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Cross-coupling of nonstabilized aziridinylmagnesiums with alkylhalides catalyzed by Cu(I) iodide: a new synthesis of amines bearing a quaternary chiral center and an asymmetric synthesis of both enantiomers of the amines from one chiral starting material

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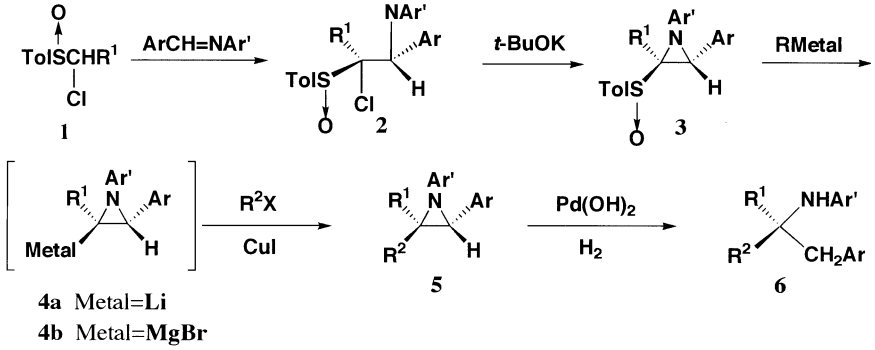
Abstract—Treatment of sulfinylaziridines, which were synthesized from 1-chloroalkyl *p*-tolyl sulfoxides and imines, with ethylmagnesium bromide gave nonstabilized aziridinylmagnesiums by a sulfoxide-magnesium exchange reaction. The cross-coupling of the aziridinylmagnesiums with various kinds of alkylhalides was realized in high yields by using Cu(I) iodide as a catalyst, and the reaction was found to be stereospecific. The coupling products were hydrogenated with $Pd(OH)_2$ in alcohol to give the amines bearing a quaternary chiral center in quantitative yields. Synthesis of both enantiomers of the amines bearing a quaternary chiral center was realized starting from optically active (*R*)-chloromethyl *p*-tolyl sulfoxide in good overall yields with perfect asymmetric induction.

Asymmetric synthesis of a quaternary carbon center has been a formidable but quite interesting challenge in synthetic organic chemistry.[1] Especially, amino compounds in which a nitrogen is bound to a stereogenic carbon have received wide attention these days, because these amines, including quaternary α-amino acids[2] and quaternary β-amino acids,[3] are medicinally and biochemically quite important. However, few methods for the creation of a chiral quaternary carbon center bound to an amino group have so far been reported.[4]

We previously reported the generation of aziridinyllithiums **4a**[5] and aziridinylmagnesiums **4b**[6] from sulfinylaziridines **3**, which were easily synthesized from 1-chloroalkyl *p*-tolyl sulfoxides **1** and imines via the adducts **2**, with an alkyllithium or Grignard reagent by sulfoxide-metal exchange.[7] The aziridinyllithiums were ethoxycarbonylated and in two steps they were derived to the α,α-dialkylamino acid esters.[5] In continuation of our studies on the generation of aziridinylmetals **4**[8] from sulfinylaziridines **3** and development of the chemistry to new synthetic methods, here we describe in detail a cross-coupling of the aziridinylmagnesiums **4b** with alkylhalides and synthesis of amines bearing a quaternary chiral carbon **6**.[9] A novel synthesis of both



Scheme 1.

Keywords: sulfoxide-magnesium exchange; aziridinylmagnesium; cross-coupling; quaternary chiral center; asymmetric synthesis of amines.
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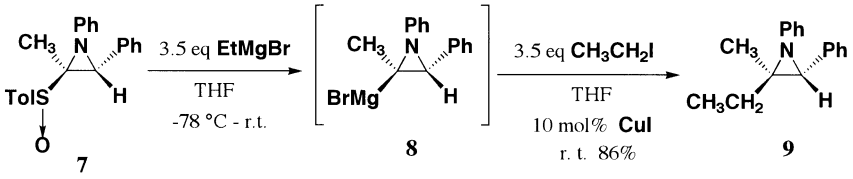


Scheme 2.

enantiomers of the amines **6** from one chiral starting material, (*R*)-chloromethyl *p*-tolyl sulfoxide, was also quite successful by this method (Scheme 1).

1. Results and discussion

1.1. Cross-coupling of the aziridinylmagnesiums with alkylhalides in the presence of Cu(I) iodide as a catalyst

In a previous paper, we reported the synthesis of sulfinylaziridine **7** and generation of the aziridinylmagnesium **8** from **7** with EtMgBr.[6] The aziridinylmagnesium **8** was found to be stable even at room temperature for several hours; however, nucleophilicity of **8** was low and, for example, the reaction of **8** with iodomethane did not take place at all.[6] We recently reinvestigated the cross-coupling of **8** with alkylhalides by using metal catalysts.[10] After some examination, we found that Cu(I) iodide worked excellently.[11]

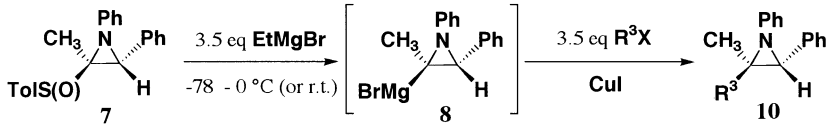
A representative example is reported as follows. To a solution of EtMgBr (3.5 equivalents) in THF at −78°C is added dropwise a solution of **7** in a minimum amount of THF. At this stage, EtMgBr does not react with **7** at all; however, the trace moisture in the solution is completely removed by the Grignard reagent. After 10 min, the cooling bath is removed (or replaced with an ice bath) and the reaction mixture is stirred for 30 min. By this treatment the sulfoxide-metal exchange takes place and the aziridinylmagnesium **8** is obtained quantitatively. To this solution, powdered and dried Cu(I) iodide is added and the reaction mixture is stirred for 5 min. Finally, the appropriate alkylhalide (3.5 equivalents) is added to the reaction mixture. In the case of iodoethane, the reaction with 10 mol% of Cu(I) iodide at room temperature for 30 min gave the coupling product **9** in 86% yield as a single product (Scheme 2).

The stereochemistry of the product **9** was investigated with the ^{1}H NMR NOESY spectrum. Clear nOe between the hydrogen on the aziridine ring and the methyl group of the ethyl substituent was observed. From this result, the structure of **9** was unambiguously determined to be *E*. At the same time, it developed that the stereochemistry of the carbon bearing the sulfinyl group of **7** was retained; namely, this reaction took place stereospecifically.

The results for the cross-coupling of the aziridinylmagnesium **8** with several halides are summarized in Table 1. Entries 1–3 show that primary iodoalkanes gave quite good yields of the desired cross-coupling products. The reaction of allyl bromide and benzyl bromide with **8** took place even more vigorously to give the desired products in high yields within 5 min at 0°C (entries 4 and 5).

In contrast to these good results, secondary iodoalkane, 2-iodopropane, did not react with **8** even though 40 mol% of Cu(I) iodide and longer reaction time were used (entry 6). In order to develop the presented method to a new synthesis of aziridines having functional groups, iodoacetonitrile, ethyl iodoacetate, bromoacetaldehyde diethyl acetal, and THP-protected iodoethanol were treated with **8**; however, all these reactions failed (entries 7–10). Finally, reaction with iodobenzene was tried (entry 11); however, this again gave none of the desired cross-coupling product. We investigated this cross-coupling reaction with other

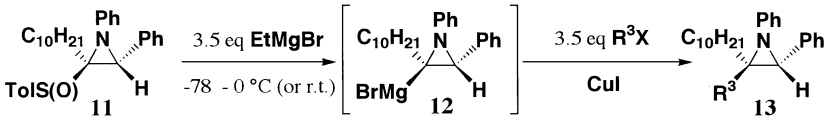
Table 1. Generation of aziridinylmagnesium **8** and cross-coupling with alkyl halides

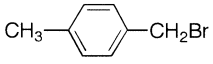
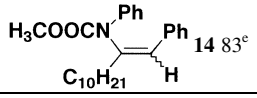


Entry	R^3X	CuI/mol%	Conditions °C (min)	Yield/%[a]
1	CH_3I	10	rt (30)	**10a** 87
2	$C_5H_{11}I$	10	rt (30)	**10b** 87
3	$C_{10}H_{21}I$	10	rt (30)	**10c** 94
4	CH_2=$CHCH_2Br$	10	0 (5)	**10d** 92
5	$PhCH_2Br$	10	0 (5)	**10e** 87
6	$(CH_3)_2CHI$	40	0 (120)	–[b]
7	$NCCH_2I$	40	0 (120)	–[b]
8	$EtOCOCH_2I$	40	rt (180)	–[b]
9	$(EtO)_2CHCH_2Br$	40	rt (180)	–[b]
10	$THPOCH_2CH_2I$	40	0 (180)	–[b]
11	PhI	40	rt (120)	–[b]

[a] Isolated yield after silica gel column chromatography. All the products were fully characterized by IR, ^{1}H NMR, MS (low and high-resolution).
[b] A complex mixture.

Table 2. Generation of aziridinylmagnesium **12** and cross-coupling with alkyl halides



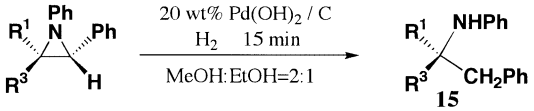
Entry	R^3X	CuI/mol%	Conditions °C (min)	Yield/%[a]
1	CH_3I	10	rt (30)	**13a** 94
2	$C_5H_{11}I$	10	rt (30)	**13b** 88
3	$C_{10}H_{21}I$	10	rt (30)	**13c** 83
4	$CH_2{=}CHCH_2Br$	10	0 (10)	**13d** 90
5	$PhCH_2Br$	10	0 (10)	**13e** 94
6		10	0 (15)	**13f** 93
7	CH_2Br_2	10	rt (15)	**13g** 15
8	CH_2I_2	20	rt (20)	– [c]
9	$TBDMSOCH_2CH_2I$	40	rt (180)	**13h** 66 [b]
10	$EtOCOCH_2I$	10	rt (15)	– [d]
11	$NCCH_2I$	20	rt (20)	– [c]
12	CH_3OCH_2Cl	20	rt (20)	– [c]
13	$H_3COCOCl$	20	rt (20)	 **14** 83[e]

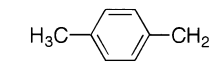
[a] Isolated yield after silica gel column chromatography. All the products were fully characterized by IR, ^1H NMR, MS (low and high-resolution).
[b] This product was isolated after deprotection of the TBDMS group by treatment of the initial product with TBAF.
[c] A complex mixture.
[d] The main product is the reduced aziridine **13** (R^3=H, 85% yield).
[e] Single isomer. The structure has not been determined.

metal catalysts, for example, Pd,[11a] Fe,[12a] Ni;[12b] however, these reactions only gave a complex mixture.

In order to discover the steric effect of this cross-coupling reaction at the carbon bearing the magnesium, the sulfinylaziridine having decyl group **11** was synthesized and the reaction was investigated (Table 2). As shown in Table 2, primary iodoalkanes gave high to quantitative yields of the desired cross-coupling products (entries 1–3). Allyl bromide and benzyl bromide also gave almost quantitative yields of the products (entries 4–6). No difference in reactivity between the aziridinyl magnesiums **8** and **12** with these haloalkanes was observed. The reaction with dibromomethane gave the desired product **13g** in low yield; however, diiodomethane gave only a complex mixture (entries 7 and 8). The reaction with TBDMS-protected 2-iodoethanol was found to be successful; however, this reaction required 40 mol% of Cu(I) iodide and longer reaction time. The product was isolated as an alcohol after treatment of the initial product with TBAF (entry 9). The reactions with ethyl iodoacetate, iodoacetonitrile, and chloromethyl methyl ether were unsuccessful (entries 10–12). Methyl chlorocarbonate reacted with the nitrogen of the aziridinyl magnesium **12** to give ring-opened product **14** in good yield (entry 13).

Table 3. Hydrogenation of the alkylated aziridines to the amines bearing a quaternary chiral center



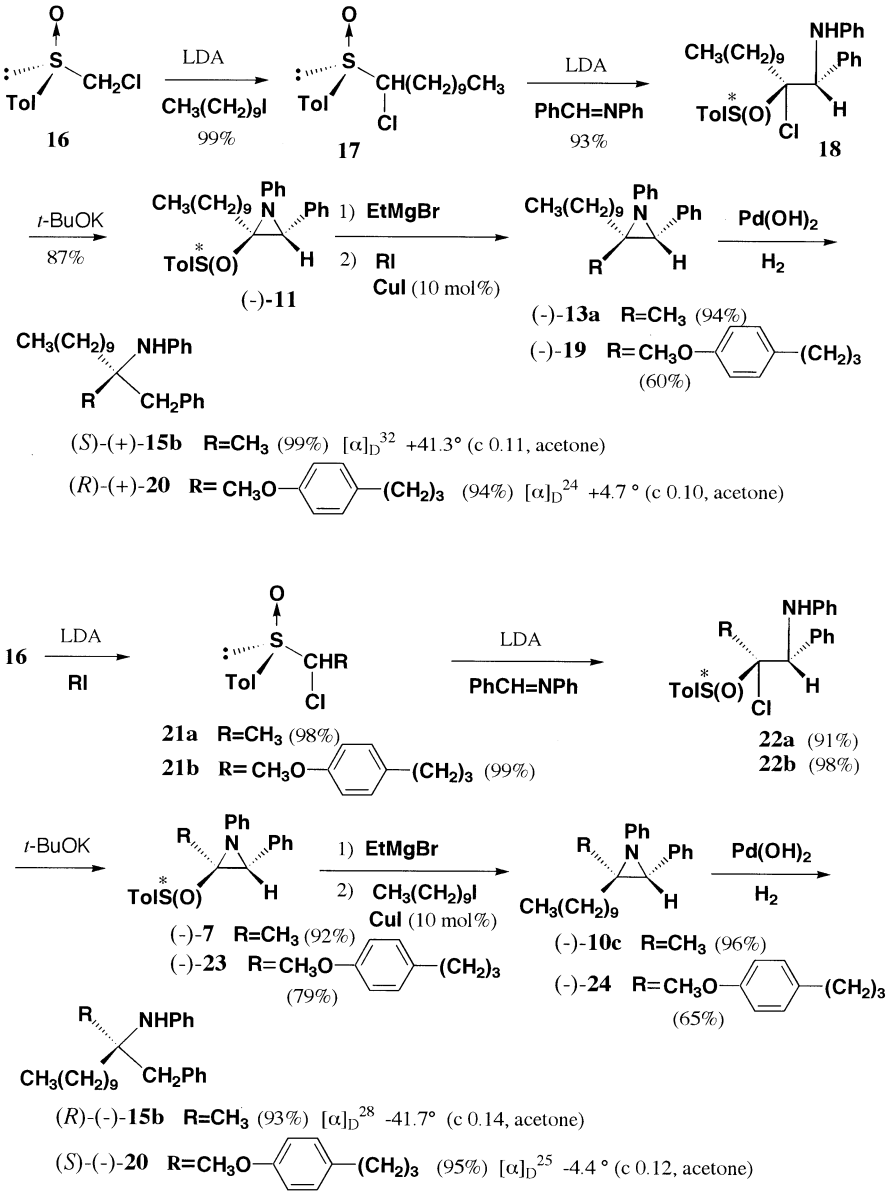
Entry		R^1	R^2	$Pd(OH)_2$ weight %	Yield/%
1	**9**	CH_3	C_2H_5	13	**15a** 98
2	**10c**	CH_3	$C_{10}H_{21}$	200	**15b** 99
3	**13a**	$C_{10}H_{21}$	CH_3	120	**15b** 93
4	**13b**	$C_{10}H_{21}$	C_5H_{11}	300	**15c** 98
5	**13e**	$C_{10}H_{21}$	$PhCH_2$	300	**15d** 97
6	**13f**	$C_{10}H_{21}$		140	**15e** 98
7	**13h**	$C_{10}H_{21}$	$HOCH_2CH_2$	200	**15f** 95[a]

[a] Methanol was used as the solvent.

1.2. Hydrogenolysis of the cross-coupling products

It has been known that aziridines are highly strained, and many types of ring-opening are possible.[13] We planned ring-opening of the cross-coupling products between the nitrogen and the benzylic carbon. The reaction would give us the amines bearing a quaternary carbon. We investigated the hydrogenolysis of the aziridines **9**, **10c**, and **13** and found that $Pd(OH)_2$ on carbon worked excellently.[14]

As shown in Table 3, the hydrogenolysis of the aziridines was conducted in a mixture of methanol and ethanol, because the solubility of **9**, **10c**, and **13** is somewhat low in methanol. The reaction took place excellently when 100–300 weight percent of 20% $Pd(OH)_2$ on carbon was used. However, when these reactions were conducted with less amount of $Pd(OH)_2$, considerable amounts of the starting materials remained. Prolonging these reactions was found not to be effective. It is worth noting that the product in entry 7 is γ,γ-disubstituted γ-amino alcohol.



Scheme 3. Asymmetric synthesis of both enantiomers of the optically active amines starting from one chiral starting material, (*R*)-chloromethyl *p*-tolyl sulfoxide **16**

1.3. The asymmetric synthesis of both enantiomers of the amines bearing a quaternary chiral carbon from one chiral starting material

As shown in Scheme 1, the final products amines **6** have two substituents, R^1 and R^2, on the stereogenic carbon. The first one (R^1) is introduced into the sulfinylaziridines **3** from **1** via the adducts **2**. The addition of the lithium α-sulfinyl carbanion of **1** to the imine was found to be highly stereoselective.[6] The second one (R^2) is introduced into the aziridine ring stereospecifically as described above. If the order of the introduction of the two substituents is changed and optically active sulfoxide is used, we would be able to obtain both enantiomers of the amines bearing a quaternary chiral center from one chiral starting material, (*R*)-chloromethyl *p*-tolyl sulfoxide **16**[15] (Scheme 3).

First, optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide **16** was decylated to give **17** as a mixture of two diastereomers. The lithium α-carbanion of **17** was added to benzalaniline to afford stereoselectively only one adduct **18**, which was treated with potassium *tert*-butoxide to give the optically active sulfinylaziridine (−)-**11** in high overall yield. As already reported, the absolute configuration of the sulfinylaziridine (−)-**11** was determined to be as shown in Scheme 3.[6]

The optically active (−)-**11** was treated with 3.5 equivalents of EtMgBr followed by iodomethane in the presence of 10 mol% of Cu(I) iodide to give the aziridine (−)-**13a** in 94% yield. The reaction with 3-(4-methoxyphenyl)-1-iodopropane gave (−)-**19** in somewhat lower yield (60%). The aziridines were hydrogenolized with $Pd(OH)_2$ in a mixture of methanol-ethanol to give (*S*)-(+)-**15b** and (*R*)-(+)-**20** in almost quantitative yields. The optical purity of these two amines was easily determined by using a chiral stationary

column (CHIRALCEL OD (Daicel); hexane or hexane: 2-propanol=200:1 as a developing solvent). The enantiomeric excess (ee) of both amines was found to be over 99%.

Next, we tried to synthesize the enantiomers of the amines from the same starting sulfoxide (*R*)-**16**. (*R*)-Chloromethyl *p*-tolyl sulfoxide **16** was alkylated with iodomethane and 3-(4-methoxyphenyl)-1-iodopropane to give **21a** and **21b**, respectively, in high yields as a mixture of two diastereomers. The products were again treated with lithium diisopropylamide followed by benzalaniline to afford the adducts **22a** and **22b** stereoselectively as single isomers. These were treated with potassium *tert*-butoxide to give the sulfinylaziridines (−)-**7** and (−)-**23** in good overall yields. Generation of the aziridinylmagnesiums and the cross-coupling with iododecane were carried out as described above to give the desired aziridines (−)-**10c** and (−)-**24**. The yield of the optically active aziridine (−)-**10c** was excellent; however, again the cross-coupling with 3-(4-methoxyphenyl)-1-iodopropane gave somewhat lower yield. The hydrogenolysis of the aziridines (−)-**10c** and (−)-**24** gave the amines (*R*)-(−)-**15b** and (*S*)-(−)-**20**, respectively, in 93% and 95% yields. As shown in Scheme 3, the values of the specific rotation of the optically active amines **15b** and **20** are almost the same; however, the signs are opposite. The enantiomeric excess of the products (*R*)-(−)-**15b** and (*S*)-(−)-**20** was determined with a chiral column as described above and ee of these amines was found to be over 99%.

In conclusion, we have established a new method for synthesizing amines bearing a quaternary chiral carbon from 1-chloroalkyl *p*-tolyl sulfoxides, imines, and alkylhalides. The key step of this method is the generation of aziridinylmagnesiums and stereospecific cross-coupling of the anions with alkylhalides. Based on the presented method, we were able to synthesize both enantiomers of the amines from one chiral starting material, (*R*)-chloromethyl *p*-tolyl sulfoxide, in optically pure form.

2. Experimental

2.1. General

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 400 and 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (MERCK) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry solvent, THF was distilled from benzophenone ketyl; HMPA and diisopropylamine were distilled from CaH_2.

2.1.1. Sulfinylaziridines 7, 11, (−)-7, and (−)-11. The synthesis of these sulfinylaziridines has been reported in a previous paper; see lit.[6]

2.1.2. (*E*)-2-Ethyl-2-methyl-1,3-diphenylaziridine (9). A solution of **7** (80 mg, 0.24 mmol) in a minimum amount (about 0.5 ml) of dry THF was added dropwise with stirring to a solution of EtMgBr (1.02 mol/l in THF; 0.83 ml, 0.84 mmol) in 5 ml of THF in a flame-dried flask at −78°C. After being stirred for 10 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 30 min to give aziridinylmagnesium **8**. To this solution, Cu(I) iodide (4 mg, 10 mol%) was added and after 5 min, iodoethane (0.067 ml, 0.84 mmol) was added and the reaction mixture was stirred for 30 min. The reaction was quenched by adding saturated aqueous NH_4Cl and the solution was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford 49 mg (86%) of **9** as a colorless oil. IR (neat) 3026, 2962, 2924, 1598, 1493, 1269 cm^{-1}; ^{1}H NMR δ 0.86–0.94 (1H, m), 1.07 (3H, t, J=7.5 Hz), 1.09 (3H, s), 1.69–1.76 (1H, m), 3.13 (1H, s), 6.88–7.00 (3H, m), 7.20–7.41 (7H, m). MS *m/z* (%) 237 (M^+, 37), 167 (75), 91 (100). Calcd for $C_{17}H_{19}N$: M, 237.1516. Found: *m/z* 237.1510.

2.1.3. 2,2-Dimethyl-1,3-diphenylaziridine (10a). Colorless oil; IR (neat) 2955, 2922, 1597, 1488, 1255 cm^{-1}; ^{1}H NMR δ 1.11 (3H, s), 1.17 (3H, s), 3.14 (1H, s), 6.91–6.98 (3H, m), 7.22–7.43 (7H, m). MS *m/z* (%) 223 (M^+, 42), 208 (18), 167 (100). Calcd for $C_{16}H_{17}N$: M, 223.1359. Found: *m/z*223.1359.

2.1.4. (*E*)-2-Methyl-2-pentyl-1,3-diphenylaziridine (10b). Colorless oil; IR (neat) 3027, 2929, 1597, 1487, 1270 cm^{-1}; ^{1}H NMR δ 0.70–0.85 (1H, m), 0.89 (3H, t, J=6.7 Hz), 1.10 (3H, s), 1.20–1.80 (7H, m), 3.12 (1H, s), 6.90–7.00 (3H, m), 7.18–7.44 (7H, m). MS *m/z* (%) 279 (M^+, 30), 236 (59), 167 (60), 118 (60), 91 (100). Calcd for $C_{20}H_{25}N$: M, 279.1985. Found: *m/z* 279.1970.

2.1.5. (*E*)-2-Decyl-2-methyl-1,3-diphenylaziridine (10c). Colorless oil; IR (neat) 2924, 2853, 1598, 1488, 1266 cm^{-1}; ^{1}H NMR δ 0.78 (2H, m), 0.88 (3H, t, J=7.0 Hz), 1.08 (3H, s), 1.24 (10H, m), 1.42–1.77 (6H, m), 3.13 (1H, s), 6.91–6.97 (3H, m), 7.20–7.42 (7H, m). MS *m/z* (%) 349 (M^+, 25), 236 (75), 91 (100). Calcd for $C_{25}H_{35}N$: M, 349.2767. Found: *m/z* 349.2767. **(−)-10c**: Colorless oil; $[\alpha]_D^{29}$ −106.6° (c 0.1, acetone).

2.1.6. (*E*)-2-Allyl-2-methyl-1,3-diphenylaziridine (10d). Colorless oil; IR (neat) 3062, 3029, 1639, 1596, 1488, 1264 cm^{-1}; ^{1}H NMR δ 1.10 (3H, s), 1.67 (1H, dd, J=6.7, 14 Hz), 2.44 (1H, dd, J=6.7, 14 Hz), 3.22 (1H, s), 5.06 (1H, d, J=5.0 Hz), 5.09 (1H, s), 5.83–5.91 (1H, m), 6.93–6.98 (3H, m), 7.22–7.41 (7H, m). MS *m/z* (%) 249 (M^+, 37), 248 (100), 234 (30). Calcd for $C_{18}H_{19}N$: M, 249.1515. Found: *m/z* 249.1497.

2.1.7. (*E*)-2-Benzyl-2-methyl-1,3-diphenylaziridine (10e). Colorless oil; IR (neat) 3060, 3027, 2923, 1598, 1487, 1261 cm^{-1}; ^{1}H NMR δ 1.04 (3H, s), 2.16 (1H, d, J=14 Hz), 3.00 (1H, d, J=14 Hz), 3.52 (1H, s), 7.00–7.13 (3H, m), 7.23–7.37 (12H, m). MS *m/z* (%) 299 (M^+, 60), 208 (76), 167 (100), 91 (87). Calcd for $C_{22}H_{21}N$: M, 299.1672. Found: *m/z* 299.1664.

2.1.8. (*Z*)-2-Decyl-2-methyl-1,3-diphenylaziridine (13a).

Colorless oil; IR (neat) 2924, 2853, 1733, 1598, 1488, 1272 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7.0 Hz), 1.13 (3H, s), 1.11–1.46 (18H, m), 3.15 (1H, s), 6.90–6.98 (3H, m), 7.22–7.43 (7H, m). MS *m/z* (%) 349 (M^+, 32), 236 (80), 91 (100). Calcd for $C_{25}H_{35}N$: M, 349.2767. Found: *m/z* 349.2764. **(−)-13a**: Colorless oil; $[\alpha]_D^{28}$ −80.0° (c 0.17, acetone).

2.1.9. (*Z*)-2-Decyl-2-pentyl-1,3-diphenylaziridine (13b). Colorless oil; IR (neat) 2925, 2854, 1598, 1488, 1270 cm^{-1}; ^1H NMR δ 0.57–0.63 (2H, m), 0.88 (6H, t, J=7.0 Hz), 1.24–1.30 (16H, m), 1.39–1.44 (2H, m), 1.45–1.57 (4H, m), 1.85–1.91 (2H, m), 3.16 (1H, s), 6.91–6.97 (3H, m), 7.21–7.41 (7H, m). MS *m/z* (%) 405 (M^+, 33), 223 (60), 91 (100). Calcd for $C_{29}H_{43}N$: M, 405.3396. Found: *m/z* 405.3386.

2.1.10. 2,2-Didecyl-1,3-diphenylaziridine (13c). Colorless oil; IR (neat) 2923, 2853, 1598, 1488 cm^{-1}; ^1H NMR δ 0.56–0.62 (2H, m), 0.88 (6H, t, J=7.0 Hz), 1.19–1.29 (34H, m), 3.16 (1H, s), 6.91–6.97 (3H, m), 7.21–7.41 (7H, m). MS *m/z* (%) 475 (M^+, 1), 405 (17), 335 (25), 223 (50), 91 (100). Calcd for $C_{34}H_{53}N$: M, 475.4174. Found: *m/z* 475.4161

2.1.11. (*E*)-2-Allyl-2-decyl-1,3-diphenylaziridine (13d). Colorless oil; IR (neat) 3062, 3028, 2924, 2853, 1639, 1598, 1487, 1261 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7.0 Hz), 1.23 (14H, m), 1.40–1.59 (5H, m), 2.57 (1H, dd, J=7.9, 14 Hz), 3.25 (1H, s), 5.06 (1H, m), 5.09 (1H, m), 5.86 (1H, m), 6.92–6.98 (3H, m), 7.22–7.40 (7H, m). MS *m/z* (%) 375 (M^+, 35), 374 (100), 360 (9). Cacld for $C_{27}H_{37}N$: M, 375.2924. Found: *m/z* 375.2896.

2.1.12. (*E*)-2-Benzyl-2-decyl-1,3-diphenylaziridine (13e). Colorless oil; IR (neat) 3062, 3027, 2923, 2853, 1599, 1487, 1255 cm^{-1}; ^1H NMR δ 0.79–0.83 (1H, m), 0.87 (3H, t, J=7.0 Hz), 1.20–1.33 (15H, m), 1.60–1.77 (2H, m), 2.00 (1H, d, J=14 Hz), 3.14 (1H, d, J=14 Hz), 3.54 (1H, s), 6.98–7.03 (3H, m), 7.20–7.38 (12H, m). MS *m/z* (%) 425 (M^+, 10), 167 (37), 91 (100). Calcd for $C_{31}H_{39}N$: M, 425.3080. Found: *m/z* 425.3079.

2.1.13. (*E*)-2-Decyl-2-(4-methylphenyl)methyl-1,3-diphenylaziridine (13f). Colorless oil; IR (neat) 3024, 2923, 2853, 1597, 1488, 1453, 1270 cm^{-1}; ^1H NMR δ 0.77 (2H, dt, J=4.6, 13 Hz), 0.88 (3H, t, J=7 Hz), 1.23–1.72 (16H, m), 1.95 (1H, d, J=14 Hz), 2.32 (3H, s), 3.10 (1H, d, J=14 Hz), 3.53 (1H, s), 6.95–7.43 (14H, m). MS *m/z* (%) 439 (M^+, 50), 181 (83), 91 (100). Calcd for $C_{32}H_{41}N$: M, 439.3239. Found: *m/z* 439.3253.

2.1.14. (*E*)-2-Bromomethyl-2-decyl-1,3-diphenylaziridine (13g). Colorless oil; IR (neat) 2924, 2853, 1599, 1488, 1452, 1410 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7.0 Hz), 1.23–1.81 (18H, m), 2.96 (1H, dd, J=1.2, 11 Hz), 3.41 (1H, s), 3.62 (1H, d, J=11 Hz), 6.96–7.45 (10H, m). MS *m/z* (%) 427 (M^+, 0.4), 348 (56), 244 (100). Cacld for $C_{25}H_{34}NBr$: M, 427.1874. Found: *m/z* 427.1870.

2.1.15. (*E*)-2-Decyl-2-(2-hydroxyethyl)-1,3-diphenylaziridine (13h). A solution of **11** (473.7 mg, 1 mmol) in a minimum amount (about 0.5 ml) of dry THF was added dropwise with stirring to a solution of EtMgBr (3.5 mmol) in 20 ml of THF in a flame-dried flask at −78°C. After 10 min, the reaction mixture was allowed to warm to room temprature and stirred for 30 min to give aziridinylmagnesium **12**. To this solution, Cu(I) iodide (76 mg, 40 mol%) was added. The reaction mixture was stirred for 5 min and then 1-O-(*tert*-butyldimethylsilyl)-2-iodoethane (1 g, 3.5 mmol) was added and the reaction mixture was stirred for 180 min. To this solution tetrabutylammonium fluoride (TBAF; THF solution, 9.8 mmol) was added and the reaction was monitored on TLC. The reaction was quenched by adding saturated aqueous NH_4Cl and the whole solution was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford 250 mg (66%) of **13h** as a colorless oil; IR (neat) 3385 (OH), 2925, 2854, 1598, 1488 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7.0 Hz), 1.24–1.34 (18H, m), 1.37–1.43 (1H, m), 1.58 (1H, m), 2.14 (1H, ddd, J=6.8, 4.9, 13 Hz), 3.29 (1H, s), 3.78–3.84 (2H, m), 6.91–6.99 (3H, m), 7.22–7.42 (7H, m). MS *m/z* (%) 379 (M^+, 24), 253 (30), 167 (29), 91 (100). Calcd for $C_{26}H_{37}NO$: M, 379.2875. Found: *m/z* 379.2874.

2.1.16. Methyl *N*-(1-decyl-2-phenylethenyl)-*N*-phenyl carbamate (14). Colorless oil; IR (neat) 2924, 2853, 1714 (CO), 1597, 1494, 1439, 1318 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=6.8 Hz), 1.17–1.37 (14H, m), 1.49–1.58 (2H, m), 2.32 (2H, t, J=8 Hz), 3.76 (3H, s), 6.53 (1H, s), 7.20–7.40 (10H, m). MS *m/z* (%) 393 (M^+, 78), 302 (43), 267 (100). Calcd for $C_{26}H_{35}NO_2$: M, 393.2668. Found: *m/z* 393.2671.

2.1.17. 1-Methyl-1-phenyl-2-phenylaminododecane (15b). Palladium hydroxide (20 wt% Pd (dry basis) on carbon; 140 mg, 200 wt%) was added to a solution of **10c** (70.7 mg) in 6 ml of a mixture of MeOH:EtOH= 2:1. The reaction mixture was stirred for 15 min under hydrogen atmosphere. The catalyst was filtered off and the solvent was evaporated under vacuum to afford 70.7mg (99%) of pure **15b** as a colorless oil; IR (neat) 3421 (NH), 3025, 2925, 2852, 1600, 1496 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7.0 Hz), 1.20 (3H, s), 1.24 (12H, m), 1.39–1.41 (2H, m), 1.48–1.56 (2H, m), 1.73–1.81 (2H, m), 2.82 (1H, d, J=13 Hz), 3.07 (1H, d, J=13 Hz), 3.40 (1H, b), 6.69–6.72 (3H, m), 7.07–7.42 (7H, m). MS *m/z* (%) 351 (M^+, 3), 260 (100). Calcd for $C_{25}H_{37}N$: M, 351.2923. Found: *m/z* 351.2918. **(*R*)-(−)-15b**: Colorless oli; $[\alpha]_D^{28}$ −41.7° (c 0.14, acetone). **(*S*)-(+)-15b**: Colorless oli; $[\alpha]_D^{32}$ +41.3° (c 0.11, acetone).

2.1.18. 2-Benzyl-2-phenylaminobutane (15a). Colorless oil; IR (neat) 3415 (NH), 2968, 1599, 1495, 1453, 1313 cm^{-1}; ^1H NMR δ 0.94 (3H, t, J=7.7 Hz), 1.17 (3H, s), 1.57, 1.85 (each 1H, dq, J=7.5, 15 Hz), 2.84, 3.07 (each 1H, d, J=13 Hz), 6.61–6.76 (3H, m), 7.09–7.31 (7H, m). MS *m/z* (%) 239 (M^+, 0.9), 148 (100). Cacld for $C_{17}H_{21}N$: M, 239.1688. Found: *m/z* 239.1680.

2.1.19. 6-Benzyl-6-phenylaminohexadecane (15c). Colorless oil; IR (neat) 3417 (NH), 3027, 2927, 2853, 1600, 1495, 1454 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7.3 Hz), 0.88 (3H, t, J=6.6 Hz), 1.24–1.64 (26H, m), 2.93 (2H, s), 3.31 (1H, b), 6.64–6.73 (3H, m), 7.05–7.27 (7H, m). MS *m/z* (%) 407 (M^+, 0.8), 316 (100). Cacld for $C_{29}H_{45}N$: M, 407.3550. Found: *m/z* 407.3561.

2.1.20. 2-Benzyl-1-phenyl-2-phenylaminododecane (15d). Colorless oil; IR (neat) 3420 (NH), 2924, 2853, 1600, 1497, 1456 cm^{-1}; ^1H NMR δ 0.82–0.89 (3H, m), 1.24–1.38 (18H, m), 2.90 (2H, d, J=14 Hz), 3.26 (2H, d, J=14 Hz), 6.71–6.76 (2H, m), 7.13–7.25 (13H, m). MS m/z (%) 426 ([M-H]$^+$, 0.5), 336 (100). Cacld for $C_{31}H_{40}N$: M, 426.3158. Found: m/z 426.3150.

2.1.21. 2-Benzyl-1-(4-methylphenyl)-2-phenylaminododecane (15e). Colorless oil; IR (neat) 3386 (NH), 2922, 2851, 1600, 1598, 1508, 1496, 1456 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=7.0 Hz), 1.20–1.54 (18H, m), 2.30 (3H, s), 2.89 (2H, t, J=14 Hz), 3.23 (2H, t, J=14 Hz), 3.45 (1H, bs), 6.70–6.77 (3H, m), 7.03–7.25 (11H, m). MS m/z (%) 441 (M$^+$, 0.3), 440 (0.8), 350 (60), 336 (100). Calcd for $C_{32}H_{43}N$: M, 441.3395. Found: m/z 441.3384.

2.1.22. 3-Benzyl-3-phenylamino-1-tridecanol (15f). Colorless oil; IR (neat) 3370 (NH, OH), 2925, 2853, 1600, 1496 cm^{-1}; ^1H NMR δ 0.89 (3H, t, J=7.0 Hz), 1.20–1.60 (18H, m), 1.88 (1H, m), 2.03 (1H, m), 2.9 (1H, d, J=11 Hz), 3.05 (1H, d, J=11 Hz), 3.83–3.91 (2H, m), 6.77–7.28 (10H, m). MS m/z (%) 381 (M$^+$, 1), 290 (100). Calcd for $C_{26}H_{39}NO$: M, 381.3031. Found: m/z 381.3036.

2.1.23. (2*R*,3*R*)-(−)-2-Decyl-2-[3-(4-methoxyphenyl)propyl]-1,3-diphenylaziridine (19). Colorless oil; IR (neat) 2923, 2853, 1597, 1513, 1487, 1453, 1246 cm^{-1}; ^1H NMR δ 0.70 (1H, m), 0.88 (3H, t, J=6.8 Hz), 0.91–0.95 (1H, m), 1.24–2.47 (20H, m), 2.43–2.61 (2H, m), 3.17 (1H, s), 3.79 (3H, s), 6.80–7.40 (14H, m). MS m/z (%) 483 (M$^+$, 26), 362 (100). Calcd for $C_{34}H_{45}NO$: M, 483.3501. Found: m/z 483.3489. $[\alpha]_D^{27}$ −71.6° (c 0.18, acetone).

2.1.24. (*R*)-(+)-4-Benzyl-1-(4-methoxyphenyl)-4-phenylaminotetradecane (20). Colorless oil; IR (neat) 3422 (NH), 2924, 2853, 1600, 1513, 1456, 1246 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7.0 Hz), 1.20–1.30 (20H, m), 1.59–1.65 (2H, m), 2.51 (4H, m), 3.78 (3H, s), 6.63–7.26 (14H, m). MS m/z (%) 485 (M$^+$, 0.6), 484 (1), 394 (100). Cacld for $C_{34}H_{47}NO$: M, 485.3658. Found: m/z 485.3676. $[\alpha]_D^{24}$ +4.7° (c 0.10, acetone). **(*S*)-(−)-20**: $[\alpha]_D^{25}$ −4.4° (c 0.12, acetone).

2.1.25. 1-Chloro-4-(4-methoxyphenyl)-1-(*p*-tolylsulfinyl)-butane (21b). A solution of **16** (164 mg, 0.87 mmol) in a minimum amount of dry THF was added dropwise with stirring to a solution of LDA (1.11mmol) in 2 ml of THF in a flame-dried flask at −70°C. After 10 min, 314 mg (1.13 mmol) of 3-(4-methoxyphenyl)-1-iodopropane was added to the reaction mixture. The reaction mixture was stirred and allowed to warm to −35°C and then saturated aqueous NH_4Cl was added. The solution was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford **21b** (289 mg, 99%) as a colorless oil; a mixture of two diastereomers; IR (neat) 2944, 1513, 1245, 1055 (SO), 811 cm^{-1}; ^1H NMR δ 1.58–2.01 (3H, m), 2.19–2.28 (1H, m), 2.43 (3H, s), 2.52–2.63 (2H, m), 3.80 (3H, s), 4.38 (0.5H, dd, J=3.0, 9.5 Hz), 4.48 (0.5H, dd, J=3.9, 9.7 Hz), 6.80–7.61 (8H, m). MS m/z (%) 336 (M$^+$, 1), 319 (1), 197 (25), 161 (71), 121 (100). Cacld for $C_{18}H_{21}ClO_2S$: M, 336.0950. Found: m/z 336.0960.

2.1.26. (1*R,2*R**,*R**$_S$)-2-Chloro-5-(4-methoxyphenyl)-1-phenyl-1-(phenylamino)-2-(*p*-tolylsulfinyl)pentane (22b).** A solution of **21b** (49 mg, 0.14 mmol) in a minimum amount (about 0.5 ml) of dry THF was added dropwise with stirring to a solution of LDA (0.52 mmol) in 3.6 ml of THF in a flame-dried flask at −60°C. After 10 min, a solution of benzalaniline (94 mg, 0.52 mmol) in THF was added to the reaction mixture and the reaction mixture was stirred for 10 min. The reaction was quenched with saturated aqueous NH_4Cl. The whole solution was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to give racemic **22b** (74 mg, 98%) as crystals. Recrystallization of the product from AcOEt-hexane gave colorless crystals; mp 151–152.5°C. IR (KBr) 3291 (NH), 2952, 1700, 1512, 1244, 1037 (SO) cm^{-1}; ^1H NMR δ 1.92–2.74 (6H, m), 2.34 (3H, s), 3.79 (3H, s), 4.14 (1H, s), 6.26–7.70 (18H, m). MS m/z (%) 517 (M$^+$, 0.2), 377 (26), 140 (34), 121 (100). Anal. Cacld for $C_{31}H_{32}ClNO_2S$: C, 71.93; H, 6.23; Cl, 6.76; N, 2.71; S, 6.19. Found: C, 71.62; H, 6.12; Cl, 7.02; N, 2.69; S, 6.12. High Mass: M, 517.1842. Found: m/z 517.1848. **(1*R*,2*R*,*R*$_S$)-(−)-22b**: Colorless crystals; mp 167–168°C (Hex:EtOAc=1:1); IR (KBr) 3294 (NH), 2952, 1700, 1599, 1512, 1246, 1037 (SO) cm^{-1}; $[\alpha]_D^{23}$ −230° (c 0.1, $CHCl_3$).

2.1.27. (2*R,3*R**,*R**$_S$)-2-[3-(4-Methoxyphenyl)propyl]-2-(*p*-tolylsulfinyl)-1,3-diphenylaziridine (23).** To a solution of **22b** (174 mg, 0.34 mmol) in a 1:1 mixture of *t*-BuOH-THF (8.6 ml) was added 110 mg (0.98 mmol) of *t*-BuOK. The reaction mixture was stirred and heated at 70°C for 20 min. The reaction was quenched with saturated aqueous NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed with water and dried over $MgSO_4$. After usual work-up, the product was purified by silica gel column chromatograpyh to give 127.8 mg (79%) of **23** as colorless crystals; mp 170–171°C (Hex:EtOAc=1:1); IR (KBr) 3027, 2920, 1595, 1509, 1253, 1034 (SO) cm^{-1}; ^1H NMR δ 1.01–1.20 (2H, m), 1.91–2.02 (1H, m), 2.06–2.17 (1H, m), 2.28–2.34 (1H, m), 2.36 (3H, s), 2.53–2.60 (1H, m), 3.81 (3H, s), 4.60 (1H, s), 6.79–7.46 (18H, m). MS m/z (%) 481 (M$^+$, 0.3), 465 (0.7), 342 (100). Anal. Cacld for $C_{31}H_{31}NO_2S$: C, 77.30; H, 6.49; N, 2.91; S, 6.66. Found: C, 77.00; H, 6.32; N, 2.89; S, 6.67. High Mass: M, 481.2075. Found: m/z 481.2083. **(2*R*,3*R*,*R*$_S$)-(−)-23**: Colorless crystals; mp 110–111°C (Hex:EtOAc=1:1); IR (KBr) 2925, 1595, 1511, 1234, 1051, 1034 (SO) cm^{-1}; $[\alpha]_D^{22}$ −2.3° (c 0.1, acetone),

2.1.28. (2*S,3*R**)-2-Decyl-2-[3-(4-methoxyphenyl)propyl]-1,3-diphenylaziridine (24).** Colorless oil; IR (neat) 2926, 2855, 1598, 1512, 1487, 1453, 1415, 1300, 1245, 1175, 1037 cm^{-1}; ^1H NMR δ 0.58 (1H, m), 0.86 (3H, t, J=7.0 Hz), 0.98 (1H, m), 1.23 (14H, m), 1.46 (2H, m), 1.85 (4H, m), 2.46 (1H, m), 2.55 (1H, m), 3.17 (1H, s), 3.78 (3H, s), 6.79–7.39 (14H, m). MS m/z (%) 483 (M$^+$, 24), 362 (100), 342 (29), 223 (71). Cacld for $C_{34}H_{45}NO$: M, 483.3501. Found: m/z 483.3499. **(2*S*,3*R*)-(−)-24**: Colorless oil; $[\alpha]_D^{26}$ −99.7° (c 0.11, acetone).

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References

1. Some recent reviews for the construction of quaternary carbon centers: (a)Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angev. Chem. Int. Ed.* **1998**, *37*, 388. (d) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.
2. (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (c) Sano, S.; Nagao, Y. J. *Syn. Org. Chem. Jpn.* **2000**, *58*, 756.
3. (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) In *Enantioselective Synthesis of α-Amino Acids*, Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (c) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12 and references therein.
4. (a) Willems, J. G. H.; de Vries, J. G.; Nolte, R. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 3917. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (c) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. (d) North, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2209.
5. (a) Satoh, T.; Ozawa, M.; Takano, K.; Kudo, M. *Tetrahedron Lett.* **1998**, *39*, 2345. (b) Satoh, T.; Ozawa, M.; Takano, K.; Chyouma, T.; Okawa, A. *Tetrahedron* **2000**, *56*, 4415.
6. Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973.
7. Satoh, T. J. *Syn. Org. Chem. Jpn.* **1996**, *54*, 481.
8. A review for the aziridinyl anions: Satoh, T. *Chem. Rev.* **1996**, *96*, 3303.
9. Preliminary results of this study were reported as a communication:Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron Lett.* **2000**, *41*, 6495.
10. *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
11. (a) Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2831. (b) Cahiez, G.; Chaboche, C.; Jezequel, M. *Tetrahedron* **2000**, *56*, 2733.
12. (a) Neumann, S. M.; Koch, J. K. *J. Org. Chem.* **1975**, *40*, 599. (b) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199. (c) Wakefield, B. J. In *Organomagnesium Methods in Organic Synthesis*, Academic Press: London, 1995; pp 151–169.
13. (a) Kametani, T.; Honda, T. *Advances in Heterocyclic Chemistry*, Katritzky, A. R., Ed.; Academic Press: New York, 1986; 39, pp 181. (b) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 2537. (c) McCoull, W. M.; Davis, F. A. *Synthesis* **2000**, 1347.
14. (a) Lim, Y.; Lee, W. K. *Tetrahedron Lett.* **1995**, *36*, 8431. (b) Choi, S.-K.; Lee, J.-S.; Kim, J.-H.; Lee, W. K. *J. Org. Chem.* **1997**, *62*, 743. (c) Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. (d) Chang, J.-W.; Bae, J. H.; Shin, S.-H.; Park, C. S.; Choi, D.; Lee, W. K. *Tetrahedron Lett.* **1998**, *39*, 9193.
15. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130.