulting in the recovery of most of **1a** (85 and 78%, respectively). Remarkable change of the products was observed when the reaction was carried out in DMF containing a small amount of water (5 molar equiv); thus, after stirring for 3 h, norcephalosporin **5** (75%) was mainly formed (entry 8).

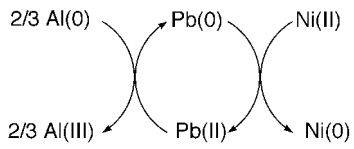
The cross-coupling reaction of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** with vinyl bromide **2a** was investigated by use of other combinations of low valent metal, metal salt, and the Ni-catalyst (Table 2). In place of $PbBr_2$, $PbCl_2$ could be used with only minor change of the products yields (entry 2) while $BiCl_3$ and $SnCl_2$ were less effective (entries 3 and 4) and $CrCl_2$ could not promote any appreciable reactions (entry 5). Aluminum is the best choice among so far examined low valent metals (entries 6−10); thus, the yield of the desired coupling product **3a** decreased in the order: Al (78%) > Mn (60%) > Zn (18%) > Pb (15%) > Sn, Mg (−).

Table 3. Effect of the Amount of Vinyl Bromide[a]

entry	bromide **2a**[b] (equiv)	yield[c] (%) 3a	4	5
1	1	39	19	13
2	2	45	21	12
3	3	60	17	10
4	4	63	12	12
5	5	78	15	6
6	8	75	16	6

[a] Carried out with **1a** (0.2 mmol), Al (1.5 mmol), $PbBr_2$ (0.02 mmol) and $NiBr_2$(bpy) (0.06 mmol) in DMF (2 mL) at room temperature. [b] Molar equivalents based on **1a**. [c] Determined by HPLC.

Scheme 3

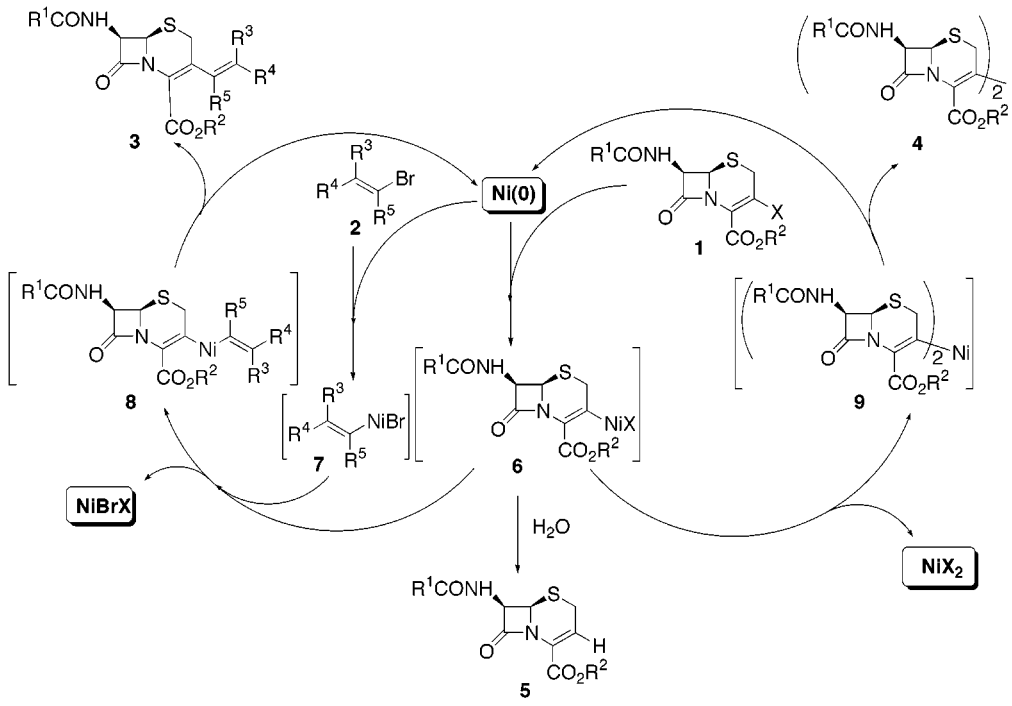


The ratio of the products **3a**, **4**, and **5** was significantly changed depending on the ratio of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** and vinyl bromide **2a** (Table 3). When a mixture of **1a** and **2a** in a molar ratio of 1 to 1 (entry 1) was allowed to react in an Al/$PbBr_2$/$NiBr_2$(bpy)/DMF system, a mixture of the cross-coupling product **3a** and homo-coupling product **4** in a ratio of 2:1 was formed together with a small amount of **5** (13%). The ratio of **3a** to **4** increased up to 5:1 when a 5-fold excess amount of **2a** was used (entry 5). Further increase of the amount of vinyl bromide **2a** up to an 8-fold excess resulted in no significant change of the product ratio (entry 6). The yield of norcephalosporin **5** was slightly decreased by increasing the amount of vinyl bromide **2a**.

Although the reaction mechanism is not clear at present, it is likely that Al(0)/Al(III), Pb(0)/Pb(II), and Ni(0)/Ni(II) redox system promotes the transformation of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** to 3-vinyl-Δ^3-cephem **3a**. The Ni(0) complex would be initially formed and then regenerated in the Al/$PbBr_2$/$NiBr_2$(bpy) redox system, in which, aluminum would release the required electrons ($2e^-$) through a Pb(0)/Pb(II) redox mediatory system as illustrated in Scheme 3.[9] Direct electron transfer from aluminum to Ni(II) complex would not efficiently occur since no appreciable reaction occurred in the absence of $PbBr_2$ (Table 1, entry 3)

A plausible mechanism of thus-formed Ni(0) complex-promoted cross-coupling of 3-(trifluoromethyl-sulfonyloxy)-Δ^3-cephem **1a** and vinyl bromide **2a** is illustrated in Scheme 4 (X = OTf; R^3, R^4, and R^5 = H). The first stage of the reaction would involve oxidative addition of Ni(0) complex with **1a** and **2a**, affording Ni(II) complexes **6** and **7**, respectively. Subsequent reaction of **6** and **7** would afford an intermediate **8** which would, in turn, undergo reductive elimination to afford the cross-coupling product **3a**. On the other hand, disproportionation of Ni(II) complex **6**, leading to a symmetrical Ni(II) complex **9**, followed by the reductive elimination would afford the homo-coupling product **4**. Disproportionation of Ni(II) complex **7** would also take place to generate the corresponding homocoupling product (1,3-butadiene).

Scheme 4



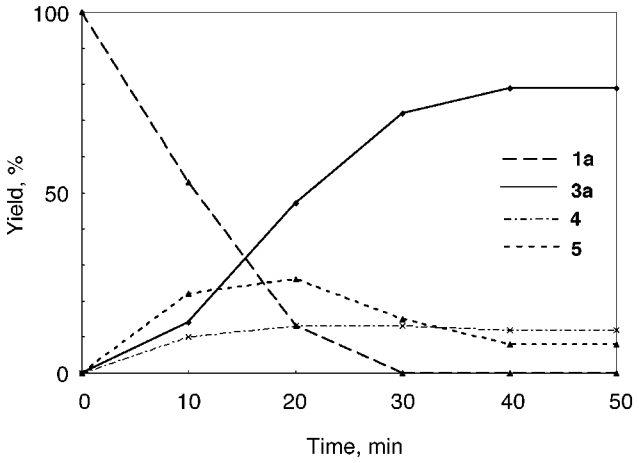


Figure 1. Time course of the cross-coupling of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** and vinyl bromide **2a** under the same conditions as shown in Table 1, entry 1.

During the course of the reactions, Ni(0), Ni(II)BrX and Ni(II)X_2 (X = OTf) complexes would be liberated. The Ni(0) complex would be used again for the formation of the Ni(II) complexes **6** and **7** while the liberated Ni(II) salts, e.g., Ni(II)BrX and Ni(II)X_2, would be reduced through two electron-uptake in the Al/Pb/Ni multiredox system as described above (Scheme 3) and used for the generation of Ni(II)-complexes **6** and **7**, completing the Ni(0)/Ni(II) catalytic cycle.

The formation of norcephalosporin **5** is reasonably understood by assuming hydrolysis of the intermediary Ni(II) complex **6** with moisture of the reaction media. Indeed, when the reaction was carried out in wet DMF (Table 1, entry 8), norcephalosporin **5** was obtained predominantly.

To obtain more insight of the cross coupling reaction in the Al/$PbBr_2$/$NiBr_2$(bpy)/NMP system, the time-course of the reaction was followed by HLPC (Figure 1). At the initial stage of the reaction, the cross-coupling product **3a** was formed together with the homocoupling product **4** and norcephalosporin **5**. After 20 min, the yield of norcephalosporin **5** reached to maximum (25%) and then gradually decreased. On the other hand, the cross-coupling product **3a** continuously increased throughout the reaction even after the starting material **1a** was completely consumed (30 min). These facts suggest that the oxidative addition of Ni(0) with **1a** takes place more efficiently than that with vinyl bromide **2a** and a considerable amount of the Ni(II) complex **6** is accumulated in the reaction mixture and gradually reacts with the Ni(II) complex **7**, affording the cross-coupling product **3a**. The Ni(II)-complex **6** was detected on HPLC analysis as norcephalosporin **5** generated by hydrolysis partly with moisture in the reaction media and mainly during workup process. Homo-coupling of **6** through symmetrical Ni(II) complex **9** seems less efficient than the cross-coupling presumably due to the steric repulsion between two bulky cephem moieties in **9**. Notably, major part of the homocoupling product **4** was formed at initial 20 min, at which period, the concentration of **6** would be high enough to promote the homocoupling leading to **4**.

Cross-Coupling of 3-Chloro-Δ^3-cephem 1b with Vinyl Bromide 2a in an Al/$PbBr_2$/$NiBr_2$(bpy) System. As another access to 3-vinyl-Δ^3-cephem **3a**, the reaction of 3-chloro-Δ^3-cephem **1b** (X = Cl) with vinyl bromide **2a** was carried out in a manner similar to those for 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (Table 1, entry 1). A mixture of 3-chloro-Δ^3-cephem **1b** with 5 molar equiv of vinyl bromide **2a** in NMP (or DMF) in the presence of Al (7.5 molar equiv), $PbBr_2$ (0.1 molar equiv), and $NiBr_2$(bpy) (0.3 molar equiv) was stirred at room temperature for 1 h (or 0.3 h) to afford only 54% (or 40%) yield of the desired product **3a** together with considerable amounts of **5** (22 or 15%) and recovered **1b** (23 or 14%) (Table 4, entries 1 and 2). Even when 10-fold excess of vinyl bromide **2a** was used, the yield of **3a** was only slightly increased to 50% (entry 3). It is interesting to note that the homocoupling product **4** could not be

Table 4. Reaction of 3-Chloro-Δ^3-cephem with Vinyl Bromide[a]

entry	vinyl bromide **2a** (equiv)	solvent	time (h)	yield[b] (%) **3a**	**4**	**5**	**1a**
1	5	NMP	1	54		22	23
2	5	DMF	0.3	40		15	14
3	10	DMF	0.5	50		17	7
4	1.5 × 4[d]	NMP	1	85		14	
5	2 × 4[d]	DMF	1	59		22	6

[a] Carried out with **1b** (o.2 mmol), Al (1.5 mmol), $PbBr_2$ (0.02 mmol), and $NiBr_2$(bpy) (0.06 mmol) in the solvent (2 mL) at room temperature. [b] Determined by HPLC. [c] Recovered **1b**. [d] Portionwise addition at 10 min interval.

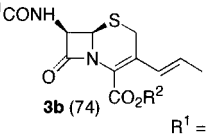
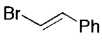
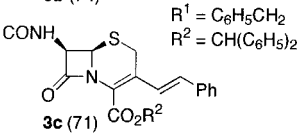
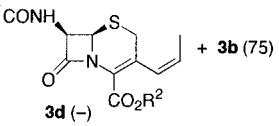
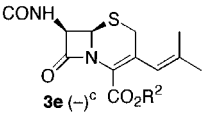
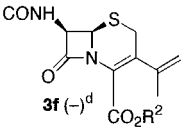
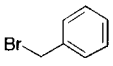
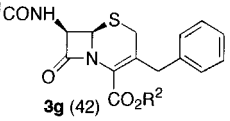
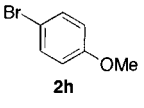
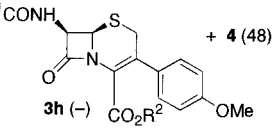
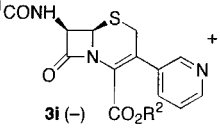
detected in the reactions of **1b**. These results are reasonably explained by assuming that the oxidative addition of Ni(0) complex with 3-chloro-Δ^3-cephem **1b** would not so efficiently occur as in the case of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a**; thus, the concentration of the Ni(II) complex **6** (X = Cl) seems not high enough for the formation of an appreciable amount of the homocoupling product **4**, while the oxidative addition Ni(0) complex with vinyl bromide **2a** would take place predominantly to generate a high concentration of the Ni(II) complex **7**, facilitating the disproportionation of the vinyl-Ni(II) complex **7** leading to the corresponding homocoupling product (1,3-butadiene). Consequently, most of the vinyl bromide **2a** would be consumed before the desired cross-coupling reaction was completed.

A significant increase of the yield of the desired **3a** was attained by portionwise addition of vinyl bromide **2a** throughout the reaction period. Into a mixture of **1b**, Al, $PbBr_2$, and $NiBr_2$(bpy) (1:7.5:0.1:0.3 mol/mol) in NMP, 1.5 molar equiv of vinyl bromide **2a** was added four times at 10 min intervals, affording 85% yields of the desired product **3a** (entry 4). A similar attempt in DMF also resulted in a considerable increase of the yield of **3a** (entry 5).

Similar reactions with 3-(methylsulfonyloxy)- and 3-(*p*-tolylsulfonyloxy)-Δ^3-cephem **1c** (X = OMs) and **1d** (X = OTs) were also attempted by portionwise addition of vinyl bromide **2a** (2 equiv × 4) in the Al (7.5 molar equiv)/$PbBr_2$ (0.1 molar equiv)/$NiBr_2$(bpy) (0.3 molar equiv)/NMP system. The desired product **3a** was, however, obtained in only 28% and 2% yields together with recovered **1c** (36%) and **1d** (76%), respectively, suggesting that methylsulfonyloxy and *p*-tolylsulfonyloxy groups are not reactive enough for the generation of a significant amount of the corresponding Ni(II) complexes **6**.

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with Alkenyl, Benzyl, and Aryl Halides 2b−i in an Al/$PbBr_2$/$NiBr_2$(bpy) System. Application of the Al/$PbBr_2$/$NiBr_2$(bpy)-promoted cross-coupling to synthesis of various C(3)-alkenyl substituted Δ^3-cephems **3** was investigated (Table 5, entries 1−5). The reaction of the 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** with *trans*-1-bromo-1-propene **2b** (5 molar equiv) in the Al (7.5 molar equiv)/$PbBr_2$ (0.1 molar equiv)/$NiBr_2$(bpy) (0.3 molar equiv)/NMP system proceeded smoothly to afford 3-(*trans*-propeneyl)-Δ^3-cephem **3b** in 74% yield (entry 1). The cross-coupling of **1a** with *trans*-β-bromostyrene **2c** was similarly performed to afford 3-styryl-Δ^3-cephem **3c** in 71% yield (entry 2). On the other hand, the reaction of **1a** with *cis*-1-bromo-1-propene **2d** afforded no detectable amount of the 3-(*cis*-propeneyl)-Δ^3-cephem **3d** but its trans isomer **3b** in 75% yield (entry 3). With 1-bromo-

Table 5. Cross-Coupling of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem and Bromides[a]

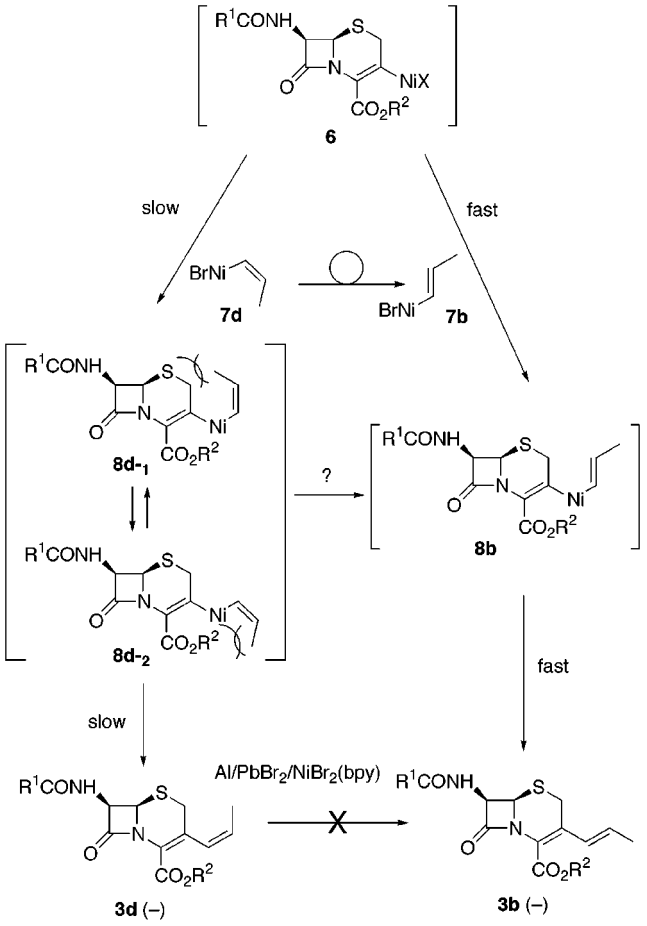
Entry	Bromide **2**	Time, h	Product (Yield, %)[b]
1	 **2b**	1	 **3b** (74)
2	 **2c**	1	 **3c** (71) $R^1 = C_6H_5CH_2$, $R^2 = CH(C_6H_5)_2$
3	 **2d**	1	 + **3b** (75) **3d** (–)
4	 **2e**	1	 **3e** (–)[c]
5	 **2f**	4	 **3f** (–)[d]
6[e]	 **2g**	0.3	 **3g** (42)
7	 **2h**	4	 + **4** (48) **3h** (–)
8	 **2i**	1.4	 + **4** (26) **3i** (–)

[a] Carried out with **1a** (0.2 mmol) and **2** (1 mmol), Al (1.5 mmol), $PbBr_2$ (0.02 mmol), and $NiBr_2$(bpy) (0.06 mmol) in NMP (2 mL) at room temperature. [b] Determined by HPLC. [c] A complex mixture involving a small amount of **5** (22%) was obtained. [d] A complex mixture involving **4** (28%) and **5** (7%) was obtained. [e] Carried out in DMF (2 mL).

2-methylpropene **2e** and 2-bromopropene **2f**, no corresponding alkenylation products **3e** and **3f** were obtained. These failures would be attributed to the steric congestion in the intermediates **8** owing to either the α- or cis-β-substituent (CH_3) of the alkenyl moieties, which would severely inhibit the formation and/or the reductive elimination of **8**. The formation of the trans isomer **3b** from *cis*-1-bromopropene **2d** can be explained on a similar basis; thus, the formation of **8d** and/or subsequent reductive elimination would not be allowed to occur because of the steric repulsion between the Δ^3-cephem moiety and β-methyl group of cis-propenyl moiety as illustrated in Scheme 5. Isomerization of *cis*-propenyl-Ni(II) complex **7d** to the corresponding trans isomer **7b**[12] followed by the reaction with **6** and reductive elimination

(12) Similar cis/trans isomerization was partly observed in a homocoupling reaction of alkenyl halids through alkenyl-Ni(II) complexes: Takagi, K.; Hayama, N. *Chem. Lett.* **1983**, 637. See also ref 9a.

Scheme 5



of **8b** would afford the *trans*−isomer **3b**. The isomerization of **8d** to **8b** is not completely excluded at present while isomerization of **3d** to **3b** is not provable since the cis isomer **3d**, prepared by the reported procedure,[5e] could survive (1 h) without cis/trans isomerization in the Al/$PbBr_2$/$NiBr_2$(bpy) system.

Cross-coupling of the 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** with benzyl and aryl bromides **2g**−**i** in the Al/$PbBr_2$/$NiBr_2$(bpy)/NMP(or DMF) system was briefly investigated (Table 5, entries 6−8). The cross-coupling of **1a** with benzyl bromide **2g** occurred in the Al/$PbBr_2$/$NiBr_2$(bpy) system to afford 3-benzyl-Δ^3-cephem **3g** (42%) whereas with *p*-methoxyphenyl and 3-pyridyl bromides **2h** and **2i**, no appreciable cross-coupling products **3h** and **3i** were obtained, affording the homocoupling products **4** in 48 and 26% yield, respectively.

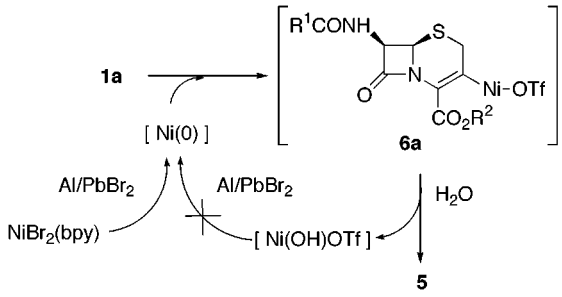
Preparation of Norcephalosporin. Norcephalosporin **5** is a potent precursor of an important class of *β*-lactam antibiotics.[13] The reduction of the 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** may offer a straightforward route to **5** and hence we investigated the reaction of **1a** in the Al/$PbBr_2$/$NiBr_2$(bpy)/wet NMP system (Table 6). At first, reaction of **1a** with an Al/$PbBr_2$/$NiBr_2$(bpy) combination (7.5/0.3/0.1 mol/mol) in dry NMP was carried out at room temperature. After 2 h, most of **1a** was consumed, affording the homocoupling product **4** (42%)

Table 6. Reduction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem in Al/$PbBr_2$/$NiBr_2$(bpy) Systems[a]

				yield[b] (%)		
entry	$NiBr_2$(bpy) (equiv)	H_2O (equiv)	time (h)	**4**	**5**	**1a**
1	0.3		2	42	9	
2	0.3	5	5		29	43
3	0.4	5	5		47	32
4	0.5	5	5		69	9
5	1	5	5		83	

[a] Carried out with **1a** (o.2 mmol), Al (1.5 mmol), and $PbBr_2$ (0.02 mmol) in NMP (2 mL) at room temperature. [b] Determined by HPLC.

Scheme 6



and a small amount of norcephalosporin **5** (9%) (entry 1). When a similar reaction was carried out in the presence of 5 molar equiv of water, even after 5 h, only 29% yield of norcephalosporin **5** was formed and, notably, a significant amount of **1a** (43%) was recovered (entry 2). At the stage of hydrolysis of the in situ generated Ni(II) complex **6**, nickel(II) hydroxide (Ni(OH)OTf) would be liberated, which seems not efficiently reduced to Ni(0) complex in the Al/$PbBr_2$ redox system (Scheme 6); indeed, increasing the amount of $NiBr_2$(bpy) increased the yield of **5** significantly (entries 3−5), and almost 1 molar equivalent of $NiBr_2$(bpy) was required to complete the reaction, affording 83% yield of **5**.[14] In all experiments in wet NMP (entries 2−5), no detectable amount of the homocoupling product **4** was formed, suggesting that hydrolysis of the in situ generated Ni(II) complex **6** to **5** would smoothly proceed before the disproportionation leading to **4** through the symmetrical Ni(II) complex **9**.

Conclusion

Cross-coupling of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** with vinyl bromide **2a** could be performed successfully in an Al/$PbBr_2$/$NiBr_2$(bpy) (7.5/0.1/0.3 mol/mol)/NMP or DMF system to afford 3-vinyl-Δ^3-cephem **3a** (78−85%). A similar cross-coupling of 3-chloro-Δ^3-cephem **1b** with vinyl bromide **2a** was attained by portionwise addition of vinyl bromide at 10 min interval. A plausible reaction mechanism involving Ni(0)/Ni(II), Pb(0)/Pb(II), and Al(0)/Al(III) redox-promoted reactions (Scheme 4) is proposed, wherein oxidative addition of in situ generated Ni(0) with **1** and **2a** followed by the

(13) (a) Yamanaka, H.; Kawabata, K.; Miyai, K.; Takasugi, H.; Kamimura, T.; Mine, Y.; Takaya, T. *J. Antibiot.* **1986**, *39*, 101. (b) Hamashima, Y.; Kubota, T.; Minami, K.; Ishikura, K.; Konoike, T.; Yoshioka, M.; Yoshida, T.; Nakashimizu, H.; Motokawa, K. *J. Antibiot.* **1987**, *40*, 1468. (c) Tanaka, H.; Yamaguchi, Y.; Sumida, S.; Torii, S. *J. Chem. Soc., Chem. Commun.* **1996**, 2705 and references therein.

(14) In contrast, the reduction of the 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** in wet DMF in the presence of excess vinyl bromide **2a** (Table 1, entry 8) was successfuly performed by use of only 0.3 molar equivalent of $NiBr_2$(bpy). The result can be reasonably understood by assuming that a significant amount of $AlBr_3$ generated from the homocoupling of vinyl-Ni(II) bromide **7** would react with water to give Al(OH)$_3$ and HBr. The latter would, in turn, react with the Ni(II) complex **6** to afford **5** and nickel bromide (NiBrOTf) which would be reduced to the Ni(0) complex in the Al/$PbBr_2$/$NiBr_2$(bpy) system.

reaction of thus formed Ni(II) complexes **6** and **7** leading to asymmetrical Ni(II) complex **8** and subsequent reductive elimination afford the cross-coupling product **3a**. The in situ generated Ni(0)-promoted reaction was successfully applied to the cross-coupling of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** with *trans*-1-alkenyl bromides **2b** and **2c** and benzyl bromide **2g** but not with aryl bromides **2h** and **2i**. Reduction of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** to norcephalosporin **5** was also achieved by the reaction in wet NMP in the presence of Al, $PbBr_2$, and $NiBr_2$(bpy) (7.5/0.1/1 mol/mol).

Experimental Section

IR spectra were obtained on a Japan Spectroscopic Co., Ltd. JASCO FT/IR-VALOR-III spectrometer in wavenumber (cm^{-1}). ^1H NMR spectra were recorded with a Varian Gemini 200 (200 MHz). The ^1H NMR signals are expressed in ppm downfield from internal tetramethylsilane (0 ppm). High-performance liquid chromatography (HPLC) was executed with Shimadzu HPLC instrument equipped with LC-10AT pump, SPD-6A UV detector and C-R6A integrator. All HPLC analyses were performed under the following conditions, column: YMC-Pack AM-312 ODS-AM AM-312 (6.0 mm $\Phi \times$ 150 mm); mobile phase CH_3CN/H_2O = 2/1; flow rate: 1.5 mL/min; detection: UV 290 nm. Elemental analyses were performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer.

DMF, NMP, and CH_3CN were distilled over calcium hydride and stored over 4A molecular sieves. THF was distilled over sodium and benzophenone before use. All other chemicals were purchased from commercial sources and used without further purification.

3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a. To a mixture of 3-hydroxycephem[10] (3.14 g, 6.26 mmol) and diisopropylethylamine (1.12 mL, 6.27 mmol) in dichloromethane (40 mL) was added trifluoromethanesulfonic anhydride (1.27 mL, 7.49 mmol) at −78 °C. After being stirred at −78 °C for 30 min, the mixture was diluted with dichoromethane (300 mL), washed with water, and dried ($MgSO_4$). After evaporation of the solvents, the residue was triturated with ether to afford 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (3.6 g, 91%) as an amorphous solid whose ^1H NMR and IR spectra are identical with those of authentic sample.[15]

3-Chloro-Δ^3-cephem 1b. 3-Chloro-Δ^3-cephem **1b** was prepared according to the previously reported procedure.[11] As an alternative method,[15] reaction of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (1.66 g, 2.62 mmol) with LiCl (1.11 g, 26.2 mmol) in dry tetrahydrofuran (25 mL) was also carried out at room temperature under argon atmosphere. After being stirred for 24 h at room temperature, the mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvents followed by trituration with ether afforded 3-chloro-Δ^3-cephem **1b** (1.29 g, 95%).

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with Vinyl Bromide 2a in an Al/$PbBr_2$/$NiBr_2$(bpy)/NMP System (Table 1, Entry 1). To a mixture of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (127 mg, 0.2 mmol), finely cut aluminum foils (41 mg, 1.5 mmol), $PbBr_2$ (7 mg, 0.02 mmol), and $NiBr_2$(bpy) (22 mg, 0.06 mmol) was added a solution of vinyl bromide (107 mg, 1.0 mmol) in NMP (2 mL) under argon atmosphere. After being stirred for 20 min at room temperature, an aliquot of the reaction mixture was submitted to HPLC analysis, showing the presence of 3-vinyl-Δ^3-cephem **3a** (85%), homo-coupling product **4** (10%) and norcephalosporin **5** (4%). The mixture was diluted with EtOAc and poured into ice cold aqueous 5% HCl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed (silica gel; EtOAc/toluene: 1/5) to afford 3-vinyl-Δ^3-cephem **3a** (75 mg, 73%) together with homo-coupling product **4** (5 mg, 5%) and norcephalosporin **5** (2 mg, 2%).

3-Vinyl-Δ^3-cephem 3a:[5c] IR (KBr) 3283, 3063, 3032, 2956, 1774, 1720, 1663, 1526, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (d, J = 18.0 Hz, 1H), 3.59 (d, J = 18.0 Hz, 1H), 3.63 (d, J = 14.9 Hz, 1H), 3.67 (d, J = 14.9 Hz, 1H), 4.99 (d, J = 4.8 Hz, 1H), 5.26 (d, J = 11.3 Hz, 1H), 5.42 (d, J = 17.9 Hz, 1H), 5.84 (dd, J = 4.8, 9.2 Hz, 1H), 6.09 (d, J = 8.9 Hz, 1H), 6.95 (s, 1H), 6.98 (dd, J = 11.3, 17.9 Hz, 1H), 7.19−7.37 (m, 15H).

Homocoupling Product 4: IR (KBr) 3305, 1728, 1496 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.03 (d, J = 18.3 Hz, 2H), 3.63 (d, J = 18.3 Hz, 2H), 3.61 (d, J = 18.0 Hz, 2H), 3.66 (d, J = 18.0 Hz, 2H), 4.18 (d, J = 5.0 Hz, 2H), 5.71 (dd, J = 5.0, 9.1 Hz, 2H), 5.91 (d, J = 9.1 Hz, 2H), 6.70 (s, 2H), 7.19−7.37 (m, 30H). Anal. Calcd for $C_{56}H_{46}O_8N_4S_2$: C, 69.55; H, 4.79; N, 5.79. Found: C, 69.71; H, 4.93; N, 5.50.

Norcephalosporin 5:[5c] IR (KBr) 3295, 3065, 1782, 1713, 1653, 1534, 1496 cm^{-1}; ^1H NMR δ 3.36 (dd, J = 6.1, 19.4 Hz, 1H), 3.38 (dd, J = 2.7, 19.4 Hz, 1H), 3.63 (d, J = 16.0 Hz, 1H), 3.68 (d, J = 16.0 Hz, 1H), 4.93 (d, J = 4.8 Hz, 1H), 5.90 (dd, J = 4.8, 9.4 Hz, 1H), 6.08 (d, J = 9.4 Hz, 1H), 6.62 (dd, J = 2.7, 6.1 Hz, 1H), 6.94 (s, 1H), 7.22−7.46 (m, 15H).

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with Vinyl Bromide 2a in an Al/$PbBr_2$/$NiBr_2$(bpy)/Wet DMF System (Table 1, Entry 8). To a mixture of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (127 mg, 0.2 mmol), finely cut aluminum foils (41 mg, 1.5 mmol), $PbBr_2$ (7 mg, 0.02 mmol), and $NiBr_2$(bpy) (22 mg, 0.06 mmol) was added a solution of vinyl bromide **2a** (107 mg, 1.0 mmol) in DMF (2 mL) containing water (18 μL, 1.0 mmol) under argon atmosphere. After being stirred for 3 h at room temperature, an aliquot of the reaction mixture was submitted to HPLC analysis, showing the presence of 3-vinyl-Δ^3-cephem **3a** (2%) and norcephalosporin **5** (75%). The mixture was diluted with EtOAc (ca. 30 mL) and poured into ice cold aqueous 5% HCl and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed (silica gel; EtOAc/toluene: 1/5) to afford 3-vinyl-Δ^3-cephem **3a** (2 mg, 2%) and norcephalosporin **5** (72 mg, 74%) whose ^1H NMR and IR spectra are identical with those of the authentic samples obtained above.

Reaction of 3-Chloro-Δ^3-cephem 1b with Vinyl Bromide 2a in an Al/$PbBr_2$/$NiBr_2$(bpy)/NMP System (Table 4, Entry 4). To a mixture of 3-chloro-Δ^3-cephem **1b** (105 mg, 0.2 mmol), finely cut aluminum foils (41 mg 1.5 mmol) $PbBr_2$ (7 mg, 0.02 mmol), and $NiBr_2$(bpy) (22 mg,0.06 mmol) was added a solution of vinyl bromide **2a** (32 mg, 0.3 mmol) in NMP (2 mL) under argon atmosphere. After stirring for 10 min at room temperature, a solution of vinyl bromide (32 mg, 0.3 mmol) in NMP (0.5 mL) was added three times at interval of 10 min. After being stirred for additional 30 min, an aliquot of the reaction mixture was submitted to HPLC analysis showing the presence of 3-vinyl-Δ^3-cephem **3a** (85%) together with norcephalosporin **5** (14%). The reaction mixture was diluted with EtOAc (ca. 30 mL) and poured into ice-cold 5% HCl aq. and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed (silica gel; EtOAc/toluene: 1/5) to afford 3-vinyl-Δ^3-cephem **3a** (68 mg, 67%) and norcephalosporin **5** (10 mg, 10%) whose ^1H NMR and IR spectra are identical with those of the authentic samples obtained above.

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with *trans*-1-Bromo-1-propene 2b in an Al/$PbBr_2$/$NiBr_2$(bpy) System (Table 5, Entry 1). To a mixture of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (127 mg, 0.2 mmol), finely cut aluminum foils (41 mg, 1.5 mmol), $PbBr_2$ (7 mg, 0.02 mmol) and $NiBr_2$(bpy) (22 mg, 0.06 mmol) in NMP (2 mL) was added *trans*-1-bromo-1-propene **2b** (85 μL, 1.0 mmol) under argon atmosphere. After being stirred for 1 h at room temperature, an aliquot of the reaction mixture was submitted to HPLC analysis, showing the presence of 3-(*trans*-propenyl)-Δ^3-cephem **3b** (74%) and norcephalosporin **5** (8%).

(15) Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962.

The reaction mixture was worked up in a manner similar to those described above to afford 3-(*trans*-propenyl)-Δ^3-cephem **3b** (66 mg, 63%) and norcephalosporin **5** (6 mg, 6%).

3-(*trans*-Propenyl)-Δ^3-cephem 3b:[7a] IR (KBr) 3301, 3029, 1767, 1723, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (dd, J = 1.6, 6.8 Hz, 3H), 3.35 (d, J = 17.2 Hz, 1H), 3.49 (d, J = 17.2 Hz, 1H), 3.58 (d, J = 17.7 Hz, 1H), 3.68 (d, J = 17.7 Hz, 1H), 4.96 (d, J = 4.7 Hz, 1H), 5.77 (dd, J = 4.7, 8.9 Hz, 1H), 5.93 (dd, J = 6.8, 15.0 Hz, 1H), 6.35 (d, J = 8.9 Hz, 1H), 6.81 (dd, J = 15.0, 1.6 Hz, 1H), 6.95 (s, 1H), 7.26−7.45 (m, 15H).

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with *trans*-β-Bromostyrene 2c in an Al/$PbBr_2$/$NiBr_2$(bpy)/NMP System (Table 5, Entry 2). To a mixture of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (127 mg, 0.2 mmol), finely cut aluminum foils (41 mg, 1.5 mmol), $PbBr_2$ (7 mg, 0.02 mmol), and $NiBr_2$(bpy) (22 mg, 0.06 mmol) in NMP (2 mL) was added trans-β-bromostyrene **2c** (0.13 mL, 1.0 mmol) under argon atmosphere. After stirring for 60 min. at room temperature, an aliquot of the reaction mixture was submitted to HPLC analysis, showing the presence of 3-styryl-Δ^3-cephem **3c** (71%), the homo-coupling product **4** (14%), and norcephalosporin **5** (8%). The reaction mixture was worked up in a manner similar to those described above to afford 3-styryl-Δ^3-cephem **3c** (74 mg, 63%) together with the homo-coupling product **4** (12 mg, 12%) and norcephalosporin **5** (6 mg, 6%).

3-Styryl-Δ^3-cephem 3c: IR (KBr) 3337, 3031, 1779, 1700, 1655, 1531, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.52 (d, J = 17.4 Hz, 1H), 3.65 (d, J = 17.4 Hz, 1H), 3.63 (d, J = 8.0 Hz, 1H), 3.68 (d, J = 8.0 Hz, 1H), 5.02 (d, J = 4.7 Hz, 1H), 5.81 (dd, J = 4.7, 9.0 Hz, 1H), 6.39 (d, J = 9.0 Hz, 1H), 6.67 (d, J = 16.4 Hz, 1H), 7.02 (s, 1H), 7.14−7.46 (m, 20H), 7.52 (d, J = 16.4 Hz, 1H). Anal. Calcd for $C_{36}H_{30}O_4N_2S$: C, 73.70; H, 5.15; N, 4.77. Found: C, 73.44; H, 4.98; N, 4.65.

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with *cis*-1-Bromo-1-Propene 2d in an Al/$PbBr_2$/$NiBr_2$(bpy) System (Table 5, Entry 3). To a mixture of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (127 mg, 0.2 mmol), finely cut aluminum foils (41 mg, 1.5 mmol), $PbBr_2$ (7 mg, 0.02 mmol), and $NiBr_2$(bpy) (22 mg, 0.06 mmol) in NMP (2 mL) was added *cis*-1-bromo-1-propene **2d** (85 μL, 1.0 mmol) under argon atmosphere. After the mixture was stirred for 1 h at room temperature, an aliquot of the reaction mixture was submitted to HPLC analysis, showing the presence of 3-(*trans*-propenyl)-Δ^3-cephem **3b** (75%) and the homocoupling product **4** (6%). The reaction mixture was worked up in a manner similar to those described above to afford 3-(*trans*-propenyl)-Δ^3-cephem **3b** (66 mg, 63%) and homo-coupling product **4** (6 mg, 6%) whose ^1H NMR and IR spectra are identical with those of the authentic samples obtained above.

Reaction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a with Benzyl Bromide 2g in an Al/$PbBr_2$/$NiBr_2$-(bpy)/DMF System (Table 5, Entry 6). To a mixture of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (127 mg, 0.2 mmol), finely cut aluminum foils (41 mg, 1.5 mmol), $PbBr_2$ (7 mg, 0.02 mmol) and $NiBr_2$(bpy) (22 mg, 0.06 mmol) in DMF (2 mL) was added benzyl bromide **2g** (0.12 mL, 1.0 mmol) under argon atmosphere. After the mixture was stirred for 18 min at room temperature, an aliquot of the reaction mixture was submitted to HPLC analysis, showing the presence of 3-benzyl-Δ^3-cephem **3g** (42%). The mixture was worked up in a manner similar to those described above to afford 3-benzyl-Δ^3-cephem **3g** (44 mg, 38%): IR (KBr) 3281, 3063, 3031, 2964, 1781, 1723, 1662, 1529, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.11 (d, J = 18.1 Hz, 1H), 3.33 (d, J = 18.1 Hz, 1H), 3.61 (d, J = 8.0 Hz, 1H), 3.67 (d, J = 8.0 Hz, 1H), 3.54 (d, J = 14.7 Hz, 1H), 3.95 (d, J = 14.7 Hz, 1H), 4.68 (d, J = 4.7 Hz, 1H), 5.84 (dd, J = 4.7, 9.0 Hz, 1H), 6.08 (d, J = 9.0 Hz, 1H), 6.99 (s, 1H), 7.11−7.40 (m, 20H). Anal. Calcd for $C_{35}H_{30}N_2O_4S$: C, 73.15; 5.26; N, 4.87. Found: C, 73.37; H, 5.22; N, 4.74.

Reduction of 3-(Trifluoromethylsulfonyloxy)-Δ^3-cephem 1a in an Al/$PbBr_2$/$NiBr_2$(bpy)/Wet NMP System (Table 6, Entry 5). A mixture of 3-(trifluoromethylsulfonyloxy)-Δ^3-cephem **1a** (127 mg, 0.2 mmol), finely cut aluminum foils (41 mg, 1.5 mmol), $PbBr_2$ (7 mg, 0.02 mmol), and $NiBr_2$(bpy) (75 mg, 0.2 mmol) in NMP (2 mL) containing water (18 μL, 1 mmol) was stirred for 5 h at room temperature under argon atmosphere. An aliquot of the reaction mixture was submitted to HPLC analysis, showing the presence of norcephalospolin **5** (83%). The analytical sample of **5** was obtained by workup of the mixture in the manner as described above. ^1H NMR and IR spectra of thus obtained **5** are identical with those of the authentic sample obtained above.

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