Regio- and Stereoselective Copper-Catalyzed Synthesis of Vicinal Haloamino Ketones from α,β-Unsaturated Ketones

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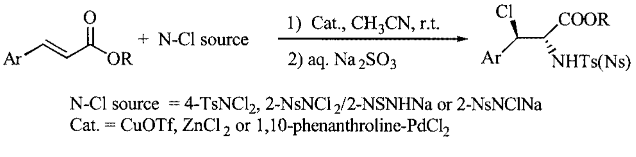
The regio- and stereoselective aminochlorination of α,β-unsaturated ketones has been developed. The reaction was conducted with *N*,*N*-dichloro-*p*-toluenesulfonamide (4-$TsNCl_2$) as the nitrogen/halogen source and CuOTf as the catalyst, at 0 °C to room temperature. This method provides an easy access to vicinal haloamino ketones, with excellent regioselectivity and up to quantitative yields. Both aromatic and aliphatic enones react well with 4-$TsNCl_2$ under the present system, but give opposite regioselectivity.

Introduction

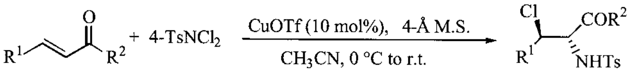
The functionalization of unsaturated carbon−carbon bonds with amine and halogen groups has long been an important topic in organic and medicinal chemistry.[1−3] Although several synthetic approaches to the vicinal haloamine functionality have been developed,[4−6] the study of efficient and highly regio- and stereoselective methods still remains challenging.[7] In fact, the catalytic aminohalogenation of α,β-unsaturated ketones and esters has not been well-documented thus far.

In the past few years, we have successfully developed the catalytic aminohalogenation of α,β-unsaturated esters utilizing several nitrogen/halogen sources such as 4-$TsNCl_2$,[6a][6c] 2-NsNNaCl (2-Ns: 2-nitrobenzenesulfonyl), or the combination of 2-$NsNCl_2$ and 2-NsNHNa[6b] in the presence of metal catalysts (Scheme 1). These processes are believed to proceed through a mechanism that involves aziridinium ion intermediates. These intermediates are analogous to the well-known bromonium ion counterparts. The stereo- and regioselectivity of the resulting haloamine products can be explained based on this hypothesis of the mechanism. Further, the mechanism is directly supported by the electrophilic diamination, which was also developed in our group.[8−12]



Scheme 1

With the successful diamination of α,β-unsaturated ketones[6−7] in hand, we turned our attention to the aminohalogenation of these substrates. In this paper we report our results of this process under optimized catalytic conditions, which provide an easy access to vicinal haloamino ketones (Scheme 2).



Scheme 2

Results and Discussion

The structural similarity of α,β-unsaturated ketones and their ester counterparts, and their similar behavior in the electrophilic diamination reactions prompted us to investigate the aminochlorination of *trans*-4-phenyl-3-buten-2-one under previous known catalytic conditions for cinnamate esters. Surprisingly, when zinc chloride was employed as the catalyst only a tiny amount of haloamine product was produced within 48 hours, and most of the olefin starting materials remained unreacted. However, it was also known that when rhodium(II) heptafluorobutyrate or iron(III) chloride with triphenylphosphane were used as catalysts diamine products were predominantly formed. Fortunately, copper(I) triflate was found to catalyze the reaction of *trans*-4-phenyl-3-buten-2-one with 4-$TsNCl_2$, and the products were obtained in 42% yield. The reaction with copper(II) triflate also gave the haloamine product, but in a lower yield.

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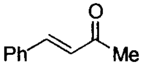
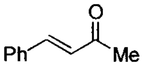
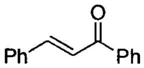
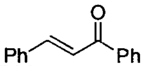
Further investigation showed that the chemical yield was improved from 42% to 67% when the reaction was conducted at lower temperature (0 °C for 2 h, and then at room temperature for an additional 10 hours) with the slow addition of 4-$TsNCl_2$ into reaction mixture by a syringe pump (Entry 1 and 2, Table 1). Similar to the situation seen for the previous α,β-unsaturated ester based system, the use of 4-Å molecular sieves together with the catalysts further increased the yield by at least 5%. Furthermore, the reaction proceeded faster than the aminohalogenation of cinnamate ester based substrates, which generally required 24 hours for complete conversion; the present reaction reached completion in about 10 hours. Aromatic chalcone substrates gave higher yields with this modification (71% and 54% for Entries 3 and 4 in Table 1, respectively).

Table 1. Effects of reaction temperature and addition times for $TsNCl_2$

Entry	Substrate	Temperature	Addition time for $TsNCl_2$	Yield (%)[a]
1		0 °C to r.t.	30 min	67
2		r.t.	5 s	42
3		0 °C to r.t.	30 min	71
4		r.t.	5 s	54

[a] The yields after purification by column chromatography.

After the reaction conditions were optimized, a series of common α,β-unsaturated ketones were therefore investigated extensively. As can be seen in Table 2, a broad substrate range exists for this reaction in which both aromatic and aliphatic enones can be employed. The substrates showed good to excellent *anti*/*syn* stereoselectivity with ratios arranging from 6:1 to > 20:1. In five cases (Entries 4−8, Table 2), only the *trans* isomers were observed. Essentially, only one regioisomer was observed for each of these cases. For the aromatic substrates with a strong electron-withdrawing group (NO_2) on the aromatic rings (Entries 7 and 8, Table 2), the reaction required a longer time (48 h), and a large amount of 4-$TsNCl_2$ (2.0 equiv.) was necessary for completion.

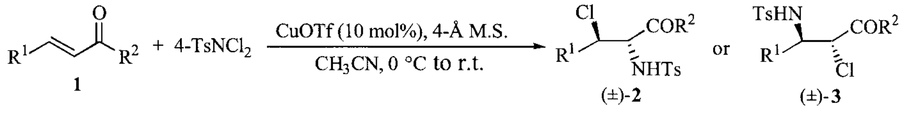
Interestingly, when aliphatic enones were used in the reaction, the opposite regioselectivity was obtained for the major isomeric products (Entries 9, 10 and 11 of Table 2) (Scheme 3). The resulting regioisomers can readily be distinguished by their NMR spectra, in which the coupling constants and correlation patterns in HMBC (Heteronuclear Multiple Bond Correlation) clearly show their structural differences. In addition, the reaction rates for the reactions with the aliphatic enones were faster, and these enones were completely consumed within 2 hours.

Since the aliphatic enones are volatile liquids, an excess amount of the starting materials can be removed simply by distillation after the reaction. We therefore used an excess of aliphatic enone in an attempt to increase the chemical yields. We were pleased to find that by slowly adding 1.0 equiv. of 4-$TsNCl_2$ to 2 equiv. of methyl vinyl ketone, nearly quantitative yields were obtained (Entries 2−4, Table 3). In fact, the crude products were almost pure, as revealed by

Table 2. Results for the aminohalogenation reactions of α,β-unsaturated ketones

Entry	R^1	R^2	Product	Stereoselectivity (*anti*/*syn*)[a]	Yield (%)[b]
1	Ph	Me	**2a**	9:1	67
2	Ph	Ph	**2b**	9:1	71
3	Ph	*p*-$MeOC_6H_4$	**2c**	6:1	74
4	Ph	*p*-ClC_6H_4	**2d**	> 20:1	65
5	Ph	*p*-FC_6H_4	**2e**	> 20:1	75
6	*o*-ClC_6H_4	Ph	**2f**	> 20:1	70
7	*p*-$O_2NC_6H_4$	Ph	**2g**	> 20:1	66[c]
8	*m*-$O_2NC_6H_4$	Ph	**2h**	> 20:1	91[c]
9	Me	Et	**3a**	7:1	56
10	H	Et	**3b**	N/A	72
11	H	Me	**3c**	N/A	> 90[d]

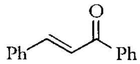
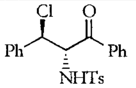
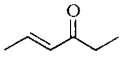
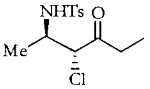
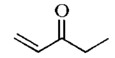
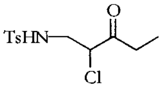
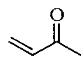
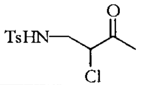
[a] > 20:1 implies that no *syn* isomer is observed by crude ^1H NMR spectroscopic determination. [b] The yields after purification by column chromatography. [c] 2.0 equiv. of 4-$TsNCl_2$ and 48 hours are needed for the reaction to be completed. [d] Decomposed during purification by column chromatography; the yield was estimated by crude ^1H NMR spectroscopic determination.



Scheme 3

crude ^1H NMR analysis. A similar improvement of the yield (14%) was observed for the chalcone substrate (85%, Entry 1 in Table 3).

Table 3. Effects of excess α,β-unsaturated ketones on yields

Entry	Substrate	Product	Stereoselectivity (*anti*/*syn*)	Yield (%)[a]
1			9:1	85
2			6:1	quant.
3			N/A	quant.
4			N/A	quant.

[a] The α,β-unsaturated ketones were used in excess, thus, the yields were calculated based on $TsNCl_2$ as the limiting reagent.

It is interesting to note that aliphatic enone-derived haloamines (see Entries 10 and 11, Table 2) show different stability during purification by column chromatography, although there is only a small difference in their structures. The product obtained from 11 decomposed to give unknown compounds after column chromatography. The modified conditions turned out be particularly useful for the aminochlorination of methyl vinyl ketone since the crude product is almost pure, thus, there is no need for further purification. However, for aliphatic substrates, the quenching operation has to be handled carefully to avoid the formation of side products. For a 2.0 mmol-scale reaction, the reaction has to be quenched by slowly pouring the reaction mixture into 20 mL of saturated aqueous Na_2SO_3 solution prior to separation and extraction.

Although the regio- and stereoselectivity for aromatic systems can be explained well by the mechanism hypothesis which involves aziridinium ion intermediates, the regioselectivity of the aliphatic substrate derived haloamines suggested that a different mechanism might exist, one which is not clear at this moment. Further mechanistic studies on this catalytic process will be conducted in the future.

Attempts to employ terminal disubstituted α,β-unsaturated ketones (e.g. mesityl oxide) for use in the present aminohalogenation reactions have not been successful. Both Cu^I and Cu^{II} triflates failed to suppress the competing diamination reaction. Instead, the aziridinium ion intermediate formed during the reaction process showed higher reactivity toward acetonitrile than the chloride anion for the aziridinium ring opening.

Conclusion

The regio- and stereoselective aminochlorination of α,β-unsaturated ketones has been developed under optimized conditions. The new method provides an easy access to vicinal haloamine ketones. The synthesis is easy to carry out with both aromatic and aliphatic α,β-unsaturated ketones. Up to quantitative yields and excellent regio- and stereoselectivity have been achieved for several enones. The opposite regioselectivity was observed for aromatic and aliphatic enones.

Experimental Section

NMR spectra were recorded at 500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR spectroscopy. $CDCl_3$ was used as the solvent and TMS as the internal standard. Chemical shifts were recorded downfield from TMS for ^1H NMR, and relative to $CDCl_3$ ($\delta = 77.0$ ppm) for ^{13}C NMR spectroscopy. The high-resolution mass spectral analysis was conducted by the mass spectroscopy laboratory of the Scripps Research Institute. Purification by column chromatography was performed with silica gel Merk 60 (230−400 mesh).

Typical Procedure for the Aminochlorination of α,β-Unsaturated Ketones (I): The enone (1.0 mmol), 4-Å molecular sieves (0.50 g), the CuOTf benzene complex (50 mg, 0.1 mmol, 10 mol %), and freshly distilled acetonitrile (2.0 mL) was placed into a dry vial. A solution of 4-$TsNCl_2$ (288 mg, 1.2 mmol) in freshly distilled acetonitrile (4.0 mL) was then slowly added to the above mixture by syringe pump over 30 min at 0 °C under argon. The resulting solution was stirred at 0 °C for 2 h, then at room temperature for 8−10 h. The reaction was quenched by saturated aqueous Na_2SO_3 (5.0 mL) solution. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with brine and dried with anhydrous sodium sulfate. Purification by flash chromatography (EtOAc/hexane, v/v, 1:4) provided the pure product.

Procedure for the Aminochlorination of α,β-Unsaturated Ketones (II): The enone (2.0 mmol), 4-Å molecular sieves (0.50 g), the CuOTf benzene complex (50 mg, 0.1 mmol, 10 mol %) and freshly distilled acetonitrile (3.0 mL) was placed into a dry vial. A solution of 4-$TsNCl_2$ (240 mg, 1.0 mmol) in freshly distilled acetonitrile (6.0 mL) was then slowly added to the above mixture by syringe pump over 1 h at 0 °C. The resulting solution was stirred at 0 °C under an argon atmosphere for 10 h. The reaction was quenched by slowly pouring the reaction solution into saturated aqueous Na_2SO_3 (20 mL) solution. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine and dried with anhydrous sodium sulfate. Purification by flash chromatography (EtOAc/hexane, v/v, 1:4) provided the pure product.

4-Chloro-4-phenyl-3-(tosylamino)butan-2-one (2a): 2a was obtained by the reaction of *trans*-4-phenyl-3-buten-2-one (146 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2a** was isolated as a white solid (236 mg, 67% yield). M.p. 115−117 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu} = 1724$ (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.56-7.60$ (m, 2 H), 7.28−7.34 (m, 5 H), 7.20−7.25 (m, 2 H), 5.37 (d, $J = 8.5$ Hz, 1 H), 5.08 (d, $J = 6.5$ Hz, 1 H), 4.40 (dd, $J = 8.5$, 6.5 Hz, 1 H), 2.41 (s, 3 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 203.8$, 143.9, 136.4, 136.1, 129.7, 129.1, 128.8, 127.4, 127.1, 66.3, 61.6, 30.1, 21.6 ppm. HRMS

(MALDI-FTMS): *m*/*z* [M^+ + 1]; $C_{17}H_{18}ClNO_3S$: calcd. 352.0769; found 352.0769.

3-Chloro-1,3-diphenyl-2-(tosylamino)propan-1-one (2b): 2b was obtained by the reaction of chalcone (208 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2b** was isolated as a white solid (294 mg, 71% yield). M.p. 49−51 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1679 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68−7.72 (m, 2 H), 7.55−7.60 (m, 1 H), 7.49−7.53 (m, 2 H), 7.37−7.42 (m, 2 H), 7.19−7.29 (m, 5 H), 7.02−7.05 (m, 2 H), 5.54 (d, *J* = 9.5 Hz, 1 H), 5.40 (dd, *J* = 9.5, 6.5 Hz, 1 H), 5.12 (d, *J* = 6.5 Hz, 1 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.9, 143.6, 136.6, 135.9, 135.1, 134.1, 129.5, 129.0, 128.7, 128.5, 127.9, 127.1, 61.9, 61.5, 21.4 ppm. HRMS (MALDI-FTMS): *m*/*z* [M^+ + Na]; $C_{22}H_{20}ClNO_3S$: calcd. 436.0745; found 436.0747.

3-Chloro-1-(4-methoxyphenyl)-3-phenyl-2-(tosylamino)propan-1-one (2c): 2c was obtained by the reaction of 4′-methoxychalcone (238 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2c** was isolated as a white solid (328 mg, 74% yield). M.p. 143−145 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1670 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69−7.74 (m, 2 H), 7.47−7.51 (m, 2 H), 7.19−7.30 (m, 5 H), 7.00−7.05 (m, 2 H), 6.85−6.90 (m, 2 H), 5.55 (d, *J* = 9.5 Hz, 1 H), 5.35 (dd, *J* = 9.5, 6.0 Hz, 1 H), 5.10 (d, *J* = 6.0 Hz, 1 H), 3.88 (s, 3 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.9, 164.4, 143.5, 136.7, 136.1, 131.2, 129.4, 129.0, 128.4, 128.0, 127.9, 127.1, 113.9, 62.0, 61.1, 55.6, 21.4 ppm. HRMS (MALDI-FTMS): *m*/*z* [M^+ + 1]; $C_{23}H_{22}ClNO_4S$: calcd. 444.1031; found 444.1028.

***cis*-Isomer:** ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69−7.74 (m, 2 H), 7.51−7.54 (m, 2 H), 7.24−7.30 (m, 5 H), 7.04−7.08 (m, 2 H), 6.88−6.91 (m, 2 H), 5.81 (d, *J* = 10.5 Hz, 1 H), 5.23 (dd, *J* = 10.5, 4.5 Hz, 1 H), 5.16 (d, *J* = 4.5 Hz, 1 H), 3.88 (s, 3 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.9, 164.4, 143.5, 136.7, 136.1, 130.9, 129.5, 129.0, 128.4, 128.0, 127.9, 127.0, 114.0, 62.1, 61.2, 55.6, 21.4 ppm.

3-Chloro-1-(4-chlorophenyl)-3-phenyl-2-(tosylamino)propan-1-one (2d): 2d was obtained by the reaction of 4′-chlorochalcone (243 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2d** was isolated as a white solid (291 mg, 65% yield). M.p. 83−85 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1683 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.63−7.68 (m, 2 H), 7.44−7.49 (m, 2 H), 7.33−7.38 (m, 2 H), 7.20−7.30 (m, 5 H), 7.01−7.05 (m, 2 H), 5.62 (d, *J* = 9.5 Hz, 1 H), 5.32 (dd, *J* = 9.5, 7.0 Hz, 1 H), 5.08 (d, *J* = 7.0 Hz, 1 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.3, 143.7, 140.7, 136.5, 135.9, 133.6, 130.0, 129.5, 129.1, 128.9, 128.6, 127.9, 127.0, 61.9, 61.0, 21.4 ppm.

3-Chloro-1-(4-fluorophenyl)-3-phenyl-2-(tosylamino)propan-1-one (2e): 2e was obtained by the reaction of 4′-fluorochalcone (226 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2e** was isolated as a colorless oil (324 mg, 75% yield). IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1682 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.73−7.78 (m, 2 H), 7.44−7.49 (m, 2 H), 7.20−7.28 (m, 5 H), 7.01−7.08 (m, 4 H), 5.70 (d, *J* = 10.0 Hz, 1 H), 5.35 (dd, *J* = 10.0, 7.0 Hz, 1 H), 5.09 (d, *J* = 7.0 Hz, 1 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.9, 167.2, 165.2, 143.6, 136.6, 136.0, 131.5, 131.4, 129.5, 129.0, 128.5, 127.9, 127.0, 115.9, 115.7, 61.9, 60.9, 21.4 ppm.

3-Chloro-3-(2-chlorophenyl)-1-phenyl-2-(tosylamino)propan-1-one (2f): 2f was obtained by the reaction of 2-chlorochalcone (243 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2f** was isolated as a white solid (314 mg, 70% yield). M.p. 159−161 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1675 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.62−7.68 (m, 2 H), 7.50−7.56 (m, 2 H), 7.47−7.52 (m, 1 H), 7.40−7.45 (m, 1 H), 7.28−7.35 (m, 2 H), 7.24−7.28 (m, 1 H), 7.11−7.17 (m, 1 H), 7.05−7.10 (m, 1 H), 6.08−7.04 (m, 2 H), 5.77 (d, *J* = 10.0 Hz, 1 H), 5.64 (broad, 1 H), 5.52 (broad, 1 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.9, 143.6, 136.5, 135.4, 133.9, 133.7, 133.0, 130.2, 130.0, 129.5, 129.4, 128.5, 128.4, 127.1, 59.1, 58.4, 21.3 ppm.

3-Chloro-3-(4-nitrophenyl)-1-phenyl-2-(tosylamino)propan-1-one (2g): 2g was obtained by the reaction of 4-nitro-chalcone (253 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2g** was isolated as a white solid (303 mg, 66% yield). M.p. 154−156 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1682 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.03−8.08 (m, 2 H), 7.79−7.84 (m, 2 H), 7.60−7.65 (m, 1 H), 7.41−7.48 (m, 6 H), 6.99−7.03 (m, 2 H), 5.73 (d, *J* = 10.0 Hz, 1 H), 5.39 (dd, *J* = 10.0, 7.5 Hz, 1 H), 5.13 (d, *J* = 7.5 Hz, 1 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.2, 147.9, 144.0, 143.2, 136.4, 134.9, 134.6, 129.5, 129.1, 128.9, 128.8, 126.9, 123.6, 60.8, 60.2, 21.3 ppm.

3-Chloro-3-(3-nitrophenyl)-1-phenyl-2-(tosylamino)propan-1-one (2h): 2h was obtained by the reaction of 3-nitro-chalcone (253 mg, 1.00 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **2h** was isolated as a white solid (417 mg, 91% yield). M.p. 173−175 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1682 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.10−8.15 (m, 1 H), 8.02−8.05 (m, 1 H), 7.77−7.82 (m, 2 H), 7.60−7.68 (m, 2 H), 7.43−7.51 (m, 5 H), 7.01−7.05 (m, 2 H), 5.61 (d, *J* = 9.5 Hz, 1 H), 5.37 (dd, *J* = 9.5, 7.5 Hz, 1 H), 5.12 (d, *J* = 7.5 Hz, 1 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.2, 148.0, 144.0, 138.5, 136.4, 135.0, 134.5, 134.2, 129.6, 129.5, 128.9, 128.8, 126.9, 123.9, 123.1, 60.9, 60.4, 21.4 ppm. HRMS (MALDI-FTMS): *m*/*z* [M^+ + Na]; $C_{22}H_{19}ClN_2O_5SNa$: calcd. 481.0595; found 481.0604.

4-Chloro-5-(tosylamino)hexan-3-one (3a): 3a was obtained by the reaction of *trans*-4-hexen-3-one (98 mg, 1.0 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (288 mg, 1.20 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **3a** was isolated as a colorless oil (170 mg, 56% yield). IR (deposit from CH_2Cl_2 solution on a NaCl plate): ṽ = 1718 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75−7.79 (m, 2 H), 7.29−7.35 (m, 2 H), 4.96 (d, *J* = 9.5 Hz, 1 H), 4.42 (d, *J* = 5.5 Hz, 1 H), 4.02

(m, 1 H), 2.55−2.76 (m, 2 H), 2.43 (s, 3 H), 1.02−1.08 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.9, 143.8, 137.6, 129.8, 127.0, 67.7, 50.8, 33.6, 21.5, 16.7, 7.5 ppm. HRMS (MALDI-FTMS): *m/z* [M^+ + Na]; $C_{13}H_{18}ClNO_3SNa$: calcd. 326.0588; found 326.0592.

2-Chloro-1-(tosylamino)pentan-3-one (3b): 3b was obtained by the reaction of ethyl vinyl ketone (126 mg, 1.50 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (432 mg, 1.80 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **3b** was isolated as a white solid (313 mg, 72% yield). M.p. 67−69 °C. IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 1721 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72−7.77 (m, 2 H), 7.30−7.35 (m, 2 H), 5.12 (t, *J* = 7.0 Hz, 1 H), 4.38 (dd, *J* = 6.0, 7.0 Hz, 1 H), 3.40−3.47 (m, 1 H), 3.28−3.34 (m, 1 H), 2.79−2.88 (m, 1 H), 2.47−2.57 (m, 1 H), 2.44 (s, 3 H), 1.08 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.8, 143.9, 136.6, 129.9, 127.0, 58.6, 44.8, 33.4, 21.5, 7.5 ppm. HRMS (MALDI-FTMS): *m*/*z* [M^+ + 1]; $C_{12}H_{17}ClNO_3S$: calcd. 290.0612; found 290.0614.

3-Chloro-4-(tosylamino)butan-2-one (3c): 3c was obtained by the reaction of methyl vinyl ketone (105 mg, 1.50 mmol) with *N*,*N*-dichloro-*p*-toluenesulfonamide (432 mg, 1.80 mmol) in the presence of 4-Å molecular sieves (500 mg) and the CuOTf benzene complex (50 mg, 0.10 mmol, 10 mol %) in acetonitrile (6.0 mL). Compound **3c** was obtained as a colorless oil without purification (405 mg, 98% yield). IR (deposit from CH_2Cl_2 solution on a NaCl plate): $\tilde{\nu}$ = 1720 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72−7.76 (m, 2 H), 7.31−7.35 (m, 2 H), 4.97 (t, *J* = 7.0 Hz, 1 H), 4.36 (dd, *J* = 5.5, 7.5 Hz, 1 H), 3.38−3.45 (m, 1 H), 3.28−3.34 (m, 1 H), 2.44 (s, 3 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.9, 143.9, 136.6, 129.9, 127.0, 59.5, 44.8, 27.4, 21.5 ppm. HRMS (MALDI-FTMS): *m*/*z* [M^+ + 1]; $C_{11}H_{15}O_3NSCl$: calcd. 276.0456; found 276.0456.

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