Copper-Catalyzed *Ritter*-Type Reaction of Unactivated Alkenes with Dichloramine-T

by **Takumi Abe**[a]), **Hiroyuki Takeda**[a]), **Yoshihisa Miwa**[b]), **Koji Yamada**[a]), **Reiko Yanada**[b]), and **Minoru Ishikura***[a])

[a]) Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan (phone & fax: +81-133-23-1245; e-mail: ishikura@hoku-iryo-u.ac.jp)
[b]) Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure, Hiroshima 737-0112, Japan

It was shown that dichloramine-T (**1**) reacted with cyclohexene in acetonitrile to give N^1-(2-chlorocyclohexyl) amidine **2a** and *N*-(2-chlorocyclohexyl)acetamide (**3**) *via* the competitive addition of acetonitrile and *N*-chloro-*N*-tosylamino anion to cyclohexenechloronium ion. This reaction can be catalyzed by $Cu(OAc)_2$, primarily affording **2a**. Furthermore, the resulting **2a** can be cyclized to benzimidazol **14a** in good yield by treating with KOH in dioxane.

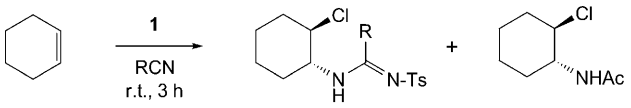
Introduction. – *N*-Chlorosulfonylamide derivatives (such as chloramine-T (TsNClNa), dichloramine-T (= *N*,*N*-dichloro-4-methylbenzenesulfonamide; $TsNCl_2$; **1**)) are known to react with various kinds of functional groups and are used extensively in various chemical transformations [1]. Recently, *Li et al.* have reported that treatment of *N*,*N*-dichloro-2-nitrobenzenesulfonamide (2-$NsNCl_2$) with cyclohexene in MeCN can produce vicinal *trans*-diamine in high yield through the ring opening of initially formed *N*-chloro-*N*-nosylaziridinium intermediate by attack of MeCN *via* an S_N2 mechanism [2]. Of particular interest was the metal-catalyzed vicinal *cis*-diamination reaction of electron-deficient alkenes (cinnamate esters, α,β-unsaturated ketones) by treating with **1**; a metal-catalyzed *Ritter*-type reaction of **1** with methyl *trans*-cinnamate in MeCN proceeded with a high degree of stereoselectivity and regioselectivity to afford *anti*-dihydroimidazoles, in which the ring opening of *N*-chloro-*N*-tosylaziridinium intermediate by attack of MeCN in a *syn*-manner with the aid of metal catalyst, followed by cyclization to the dihydroimidazole, was postulated as the key step [3].

The noticeable vicinal diamination processes prompted us to reevaluate the reaction using unactivated alkenes with **1** in MeCN. We found that initial treatment of cyclohexene with **1** in MeCN without metal catalyst did not afford the expected diamine; instead, N^1-(2-chlorocyclohexyl) amidine **2a** and *N*-(2-chlorocyclohexyl)acetamide **3** were isolated. Furthermore, the reaction was accelerated by catalyzing with $Cu(OAc)_2$, affording **2a** as a primary product. *Li et al.* have also developed a successful vicinal chloroamination reaction of **1** with electron-deficient alkenes catalyzed by $Cu(OTf)_2$ or $ZnCl_2$ in MeCN; this was again explained by the formation of the *N*-tosylaziridinium intermediate, followed by ring opening by attack of a chlorine anion [4]. Intrigued by the alteration of the reaction outcome observed by us compared to the

reports of *Li et al.*, we have further examined the reaction of **1** with unactivated alkenes. Our experimental results are described herein.

Results and Discussion. – When cyclohexene was initially subjected to the reaction with dichloramine-T (**1**; 1.5 equiv.) in MeCN at room temperature for 3 h, the amidine **2a** as a mixture of (*E*)/(*Z*) isomers in 45% yield and the known acetamide **3** [5] in 40% yield were isolated (*Table 1*, *Run 1*). The structure of **2a** was assigned based on ^{1}H-NMR NOESY experiments; the NOE correlation between H_a (δ 3.39–3.46 and 3.98–4.04; 2*m*) and H_b (δ 3.68–3.76) was negligible, while irradiation of N*H* (δ 5.71) provided large NOE effects on H_a and Me (δ 2.36; *Fig.*).

Table 1. *Reaction of Cyclohexene with Dichloramines* (**1**) *in RCN*



2 **3**

Run	Catalyst (10 mol-%)	RCN	Yield [%][a])	
			2	**3**
1	–	MeCN	45 (**2a**)	40
2	$Pd(OAc)_2$	MeCN	28 (**2a**)	12
3	$[Rh(COD)Cl]_2$	MeCN	45 (**2a**)	19
4	CuOTf	MeCN	58 (**2a**)	10
5	$Cu(OAc)_2$	MeCN	90 (**2a**)	–
6	$Cu(OAc)_2$	MeCN/H_2O 5 : 1	90 (**2a**)	–
7	$Cu(OAc)_2$	MeCN/THF 1 : 5	75 (**2a**)	–
8	$Cu(OAc)_2$	EtCN	–	–
9	$Cu(OAc)_2$	EtCN/THF 1 : 5	49 (**2b**)	–
10	$Cu(OAc)_2$	PhCN/THF 1 : 5	40 (**2c**)	–
11	$Cu(OAc)_2$	$ClCH_2CN$/THF 1 : 5	67 (**2d**)	–

[a]) Yields based on cyclohexene.

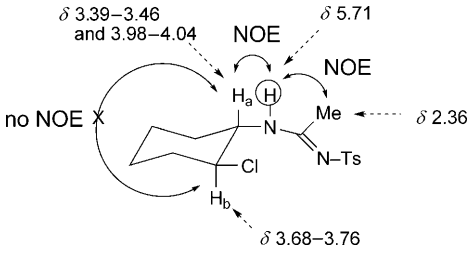


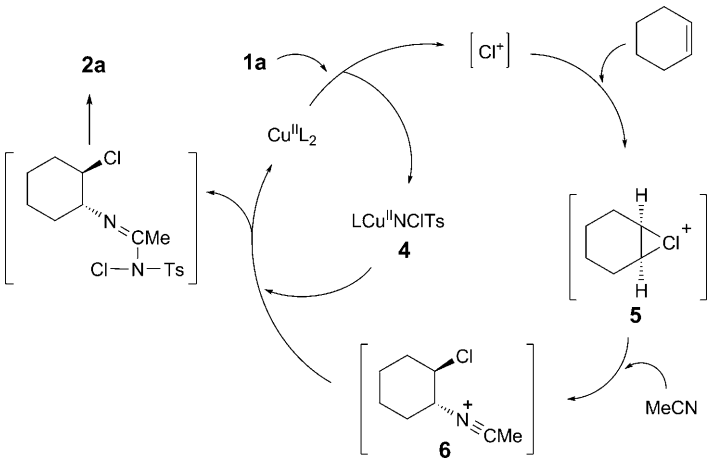
Figure. *NOE Correlations of* **2a**

Next, the reaction of cyclohexene with **1** in MeCN at room temperature was examined in the presence of various metal catalysts (10 mol-%; *Table 1*, *Runs 2–5*) [6]. In our evaluation of the effects of a metal catalyst, $Cu(OAc)_2$ proved to be highly effective, primarily producing **2a**, and was chosen for further studies. Performing the

reaction in MeCN containing H_2O (MeCN/H_2O 5:1) afforded **2a** in 90% yield, while dilution of MeCN with THF (MeCN/THF 1:5) resulted in a reduction of the yield of **2a** to 75% yield (*Table 1*, *Runs 6* and *7*, resp.). In EtCN instead of MeCN, the reaction did not proceed due to the poor solubility of the reagents; then, running the reaction in EtCN diluted with THF (EtCN/THF 1:5) led to the isolation of **2b** in 49% yield (*Table 1*, *Runs 8* and *9*, resp.). Likewise, **2c** and **2d** were obtained by reacting **1** with cyclohexene in PhCN/THF 1:5 in 40% yield and $ClCH_2CN$/THF 1:5 in 67% yield, respectively (*Table 1*, *Runs 10* and *11*, resp.).

The most plausible pathway of the Cu-catalyzed cycle is assumed to be as depicted in *Scheme 1* [7]. Cu^{II} Catalyst initially intercepts **1** to generate a chlorine cation (Cl^+) and Cu complex **4**. The formation of cyclohexene chloronium ion **5** from cyclohexene and Cl^+, and the subsequent *Ritter*-type addition of MeCN to **5** in an *anti*-manner leads to the nitrilium ion **6**. Then, **6** is readily converted to **2a** *via* facile transfer of a *N*-chloro-*N*-tosylamino (TsNCl) group from **4**.

Scheme 1

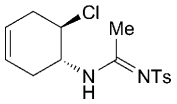
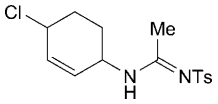
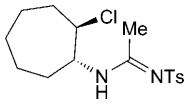
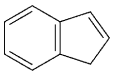
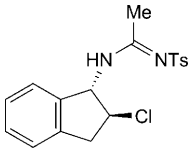
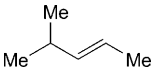
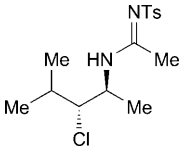
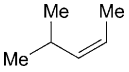
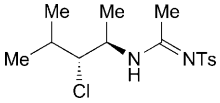
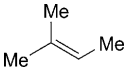
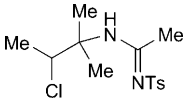


Utilizing the above conditions, we explored the reaction with a range of alkenes, obtaining amidines **7**–**13** in moderate-to-good yields (*Table 2*). Reduction of the reaction temperature to $-20°$ provided **7** and **10**–**12** in higher purity levels than at room temperature (*Table 2*, *Runs 1*, *4*–*6*). Treatment with cyclohexa-1,4-diene at $-20°$ provided **7** in high yield, while δ-chloro amidine **8** was isolated from the reaction with cyclohexa-1,3-diene. (*E*)- and (*Z*)-4-Methylpent-2-enes reacted with **1** to give **11** and **12**, respectively, with high regioselectivity and stereoselectivity (*Table 2*, *Runs 5* and *6*, resp.).

Moreover, it was possible to obtain benzimidazoles **14** and **17** in 50–70% yields by treating **2a**–**2c** and **7** with KOH in refluxing dioxane/H_2O (*Scheme 2*). In the ^{1}H-NMR NOE experiments, irradiation of H_a (δ 4.03) of **14a** produced a large NOE effect on H_b (δ 3.66–3.71), revealing that these H-atoms are in a *cis*-position to each other[1]). Under

[1]) The *trans*-isomer of **14a** is known [7].

Table 2. *Copper-Catalyzed Reaction of* **1a** *with Alkenes in MeCN*

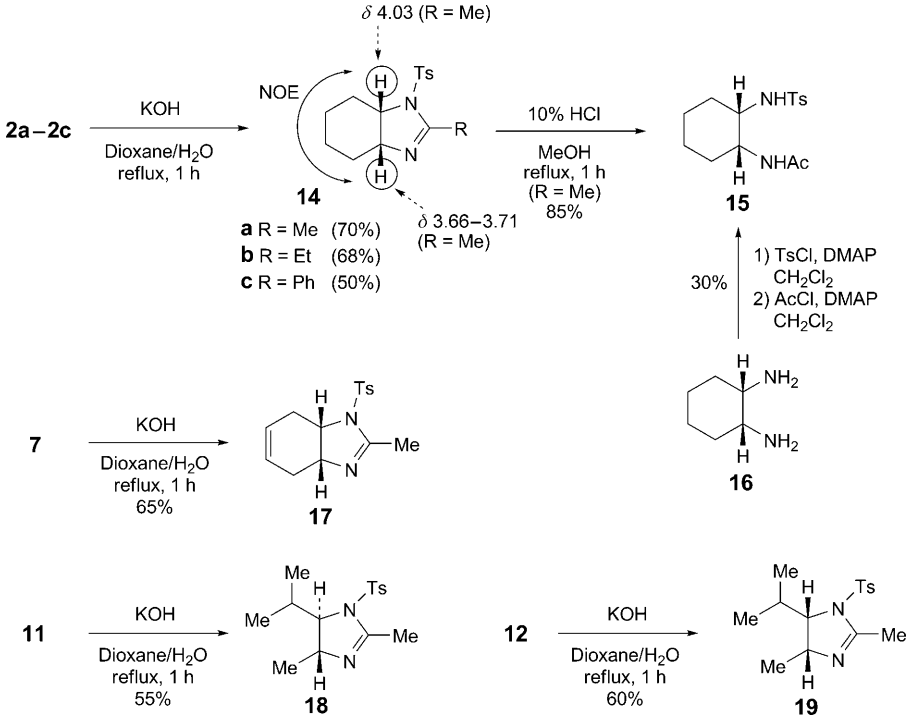
Run	Alkene	Conditions	Product		Yield [%][a])
1		– 20°, 6 h	**7**		90
2		r.t., 3 h	**8**[b])		80
3		r.t., 72 h	**9**		46
4		– 20°, 6 h	**10**		65
5		– 20°, 6 h	**11**		70
6		– 20°, 6 h	**12**		68
7		r.t., 3 h	**13**		75

[a]) Yield based on alkenes. [b]) Single stereoisomer, but configuration was not determined.

standard acidic hydrolysis conditions, **14a** was successfully converted to **15** in 85% yield. The structure of **15** was unequivocally confirmed based on the agreement of the spectral data with those of **15** derived from commercially available *cis*-cyclohexane-1,2-diamine (**16**) through sequential treatment with TsCl and AcCl. Similarly, **11** and **12** were stereoselectively cyclized to dihydroimidazoles **18** and **19**, respectively, the structures of which were confirmed based on NOE experiments.

In summary, we have described that the reaction of dichloramine-T (**1**) with cyclohexene produced amidine **2a** and acetamide **3** *via Ritter*-type addition of nitriles to chloronium ions **5**, and the reaction was also found to be catalyzed with $Cu(OAc)_2$ to afford **2a** as a primary product. This is an alternative reaction outcome to the excellent diamination protocol developed by *Li et al.* with **1** and electron-deficient alkenes.

Scheme 2



Furthermore, the cyclization of **2a** to benzimidazole **14a** by treating with KOH, followed by acidic hydrolysis, produced *cis*-diamine **15**.

Experimental Part

General. Column chromatography (CC): silica gel *60N, Kanto Chemical Co., Ltd.* M.p.: *Yamato MP21* apparatus; uncorrected. IR Spectra: *Hitachi* model *270-30* spectrometer; in cm^{-1}. NMR Spectra: *Jeol-JNM-ECA500* spectrometer; at 500 (^1H) and 125 (^{13}C) MHz; chemical shifts δ in ppm rel. to Me_4Si as internal reference and coupling constants *J* in Hz. ESI-MS: *Jeol JMS-T100LP AccuTOF* mass spectrometer; in *m/z*. EI-MS and HR-EI-MS: *Micromass AutoSpec 3100* mass spectrometer; in *m/z*.

Reaction of **1** *with Cyclohexene in MeCN.* To a soln. of **1** (360 mg, 1.5 mmol) in MeCN (5 ml), cyclohexene (82 mg, 1 mmol) was added under ice cooling. Then, the mixture was warmed to r.t. and stirred for 3 h. The solvent was evaporated, and the residue was separated by CC (SiO_2; hexane/AcOEt 3:1) to give **2a** and **3** (*Table 1*, *Run 1*).

Copper-Catalyzed Reaction of **1** *with Cyclohexene in MeCN.* After stirring a mixture of **1** (1 mmol) and $Cu(OAc)_2$ (0.1 mmol) in MeCN (5 ml) at r.t. for 0.5 h, the mixture was cooled in an ice bath, and cyclohexene (1 mmol) was added. Then, the mixture was warmed to r.t. and stirred for 3 h. The solvent was evaporated, and the residue was separated by CC (SiO_2; hexane/AcOEt 3:1) to give **2a** (*Table 1*, *Run 5*). The analogous treatment of **1** with cyclohexene in the presence of $Cu(OAc)_2$ in EtCN/THF, PhCN/THF, and $ClCH_2CN$/THF produced **2b**, **2c**, and **2d**, resp. (*Table 1*, *Runs 9–11*).

*(*E *and* Z*)-*N*-*[(1*R**,*2*R**)-2-Chlorocyclohexyl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**2a**). Colorless crystals. M.p. 133–134° (CH_2Cl_2). IR ($CHCl_3$): 3350, 1640. ^1H-NMR ($CDCl_3$): 1.12–1.45 (*m*,

3 H); 1.64–1.84 (*m*, 3 H); 2.06–2.09 (*m*, 0.3 H); 2.19–2.26 (*m*, 1.4 H); 2.29–2.34 (*m*, 0.3 H); 2.36 (*s*, 3 H); 2.39 (*s*, 3 H); 3.39–3.46 (*m*, 0.3 H); 3.68–3.76 (*m*, 1 H); 3.98–4.04 (*m*, 0.7 H); 5.71 (*d*, *J* = 7.4, 1 H); 7.25, 7.26 (2*d*, *J* = 8.0, 2 H); 7.79, 7.80 (2*d*, *J* = 8.0, 2 H). ^{13}C-NMR ($CDCl_3$): 21.1; 21.5; 21.6; 21.8; 23.9; 24.2; 24.9; 25.3; 31.6; 35.9; 57.0; 61.4; 126.3; 129.3; 129.5; 140.6; 142.2; 166.1. EI-MS: 328 (M^+). EI-HR-MS: 328.1023/330.0969 (M^+, $C_{15}H_{21}ClN_2O_2S^+$; calc. 328.1012/330.0983). Anal. calc. for $C_{15}H_{21}ClN_2O_2S$: C 54.78, H 6.44, N 8.52; found: C 54.88, H 6.48, N 8.24.

*(*E *and* Z*)*-N-*[(1*R**,2*R**)-2-Chlorocyclohexyl]*-N′-*[(4-methylphenyl)sulfonyl]propanimidamide* (**2b**). Colorless crystals. M.p. 125–127° (AcOEt/hexane). IR ($CHCl_3$): 3428, 1596, 1532. ^{1}H-NMR ($CDCl_3$): 1.13, 1.23 (2*t*, *J* = 7.5, 3 H); 1.13–1.47 (*m*, 3 H); 1.63–1.83 (*m*, 3 H); 2.04–2.10 (*m*, 0.5 H); 2.20–2.38 (*m*, 1.5 H); 2.39 (*s*, 3 H); 2.40 (*q*, *J* = 7.5, 1 H); 2.80, 2.83 (2*q*, *J* = 7.5, 0.5 H); 2.91, 2.94 (2*q*, *J* = 7.5, 0.5 H); 3.43–3.50 (*m*, 0.5 H); 3.69, 3.76 (2*dt*, *J* = 4.0, 10.0, 1 H); 3.90–3.98 (*m*, 0.5 H); 5.45 (br. *s*, 1 H); 7.25 (*d*, *J* = 8.0, 2 H); 7.81 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR ($CDCl_3$): 10.6; 11.9; 21.5; 21.6; 24.0; 24.1; 25.0; 25.3; 27.2; 27.5; 31.5; 33.5; 35.8; 36.0; 56.9; 59.4; 61.5; 62.9; 126.1; 126.2; 129.2; 129.4; 139.5; 141.1; 142.0; 142.9; 169.3; 170.3. EI-MS: 342/344 (M^+). EI-HR-MS: 342.1163/344.1136 (M^+, $C_{16}H_{23}ClN_2O_2S^+$; calc. 342.1169/344.1139). Anal. calc. for $C_{16}H_{23}ClN_2O_2S$: C 56.05, H 6.76, N 8.17; found: C 56.26, H 6.78, N 8.30.

N-*[(1*R**,2*R**)-2-Chlorocyclohexyl]*-N′-*[(4-methylphenyl)sulfonyl]benzenecarboximidamide* (**2c**). Colorless crystals. M.p. 143–145° (CH_2Cl_2). IR ($CHCl_3$): 3672, 1570. ^{1}H-NMR ($CDCl_3$): 1.20–1.34 (*m*, 2 H); 1.41–1.51 (*m*, 2 H); 1.69–1.83 (*m*, 2 H); 2.05–2.11 (*m*, 0.5 H); 2.20–2.28 (*m*, 1.5 H); 2.41, 2.36 (2*s*, 3 H); 3.34–3.42, 4.08–4.15 (2*m*, 1 H); 3.60–3.79 (*m*, 1 H); 5.42, 8.59 (2 br. *s*, 1 H); 7.13, 7.28 (2*d*, *J* = 8.0, 2 H); 7.34–7.41 (*m*, 3 H); 7.42–7.48 (*m*, 2 H); 7.59, 7.89 (2*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 21.5; 21.6; 24.0; 24.1; 25.1; 25.4; 31.8; 33.7; 35.8; 36.0; 57.6; 61.2; 61.8; 63.5; 126.5; 126.6; 127.9; 128.0; 128.2; 128.6; 128.9; 129.4; 130.9; 133.6; 134.2; 139.4; 140.7; 141.8; 143.0; 165.6; 166.4. EI-MS: 390/392 (M^+). EI-HR-MS: 390.1156/392.1136 (M^+, $C_{20}H_{23}ClN_2O_2S^+$; calc. 390.1169/392.1139). Anal. calc. for $C_{20}H_{23}ClN_2O_2S$: C 61.45, H 5.93, N 7.17; found: C 61.23, H 6.06, N 7.06.

*(*E *and* Z*)-2-Chloro*-N-*[(1*R**,2*R**)-2-chlorocyclohexyl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**2d**). Colorless crystals. M.p. 128.5–129.5° (CH_2Cl_2). IR ($CHCl_3$): 3384, 1554. ^{1}H-NMR ($CDCl_3$): 1.19–1.29 (*m*, 1 H); 1.29–1.45 (*m*, 2 H); 1.68–1.74 (*m*, 2 H); 1.74–1.84 (*m*, 1 H); 2.21–2.27 (*m*, 2 H); 2.41 (*s*, 3 H); 3.80 (*dt*, *J* = 4.5, 9.7, 1 H); 3.94–4.01 (*m*, 1 H); 4.88 (*d*, *J* = 16.6, 1 H); 4.94 (*d*, *J* = 16.6, 1 H); 6.63 (*s*, 1 H); 7.27 (*d*, *J* = 8.5, 2 H); 7.80 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 21.6; 23.7; 25.1; 31.2; 35.6; 42.3; 57.4; 60.9; 126.3; 129.4; 139.8; 142.7; 160.0. ESI$^+$-MS: 363/365/367 ($[M+H]^+$). Anal. calc. for $C_{15}H_{20}Cl_2N_2O_2S$: C 49.59, H 5.55, Cl 19.52, N 7.71, S 8.83; found: C 49.47, H 5.50, Cl 19.35, N 7.70, S 8.61.

N-*[(1*R**,2*R**)-2-Chlorocyclohexyl]acetamide* (**3**). Colorless crystals. M.p. 123–124° ([5]: 120–122° (CH_2Cl_2/hexane)). IR ($CHCl_3$): 3376, 3268, 1652. ^{1}H-NMR ($CDCl_3$): 1.17–1.41 (*m*, 3 H); 1.64–1.77 (*m*, 3 H); 1.97 (*s*, 3 H); 2.07–2.14 (*m*, 1 H); 2.18–2.25 (*m*, 1 H); 3.70 (*dt*, *J* = 4.6, 10.9, 1 H); 3.80–3.88 (*m*, 1 H); 6.09 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 23.4; 24.2; 25.4; 32.8; 36.1; 54.9; 62.6; 170.0. EI-MS: 175/177 (M^+). Anal. calc. for $C_8H_{14}ClNO$: C 54.70, H 8.03, Cl 20.18, N 7.97; found: C 54.50, H 7.97, Cl 20.01, N 7.91.

The reaction of **1** with various alkenes in the presence of $Cu(OAc)_2$ in MeCN was performed according to the procedure for the copper-catalyzed reaction of **1** with cyclohexene (*Table 1*) to give **7**–**13**.

*(*E*)*-N-*[(1*R**,6*R**)-6-Chlorocyclohex-3-en-1-yl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**7**). Colorless crystals. M.p. 101–102° (AcOEt/hexane). IR ($CHCl_3$): 3350, 1650. ^{1}H-NMR ($CDCl_3$): 1.97, 2.51 (2 br. *d*, *J* = 16.0, 1 H); 2.19, 2.44 (2 br. *d*, *J* = 17.0, 1 H); 2.40 (*s*, 3 H); 2.41 (*s*, 3 H); 2.64 (br. *d*, *J* = 17.0, 1 H); 2.80 (br. *d*, *J* = 16.0, 1 H); 3.73–3.81, 4.14–4.20 (2*m*, 1 H); 4.00–4.06, 4.24–4.31 (2*m*, 1 H); 5.59–5.64 (*m*, 3 H); 7.26, 7.27 (2*d*, *J* = 8.5, 2 H); 7.80, 7.81 (2*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 21.1; 21.5; 21.6; 23.4; 26.2; 29.2; 29.9; 30.2; 31.5; 33.7; 34.2; 34.4; 49.2; 49.9; 52.3; 55.5; 56.3; 56.9; 58.1; 67.3; 122.7; 123.5; 123.6; 124.1; 124.3; 124.4; 124.6; 126.3; 126.5; 129.3; 129.5; 130.9; 140.3; 142.4; 143.4; 166.2; 170.3; 171.4. EI-HR-MS: 326.0856/328.0836 (M^+, $C_{15}H_{19}ClN_2O_2S^+$; calc. 326.0856/328.0826). Anal. calc. for $C_{15}H_{19}ClN_2O_2S$: C 55.12, H 5.86, N 8.57; found: C 55.25, H 5.77, N 8.36.

*(*E *and* Z*)*-N-*[(1*S**,4*R**)-4-Chlorocyclohex-2-en-1-yl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**8**). Colorless crystals. M.p. 127–129° (hexane/AcOEt). IR ($CHCl_3$): 3296, 1520. ^{1}H-NMR ($CDCl_3$): 1.62 (*ddd*, *J* = 6.2, 9.0, 11.4, 1 H); 1.95 (*ddd*, *J* = 6.3, 9.1, 12.0, 1 H); 2.12–2.18 (*m*, 2 H); 2.40 (*s*, 3 H); 2.41 (*s*, 3 H); 4.49–4.54 (*m*, 1 H); 4.56–4.62 (*m*, 1 H); 5.43 (br. *d*, *J* = 6.9, 1 H); 5.73 (*dd*, *J* = 2.5,

10.0, 1 H); 5.95, 6.05 (2*ddd*, *J* = 1.7, 4.0, 10.0, 1 H); 7.27 (*d*, *J* = 8.0, 2 H); 7.78, 8.05 (2*d*, *J* = 8.0, 2 H). ^{13}C-NMR ($CDCl_3$): 21.5; 21.6; 25.4; 29.8; 46.0; 53.4; 126.4; 128.7; 129.3; 129.5; 132.3; 140.4; 142.4; 164.8. EI-MS: 326/328 (M^+). EI-HR-MS: 326.0848/328.0838 (M^+, $C_{15}H_{19}ClN_2O_2S^+$; calc. 326.0856/328.0826). Anal. calc. for $C_{15}H_{19}ClN_2O_2S$: C 55.12, H 5.86, N 8.57; found: C 55.08, H 5.98, N 8.41.

*(*E *and* Z*)*-N-*[(1*R**,2*R**)-2-Chlorocycloheptyl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**9**). Viscous oil. IR ($CHCl_3$): 3280, 1543. ^{1}H-NMR ($CDCl_3$): 1.40 – 2.25 (*m*, 10 H); 2.32, 2.35, 2.38, 2.50, 2.68 (5*s*, 6 H); 3.63 – 3.70, 4.07 – 4.14, 4.20 – 4.27 (3*m*, 1 H); 3.88 – 3.94, 3.99 – 4.05, 4.36 – 4.43, 4.53 – 4.60 (4*m*, 1 H); 6.53 (br. *s*, 1 H); 7.24, 7.26, 7.45 (3*d*, *J* = 8.0, 2 H); 7.76, 7.78, 7.79 (3*d*, *J* = 8.0, 2 H). ^{13}C-NMR ($CDCl_3$): 20.8; 21.0; 21.5; 23.1; 23.3; 23.6; 23.9; 27.0; 27.6; 28.1; 31.1; 32.4; 33.6; 33.7; 35.0; 35.3; 39.0; 51.7; 60.6; 61.9; 63.5; 66.3; 67.3; 126.2; 129.3; 129.5; 139.3; 140.6; 142.5; 143.1; 164.9; 165.3; 165.5. EI-HR-MS: 342.1170/344.1140 (M^+, $C_{16}H_{23}ClN_2O_2S^+$; calc. 342.1169/344.1139).

*(*E *and* Z*)*-N-*[(1*R**,2*R**)-2-Chloro-2,3-dihydro-1*H*-inden-1-yl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**10**). Colorless crystals. M.p. 107 – 108° (AcOEt/hexane). IR ($CHCl_3$): 3424, 1562, 1544. ^{1}H-NMR ($CDCl_3$): 2.40 (*s*, 3 H); 2.54 (*s*, 3 H); 3.24 (*d*, *J* = 17.2, 1 H); 3.39 (*dd*, *J* = 17.2, 5.1, 1 H); 4.93 (*t*, *J* = 5.1, 1 H); 5.75 (*dd*, *J* = 8.0, 5.1, 1 H); 5.99 (br. *d*, *J* = 8.0, 1 H); 7.19 (*d*, *J* = 7.4, 1 H); 7.26 (*d*, *J* = 8.5, 2 H); 7.20 – 7.32 (*m*, 3 H); 7.82 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 21.4; 21.5; 41.1; 59.2; 63.4; 123.7; 125.5; 126.6; 127.6; 128.8; 129.3; 138.2; 139.0; 140.1; 142.5; 166.1. EI-MS: 362/364 (M^+). EI-HR-MS: 364.0867/364.0821 (M^+, $C_{18}H_{19}ClN_2O_2S^+$; calc. 362.0856/364.0826). Anal. calc. for $C_{18}H_{19}ClN_2O_2S$: C 59.58, H 5.28, N 7.72; found: C 59.34, H 5.34, N 7.65.

*(*E *and* Z*)*-N-*[(1*R**,2*S**)-2-Chloro-1,3-dimethylbutyl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**11**). Colorless crystals. M.p. 106 – 107° (AcOEt/hexane). IR ($CHCl_3$): 3664. ^{1}H-NMR ($CDCl_3$): 0.90 (*d*, *J* = 6.8, 3 H); 1.05 (*d*, *J* = 6.8, 3 H); 1.16 (*d*, *J* = 6.8, 3 H); 1.76 – 1.84 (*m*, 1 H); 2.40 (*s*, 3 H); 2.42 (*s*, 3 H); 3.78 (*dd*, *J* = 2.3, 9.1, 1 H); 4.46 – 4.53 (*m*, 1 H); 5.58 (br. *s*, 1 H); 7.25 (*d*, *J* = 8.5, 2 H), 7.79 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 13.6; 19.7; 20.7; 21.4; 21.5; 32.5; 48.9; 72.9; 126.3; 129.2; 140.5; 142.3; 164.5. EI-MS: 330/332 (M^+). EI-HR-MS: 330.1164/332.1137 (M^+, $C_{15}H_{23}ClN_2O_2S^+$; calc. 330.1169/332.1139). Anal. calc. for $C_{15}H_{23}ClN_2O_2S$: C 54.45, H 7.01, N 8.47; found: C 54.56, H 7.08, N 8.55.

*(*E *and* Z*)*-N-*[(1*R**,2*R**)-2-Chloro-1,3-dimethylbutyl]*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**12**). Colorless crystals. M.p. 115 – 116° (AcOEt/hexane). IR ($CHCl_3$): 3420, 1582. ^{1}H-NMR ($CDCl_3$): 0.94 (*d*, *J* = 6.9, 3 H); 1.03 (*d*, *J* = 6.9, 3 H); 1.25 (*d*, *J* = 6.3, 3 H); 1.79 – 1.88 (*m*, 1 H); 2.39, 2.40 (2*s*, 6 H); 3.59 (*dd*, *J* = 2.3, 8.6, 1 H); 4.61 – 4.68 (*m*, 1 H); 5.57 (br. *s*, 1 H); 7.25 (*d*, *J* = 8.5, 2 H); 7.79 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 19.4; 20.0; 20.3; 21.4; 21.5; 33.0; 48.5; 74.3; 126.4; 129.2; 140.4; 142.3; 165.2. EI-MS: 330/332 (M^+). EI-HR-MS: 330.1157/332.1151 (M^+, $C_{15}H_{23}ClN_2O_2S^+$; calc. 330.1169/330.1139). Anal. calc. for $C_{15}H_{23}ClN_2O_2S$: C 54.45, H 7.01, N 8.47; found: C 54.34, H 6.96, N 8.36.

*(*E *and* Z*)*-N-*(2-Chloro-1,1-dimethylpropyl)*-N′-*[(4-methylphenyl)sulfonyl]ethanimidamide* (**13**). Colorless crystals. M.p. 142 – 143° (AcOEt/hexane). IR ($CHCl_3$): 3124. ^{1}H-NMR ($CDCl_3$): 1.36 (*s*, 3 H); 1.40 (*d*, *J* = 6.8, 3 H); 1.44 (*s*, 3 H); 2.34 (*s*, 3 H); 2.39 (*s*, 3 H); 4.81 (*q*, *J* = 6.8, 1 H); 5.64 (*s*, 1 H); 7.25, 7.39 (2*d*, *J* = 8.5, 2 H); 7.74, 7.76 (2*d*, *J* = 8.5, 2 H). ^{13}C-NMR ($CDCl_3$): 19.8; 21.5; 22.1; 22.3; 23.4; 59.6; 62.0; 126.2; 127.3; 129.3; 130.5; 140.5; 142.3; 164.7. EI-MS: 330/332 (M^+). EI-HR-MS: 316.1031/318.0995 (M^+, $C_{14}H_{21}ClN_2O_2S^+$; calc. 316.1012/318.0983). Anal. calc. for $C_{14}H_{21}ClN_2O_2S$: C 53.07, H 6.68, N 8.84; found: C 53.22, H 6.65, N 8.90.

Cyclization of Amidines **2a** – **2c**, **7**, **11**, *and* **12** *to Imidazoles* **14**, **17**, **18**, *and* **19***: General Procedure.* A mixture of amidines (1 mmol), KOH (3 mmol), H_2O (2 ml), and cat. amount of 18-crown-6 in dioxane (10 ml) was heated at 100° for 1 h. After cooling, the mixture was diluted with AcOEt (100 ml), washed with brine, and dried ($MgSO_4$). The solvent was evaporated, and the residue was separated by CC (SiO_2; hexane/AcOEt).

*(3a*R**,7a*S**)-2-Methyl-1-[(4-methylphenyl)sulfonyl]-3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazole* (**14a**). M.p. 115 – 117° (AcOEt/hexane). IR ($CHCl_3$): 1650, 1598. ^{1}H-NMR ($CDCl_3$): 1.16 – 1.28 (*m*, 1 H); 1.33 – 1.43 (*m*, 1 H); 1.43 – 1.51 (*m*, 1 H); 1.53 – 1.69 (*m*, 3 H); 1.87 – 1.94 (*m*, 1 H); 1.94 – 2.01 (*m*, 1 H); 2.26 (*d*, *J* = 2.3, 3 H); 2.43 (*s*, 3 H); 3.66 – 3.71 (*m*, 1 H); 4.03 (*dt*, *J* = 7.0, 8.2, 1 H); 7.32 (*d*, *J* = 8.0, 2 H); 7.73 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR ($CDCl_3$): 17.5; 19.6; 20.0; 21.6; 26.9; 27.9; 60.9; 63.0; 127.0; 130.0; 137.3; 144.3; 156.1. EI-MS: 292 (M^+). EI-HR-MS: 292.1245 (M^+, $C_{15}H_{20}N_2O_2S^+$; 292.1234).

*(3a*R**,7a*S**)-2-Ethyl-1-[(4-methylphenyl)sulfonyl]-3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazole* (**14b**). Colorless crystals. M.p. 164 – 164° (AcOEt/hexane). IR ($CHCl_3$): 1630. ^{1}H-NMR ($CDCl_3$): 1.20 (*t*,

$J = 7.5$, 3 H); 1.16–1.24 (*m*, 1 H); 1.29–1.39 (*m*, 1 H); 1.42–1.52 (*m*, 2 H); 1.52–1.65 (*m*, 2 H); 1.91–1.99 (*m*, 2 H); 2.41 (*s*, 3 H); 2.57, 2.59 (2*dq*, $J = 1.7$, 7.5, 1 H); 2.66, 2.70 (2*dq*, $J = 1.7$, 7.5, 1 H); 3.61 (br. *s*, 1 H); 3.99 (*dt*, $J = 8.0$, 5.7, 1 H); 7.29 (*d*, $J = 8.5$, 2 H); 7.70 (*d*, $J = 8.5$, 2 H). ^{13}C-NMR ($CDCl_3$): 11.2; 19.6; 20.1; 21.6; 24.0; 26.8; 28.0; 60.8; 63.0; 126.8; 130.0; 137.4; 144.2; 160.8. EI-MS: 306 (M^+). EI-HR-MS: 306.1401 (M^+, $C_{16}H_{22}N_2O_2S^+$; 306.1402). Anal. calc. for $C_{16}H_{22}N_2O_2S$: C 62.71, H 7.24, N 9.14; found: C 62.56, H 7.45, N 9.02.

*(3a*R*,7a*S*)-2-Phenyl-1-[(4-methylphenyl)sulfonyl]-3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazole* (**14c**). Colorless crystals. M.p. 121–122° (AcOEt/hexane). IR ($CHCl_3$): 1640. ^{1}H-NMR ($CDCl_3$): 1.15–1.36 (*m*, 2 H); 1.46–1.68 (*m*, 4 H); 2.07–2.18 (*m*, 2 H); 2.41 (*s*, 3 H); 3.38–3.43 (*m*, 1 H); 4.22 (*dt*, $J = 9.7$, 6.8, 1 H); 7.26 (*d*, $J = 7.3$, 2 H); 7.41 (*t*, $J = 7.5$, 2 H); 7.49 (*t*, $J = 7.5$, 1 H); 7.53 (*d*, $J = 8.0$, 2 H); 7.76 (*d*, $J = 8.0$, 2 H). ^{13}C-NMR ($CDCl_3$): 20.0; 21.1; 21.7; 27.1; 28.8; 61.3; 64.3; 127.0; 127.9; 129.6; 129.9; 131.0; 131.3; 136.9; 144.3; 159.3. EI-MS: 354 (M^+). EI-HR-MS: 354.1409 (M^+, $C_{20}H_{22}N_2O_2S^+$; 354.1402). Anal. calc. for $C_{20}H_{22}N_2O_2S$: C 67.77, H 6.26, N 7.90; found: C 67.88, H 6.32, N 8.01.

*(3a*R*,7a*S*)-2-Methyl-1-[(4-methylphenyl)sulfonyl]-3a,4,7,7a-tetrahydro-1*H*-benzimidazole* (**17**). Colorless crystals. M.p. 102–103° (AcOEt/hexane). IR ($CHCl_3$): 1646. ^{1}H-NMR ($CDCl_3$): 2.21 (*d*, $J = 1.7$, 3 H); 2.25 (*dt*, $J = 16.0$, 4.6, 1 H); 2.31 (*ddd*, $J = 2.3$, 6.3, 16.0, 1 H); 2.34 (*ddd*, $J = 1.7$, 4.5, 16.6, 1 H); 2.41 (*s*, 3 H); 2.48 (*dt*, $J = 16.6$, 4.6, 1 H); 4.10–4.16 (*m*, 1 H); 4.19 (*dt*, $J = 10.3$, 5.1, 1 H); 5.86–5.88 (*m*, 2 H); 7.31 (*d*, $J = 8.0$, 2 H); 7.69 (*d*, $J = 8.0$, 2 H). ^{13}C-NMR ($CDCl_3$): 17.2; 21.6; 28.1; 28.9; 60.2; 64.3; 127.0; 127.2; 128.5; 130.1; 136.3; 144.4; 156.3. EI-MS: 290 (M^+). EI-HR-MS: 290.1090 (M^+, $C_{15}H_{18}N_2O_2S^+$; calc. 290.1089).

*(4*R*,5*R*)-2,4-Dimethyl-5-(1-methylethyl)-1-[(4-methylphenyl)sulfonyl]-4,5-dihydro-1*H*-imidazole* (**18**). Viscous oil. IR ($CHCl_3$): 1644. ^{1}H-NMR ($CDCl_3$): 0.64 (*d*, $J = 6.9$, 3 H); 0.80 (*d*, $J = 6.9$, 3 H); 0.88 (*d*, $J = 7.4$, 3 H); 2.17–2.26 (*m*, 1 H); 2.30 (*d*, $J = 1.1$, 3 H); 2.42 (*s*, 3 H); 3.41 (*t*, $J = 3.5$, 1 H); 3.60–3.66 (*m*, 1 H); 7.33 (*d*, $J = 8.0$, 2 H), 7.70 (*d*, $J = 8.0$, 2 H). ^{13}C-NMR ($CDCl_3$): 14.9; 17.4; 17.5; 21.6; 22.8; 31.6; 60.5; 71.9; 127.2; 129.9; 135.7; 140.6; 144.5; 155.6. EI-MS: 332 (M^+). EI-HR-MS: 294.1422 (M^+, $C_{15}H_{22}N_2O_2S^+$; calc. 294.1402).

*(4*R*,5*S*)-2,4-Dimethyl-5-(1-methylethyl)-1-[(4-methylphenyl)sulfonyl]-4,5-dihydro-1*H*-imidazole* (**19**). Viscous oil. IR ($CHCl_3$): 1644. ^{1}H-NMR ($CDCl_3$): 0.85 (*d*, $J = 6.9$, 3 H); 1.06 (*d*, $J = 6.9$, 3 H); 1.26 (*d*, $J = 7.4$, 3 H); 1.87–1.95 (*m*, 1 H); 2.31 (*d*, $J = 2.3$, 3 H); 2.42 (*s*, 3 H); 3.38–3.46 (*m*, 1 H); 3.92 (*dd*, $J = 2.3$, 8.0, 1 H); 7.30 (*d*, $J = 8.0$, 2 H); 7.70 (*d*, $J = 8.0$, 2 H). ^{13}C-NMR ($CDCl_3$): 14.6; 17.4; 17.6; 20.5; 21.6; 28.4; 63.6; 69.4; 126.8; 130.1; 137.1; 144.3; 157.5. EI-MS: 332 (M^+). EI-HR-MS: 294.1403 (M^+, $C_{15}H_{22}N_2O_2S^+$; calc. 294.1402).

Conversion of **14a** *to* **15** *by Acid-Catalyzed Hydrolysis.* A soln. of **14a** (100 mg) and 10% aq. HCl (1 ml) in MeOH (10 ml) was heated under reflux for 2 h. After cooling, the mixture was concentrated, and the residue was made alkaline with 10% aq. NaOH. The mixture was extracted with AcOEt, the extract was washed with H_2O and dried ($MgSO_4$) to give **15** in 80% yield.

Preparation of **15** *from* **16**. To a mixture of **16** (114 mg, 1 mmol), Et_3N (0.58 ml, 4 mmol), and 4-(dimethylamino)pyridine (DMAP; 60 mg, 0.4 mmol) in CH_2Cl_2 (50 ml), TsCl (190 mg, 1 mmol) was added under ice cooling. After stirring the mixture at r.t. for 1 h, AcCl (70 mg, 1 mmol) was added under ice cooling, and the mixture was stirred at r.t. for 1 h. The mixture was concentrated, and the residue was diluted with AcOEt. The org. layer was washed with H_2O and dried ($MgSO_4$). The solvent was evaporated, and the residue was separated by CC (SiO_2; hexane/AcOEt 2:1) to give **15** in 30% yield.

N-*((1*R*,2*S*)-2-{[(4-Methylphenyl)sulfonyl]amino}cyclohexyl)acetamide* (**15**). Colorless crystals. M.p. 170–171° (AcOEt/hexane). IR ($CHCl_3$): 3376, 3268, 1652. ^{1}H-NMR ($CDCl_3$): 1.16–1.39 (*m*, 4 H); 1.42–1.65 (*m*, 3 H); 1.72–1.78 (*m*, 1 H); 1.93 (*s*, 3 H); 2.43 (*s*, 3 H); 3.38–3.44 (*m*, 1 H); 3.78–3.85 (*m*, 1 H); 4.90 (br. *s*, 1 H); 6.01 (br. *s*, 1 H); 7.32 (*d*, $J = 8.0$, 2 H); 7.75 (*d*, $J = 8.0$, 2 H). ^{13}C-NMR ($CDCl_3$): 20.1; 21.5; 23.3; 23.4; 27.6; 29.7; 49.6; 52.9; 127.8; 129.7; 137.3; 143.5; 170.3. EI-MS: 310 (M^+). Anal. calc. for $C_{15}H_{22}N_2O_3S$: C 58.04, H 7.14, N 9.02, S 10.33; found: C 58.00, H, 7.24, N 8.99, S 10.46.

REFERENCES

[1] M. M. Champbell, G. Johnson, *Chem. Rev.* **1978**, *78*, 65; D. H. Bremner, 'Synthetic Reagents', Ed. J. S. Pizey, John Wiley & Sons, New York, 1985, Vol. 6, p. 9.
[2] G. Li, S. H. Kim, H.-X. Wei, *Tetrahedron Lett.* **2000**, *41*, 8699.
[3] H.-X. Wei, S. H. Kim, G. Li, *J. Org. Chem*. **2002**, *67*, 4777; H.-X. Wei, S. Siruta, G. Li, *Tetrahedron Lett.* **2002**, *43*, 3809; S. R. S. Saibabu Kotti, C. Timmons, G. Li, *Chem. Biol. Drug Des.* **2006**, *67*, 101.
[4] G. Li, H.-X. Wei, S. H. Kim, M. Neighbors, *Org. Lett.* **1999**, *1*, 395; J.-L. Han, S.-J. Zhi, L.-Y. Wang, Y. Pan, G. Li, *Eur. J. Org. Chem*. **2007**, 1332; G. Li, S. R. S. Saibabu Kotti, C. Timmons, *Eur. J. Org. Chem.* **2007**, 2745.
[5] G. K. Rawal, A. Kumar, U. Tawar, Y. D. Vankar, *Org. Lett*. **2007**, *9*, 5171.
[6] M. K. Ghorai, K. Ghosh, K. Das, *Tetrahedron Lett*. **2006**, *47*, 5399.
[7] K. I. Booker-Milburn, D. J. Guly, B. Cox, P. A. Procopiou, *Org. Lett*. **2003**, *5*, 3313.

Received June 5, 2009