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New catalytic diamination of alkenes provides a novel access to 1-*p*-toluenesulfonyl-3-trichloromethyl-4,5-imidazolines

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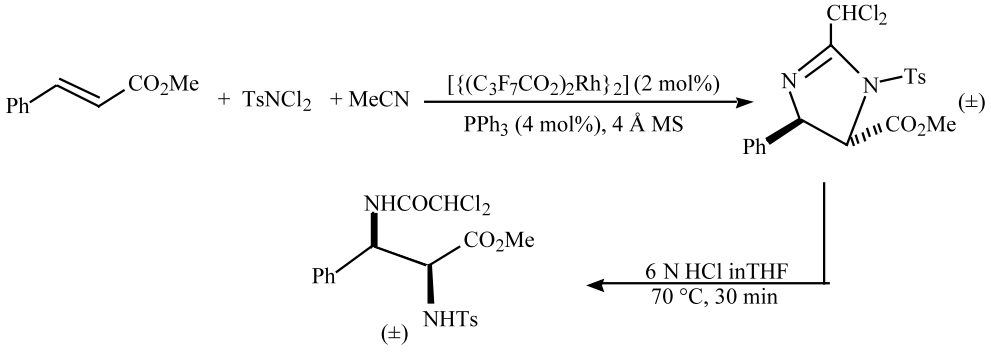
Abstract—Non-oxidative catalytic diamination reaction of α,β-unsaturated esters and ketones with *N*,*N*-dichloro-*p*-toluenesulfonamide and acetonitrile has been established for the synthesis of 1-*p*-toluenesulfonyl-3-trichloromethyl-4,5-imidazoline derivatives. Rhodium(II) acetate dimer was found to be superior to rhodium(II) heptafluorobutyrate as the catalyst for this reaction which was carried out at 55°C. Six examples were examined with chemical yields of 57–77%.

The regio- and stereoselective synthesis of vicinal diamines has become an active and challenging topic in organic chemistry because of the importance of these derivatives in medicinal and pharmaceutical research.[1,2] Enantiomerically pure diamine derivatives have been utilized as chiral auxiliaries and chiral ligands for asymmetric synthesis.[3,4] Recently, we have discovered two novel diamination reactions of olefins which are electrophilic and non-oxidative.[5] These reactions can occur with alkyl cinnamates and α,β-unsaturated ketones as the substrates to result in multifunctionalized 1,2-vicinal diamine products. The first diamination of alkyl cinnamates proceeded in a tandem manner using *N*,*N*-dichloro-2-nitrobenzenesulfonamide (2-NsNCl$_2$) and acetonitrile as the nitrogen sources without the use of any metal catalysts.[5a] The second diamination was achieved by using *N*,*N*-dichloro-*p*-toluenesulfonamide (4-TsNCl$_2$) and acetonitrile as the nitrogen sources with the aid of the complex of rhodium(II) heptafluorobutyrate and triphenylphosphine as the catalyst.[5b] The reaction gave imidazolines products at first and then α,β-differentiated vicinal diamines after acidic hydrolysis (Scheme 1).

The mechanistic hypothesis was made mainly based on the formation of aziridinium intermediate (**A**) at the initial step (Scheme 2). At the second step, the Ritter-type nucleophilic attack by MeCN opens the aziridinium ring to give nitrilium intermediate (**B**).[6,7] The cyclization of intermediate (**B**) gives rise to 1*N*-(*p*-tosyl),1*N*-chloroimidazolinium (**C**) which is followed by 1,3-displacement of 1*N*-chlorine leading to 1*N*-(*p*-tosyl),3*N*-chloroimidazolinium (**D**). Deprotonation of the 2-methyl group of (**D**) gives methylene scaffold (**E**) which enables the second S_N2' type displacement to afford 1-*p*-toluenesulfonyl-2-chloromethyl-4-phenyl-5-



Scheme 1.

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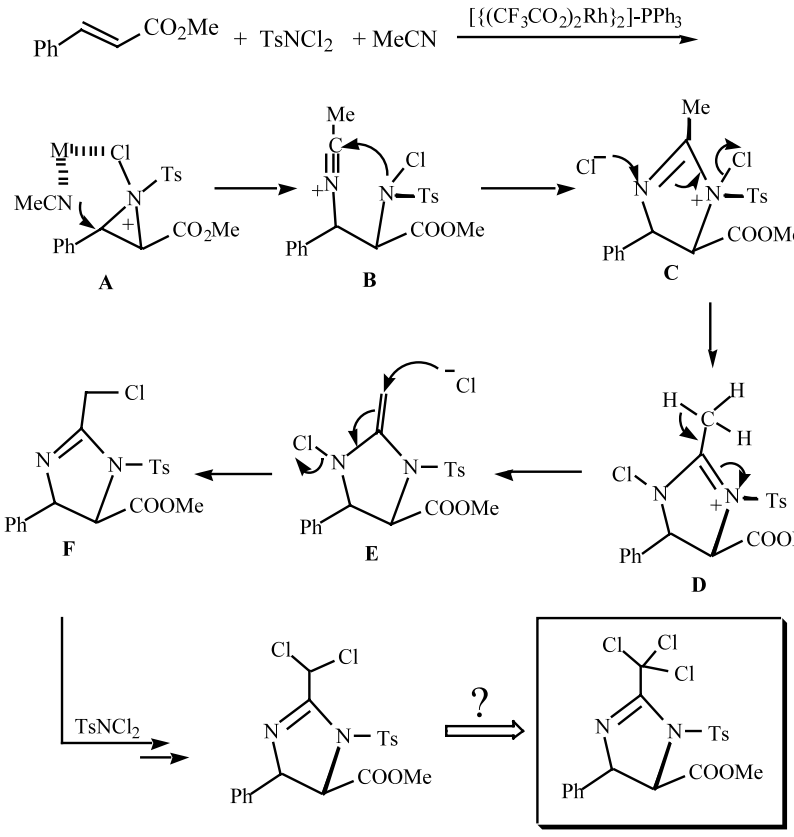


Scheme 2.

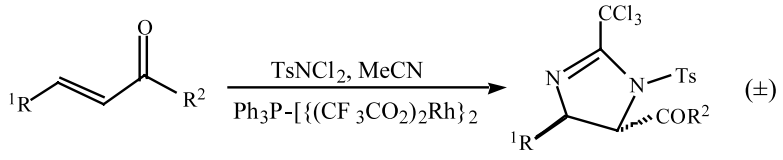
methyloxycarbonylimidazoline (**F**). The repeated deprotonation and S_N2'-type reaction results in 1-*p*-toluenesulfonyl-2-dichloromethyl-4-phenyl-5-methyloxycarbonylimidazoline.

The regioselectivity is understood based on the fact that the β-position of the aziridinium intermediate is loaded with more positive charge and therefore is attacked by acetonitrile favorably. The stereoselectivity can be explained by the hypothesis that the coordination of MeCN to the metal center occurs prior to the aziridinium ring opening.

The mechanism hypothesis suggests that it is possible to continue the third chlorination to further convert the $-CHCl_2$ group of imidazoline products into its $-CCl_3$ counterpart. In this case, the N^{β}-trichloroacetyl group of the final α,β-differentiated vicinal diamine product (Scheme 1) should be cleaved more easily upon treating with $NaBH_4$ in EtOH. In fact, the N^{β}-trichloroacetyl group has been a common protective group in organic synthesis.[8] In this communication, we report the preliminary results of the catalytic electrophilic diamination reaction of α,β-unsaturated carboxylic esters and α,β-unsaturated ketones to provide 1-*p*-toluenesulfonyl-3-trichloromethyl-4,5-imidazoline products.

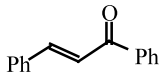
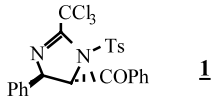
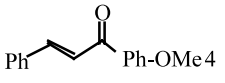
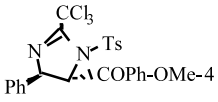
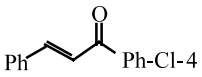
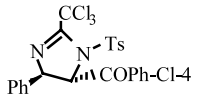
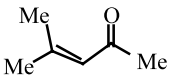
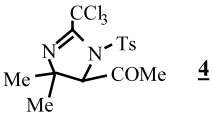
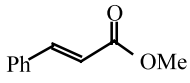
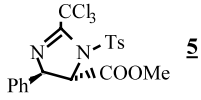
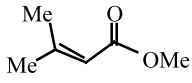
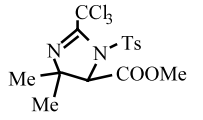
The study was initiated using chalcone as the substrate by simply performing the reaction at enhanced temperature. When temperature was increased to 35°C, 1-*p*-toluenesulfonyl-3-trichloromethyl-4,5-imidazoline started to appear, but the yield was very poor (<30%). 1-*p*-Toluenesulfonyl-3-dichloromethyl-4,5-imidazoline was still produced as the major product. However, when the temperature was increased to 55°C, the anticipated 3-trichloromethyl-4,5-imidazoline product was predominantly produced with the optimized chemical yield of more than 50% yield. It was interesting to find that when 4 Å molecular sieves were not present in the reaction system, the yield of trichloromethyl imidazoline can be further improved up to 55%.

In the previous diamination, rhodium(II) heptafluorobutyrate dimer was proven to be superior to rhodium(II) acetate dimer as the catalyst.[9] This is probably due to the poor solubility of the latter in acetonitrile solvent at room temperature. But in the current system, the rhodium(II) acetate dimer was found to be more effective than the rhodium(II) heptafluorobutyrate dimer to give higher yield (64%). Concurrently, the reaction period was also shortened to 24 h as compared to 44 h in the previous system. In fact, 3-methyl-3-buten-2-one (entry 4 of Table 1) even showed a faster rate to finish the reaction within 8 h. Similar to the previous electrophilic aminohalogenation and diamination reactions,[5,10,11] the present reaction is also easy to carry out. Essentially, it can be conducted in any capped pressure bottle of appropriate size without the need of inert atmosphere protection. In the



Scheme 3.

Table 1. Results of synthesis of 1-*p*-toluenesulfonyl-3-trichloromethyl-4,5-imidazolines[12]

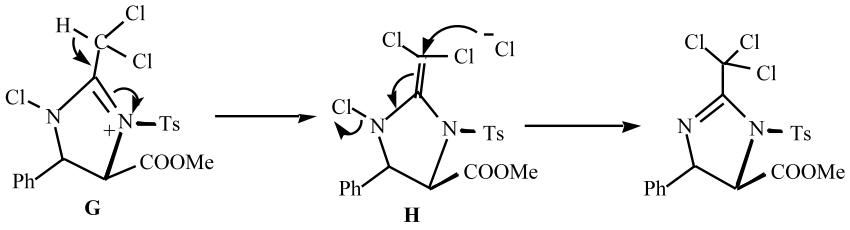
entry	substrates	product (±)	regioselectivty [a]	m.p. (°C)	yield (%) [b]
1		 **1**	>95	156-157	64
2		 **2**	>95	170 (dec)	74
3		 **3**	>95	173-174	68
4		 **4**	—	164-165	77
5		 **5**	>95	oil	57
6		 **6**	>95	oil	71

[a] Estimated by crude ^{1}H NMR determination. >95 % means no minor isomer was detected. [b] The yields after purification via column chromatography.

previous diamination, *N*,*N*-dichloro-*p*-toluenesulfonamide (4-$TsNCl_2$) was added into the reaction mixture in two portions to optimize the yield. But in this new system 4-$TsNCl_2$ can be added in one portion to make the reaction operation more concise.

As indicated in Table 1, both α,β-unsaturated esters and α,β-unsaturated ketones can be employed as the substrates for this reaction. Modest to good yields have been obtained (57–77%) for the six examples which were examined. Excellent *anti*/*syn* stereoselectivity and regioselectivity were also observed. As anticipated, the terminal disubstituted α,β-unsaturated carboxylic ester and ketone (entries 4 and 6 of Table 1) served as the substrates to give the best yields (77 and 71%, respectively). However, the terminal substitution advantage was not as obvious as that shown in the previous system, for which the extra in situ step of chlorination might be responsible. Similarly, the substrate difference between α,β-unsaturated esters and α,β-unsaturated ketones were also decreased. The use of other α,β-unsaturated esters and ketones for this reaction is currently being investigated and generating promising results in our laboratories (Scheme 3).

Under this new system, triphenylphosphine was still proven to be critical to inhibit the formation of vicinal haloamine side-product generated from aminochlorination reaction. This reaction coexists with the main diamination reaction at the original study. Both of these processes occurred through the formation of aziridinium intermediates as described before.[5,10,11] In previous system, 2.5 equiv. of *N*,*N*-dichloro-*p*-toluenesulfonamide was needed for the dichlorination of the methyl group of the imidazoline product. Surprisingly, for this further chlorination system (Scheme 4), same amount of the nitrogen/chlorine (2.5 equiv. of 4-$TsNCl_2$) source is found to be enough to achieve complete conversion.



Scheme 4.

In summary, a new catalytic system has been established to convert α,β-unsaturated esters and ketones into 4-*p*-toluenesulfonyl-3-trichloromethyl-4,5-imidazolines regio- and stereoselectively. The reaction was achieved by using rhodium(II) acetate to replace rhodium(II) heptafluorobutyrate as the catalyst. The reaction proceeded effectively at a higher temperature in the absence of 4 Å molecular sieves. The N^{β}-trichloroacetyl group from the hydrolysis of resulting 3-trichloromethyl-4,5-imidazolines can be readily deprotected under mild conditions.

Acknowledgements

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12. The representative procedure is demonstrated by the reaction of chalcone with *N*,*N*-dichloro-*p*-toluenesulfonamide (entry 1, Table 1). Into a dry vial was added triphenylphosphine (5.60 mg, 0.021 mmol), rhodium(II) trifluoroacetate dimer (6.60 mg, 0.010 mmol) and freshly distilled acetonitrile (2.50 mL). The mixture was stirred at 55°C for 1 h and appeared as a clear dark brown solution. The resulting mixture was loaded with chalcone (106 mg, 0.50 mmol) (entry 1 of Table 1) and *N*,*N*-dichloro-*p*-tolunesulfonamide (300 mg, 1.25 mmol). The reaction mixture became a light yellow slurry and was stirred at 55°C for 24 h in the capped vial without argon protection. The precipitate was filtered off and washed with EtOAc (3×5 mL). The organic solution was directly concentrated without quenching, purified via flash chromatography with hexane and EtOAc (v/v = 5:1) as the eluent to give 1-*p*-toluenesulfonyl-2-trichloromethyl-4-phenyl, 5-benzoylimidazoline (167 mg, 64%) as a white solid. Mp 156–157°C. **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.00 (m, 14H), 5.82 (d, J = 3.40 Hz, 1H), 5.01 (d, J = 3.40 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 156.9, 145.3, 137.7, 134.3, 134.1, 129.6, 129.1, 129.0, 128.8, 128.6, 128.4, 126.5, 88.5, 73.7, 70.2, 21.5. HRMS (MALDI-FTMS) m/z (MNa^+) found 543.0074, calcd for $C_{24}H_{19}Cl_3N_2O_3SNa$ 543.0099. **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.82 (m, 4H), 6.96–6.73 (m, 9H), 5.71 (d, J = 3.60 Hz, 1H), 4.99 (d, J = 3.60 Hz, 1H), 4.00 (s, 3H), 2.39 (s, 3H). **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–7.78 (m, 13H), 5.76 (d, J = 3.60 Hz, 2H), 4.98 (d, J = 3.60 Hz, 1H), 2.39 (s, 3H). **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.40 Hz, 2H), 7.39 (d, J = 8.40 Hz, 2H), 4.11 (s, 1H), 2.46 (s, 3H), 2.28 (s, 3H), 1.25 (s, 3H), 0.82 (s, 3H). **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.34 Hz, 2H), 7.12–7.7.26 (m, 5H), 6.94 (d, J = 8.34 Hz, 2H), 5.24 (d, J = 2.87 Hz, 1H), 4.80 (d, J = 2.87 Hz, 1H), 3.84 (s, 3H), 2.37 (s, 3H). **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.60 Hz, 2H), 7.37 (d, J = 8.60 Hz, 2H), 4.40 (s, 1H), 3.71 (s, 3H), 2.45 (s, 3H), 2.45 (s, 3H), 1.32 (s, 3H), 1.00 (s, 3H).