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The first transition metal–ligand complex-catalyzed regioselective and stereoselective aminohalogenation of cinnamic esters

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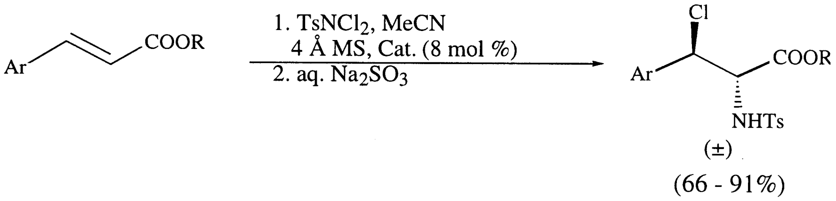
Abstract—Transition metal–ligand complex-catalyzed regio- and stereoselective aminohalogenation of cinnamic esters has been developed using *p*-$TsNCl_2$ as the nitrogen and chlorine sources. Dichloro-(1,10-phenanthroline)-palladium (II) as the catalyst can be handled very conveniently due to its property of less hygroscopic as compared with other aminohalogenation catalysts. The reaction is suggested to proceed through the mechanism involving *N*-tosyl *N*-chloro aziridinium intermediate. Eight examples are presented with modest to good yields (56–82%) and excellent stereoselectivity (>10:1). © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The vicinal haloamine compounds derived from α,β-unsaturated carboxylic esters are important building blocks in organic synthesis.[1] They can be readily converted into β-substituted α-amino acids and aziridines[2–4] upon the replacement of their halogen moieties via intermolecular and intramolecular processes. The subsequent transformations enable the concise syntheses of amino alcohols, amino aldehydes, lactones and lactams. Some haloamines can serve as GABA aminotransferase (GABA-AT) inactivators.[5] The development of highly regioselective and stereoselective synthetic approaches to the vicinal haloamine functionality has been studied for several decades. Unfortunately, it has still remained very difficult and challenging.[6,7] Recently, we reported an aminohalogenation reaction of cinnamic esters to generate *anti* alkyl 3-chloro-2-(*p*-toluenesulfonamido)-3-aryl propionates. The method employed *N*,*N*-dichloro-*p*-toluenesulfonamide ($TsNCl_2$) as the nitrogen and chlorine sources and transition metal and main group metal compounds [$Cu(OTf)_2$ and $ZnCl_2$] as catalysts (Scheme 1).[8] Our further study of this reaction is focused on the search for metal–ligand complexes as the catalysts, which should be beneficial to our ongoing exploration of the asymmetric version of the parent achiral system. In addition, some of these transition metal–ligand complexes are much less hygroscopic. They thus can be handled very conveniently during their usage. In this paper, we disclose the preliminary results of the aminohalogenation of α,β-unsaturated carboxylic esters by the use of dichloro-(1,10-phenanthroline)-palladium (II) as the catalyst. This new reaction process is represented in Scheme 2 and the results are summarized in Table 1.

2. Results and discussion

Our initial experiment started with the use of dichloro-(1,10-phenanthroline)-copper (II) as the catalyst simply because $Cu(OTf)_2$ has been proven to be effective in the original aminochlorination system. Unfortunately, the reaction was seriously deactivated. In fact, the first run of the reaction of methyl cinnamate with *N*,*N*-dichloro-*p*-toluenesulfonamide



Scheme 1.

Keywords: haloamine; aminohalogenation; catalysis.

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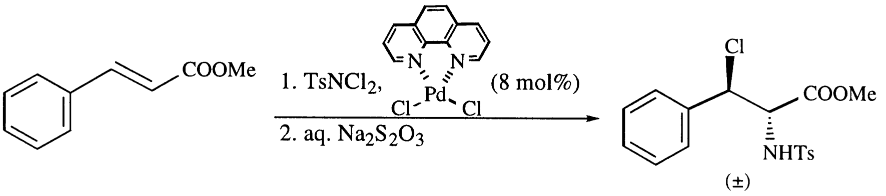
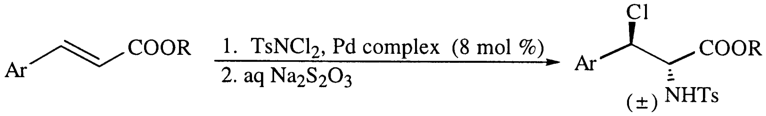
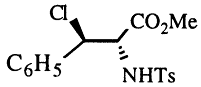
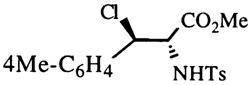
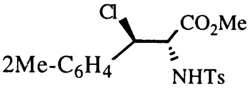
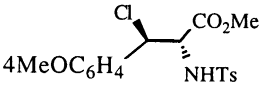
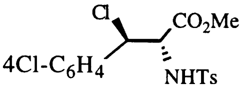
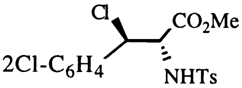
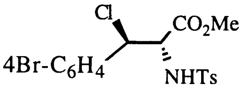
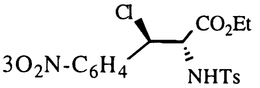


81 %
(regio and stereoselectivity > 95 %)

Scheme 2.

Table 1. Results of Pd complex-catalyzed aminochlorination of cinnamic esters



Entry	Ar	R	Product (±)	Stereoselectivly (*anti*/*syn*)[a]	Yield (%)[b]
1	C_6H_5	Me		>95	81
2	4-Me–C_6H_4	Me		>95	70
3	2-Me–C_6H_4	Me		>95	75
4	4-$MeOC_6H_4$	Me		10:1	74[c]
5	4-Cl–C_6H_4	Me		>95	82
6	2-Cl–C_6H_4	Me		>95	62
7	4-Br–C_6H_4	Me		>95	77
8[d]	3-NO_2–C_6H_4	Et		>95	56

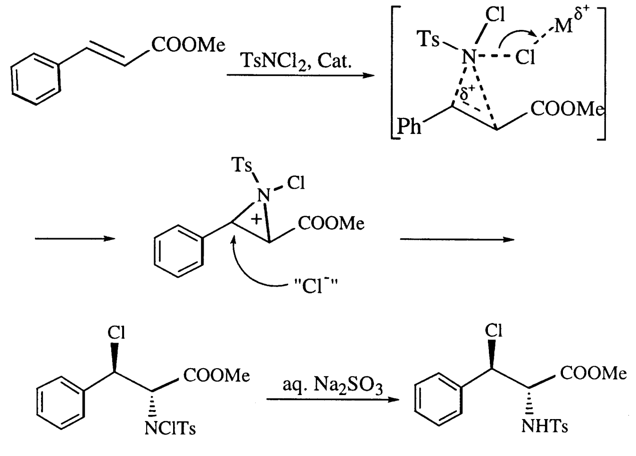
[a] Estimated by crude ^1H NMR determination, >95 means only one isomer is observed.
[b] The yields after purification via column chromatography.
[c] Combined yield of two isomers which were difficult to separate by column chromatography.
[d] 2.0 equiv. of $TsNCl_2$ and 2 days are needed.

in the presence of dihalo-(1,10-phenanthroline)-copper (II) (8 mol%) in acetonitrile resulted in only a trace amount of haloamine product in 10 h. The same reaction in several other solvents such as THF, toluene and dichloromethane proved to be unsuccessful resulting in either a small amount of complex mixtures or no products at all. Parallel experiments were then carried out by using various other metal complexes which were available to us. These complexes include dibromo-(1,10-phenanthroline)-copper (II), dichloro-(1,10-phenanthroline)-platinum (II), dichloro-(1,10-phenanthroline)-palladium (II), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)-ruthenium (II), 1,2-bis[(diphenylphosphino)ethane]dichloroiron (II), 1,2-bis[(diphenylphosphino)ethane]dichlorocobalt (II), 1,2-bis[(diphenylphosphino)ethane]dichloronickel (II), 1,2-bis-[(diphenylphosphino)ethane]dichloropalladium (II), *cis*-bis(2,2′-bipyridine)-dichlororuthenium (II) hydrate. Among the above catalyst candidates, we found that only dichloro-(1,10-phenanthroline)-palladium (II) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)-ruthenium (II) catalyzed the reaction to completion with the yield of 81 and 54%, respectively. The following synthesis was therefore focused on the use of dichloro-(1,10-phenanthroline)-palladium (II) as the catalyst for the study of the reaction scope.

Similar to our previous $ZnCl_2$- and $Cu(OTf)_2$-catalyzed system,[8a] this reaction can be performed simply by mixing the three components, olefin substrates, *N*,*N*-dichloro-*p*-toluenesulfonamide and dichloro-(1,10-phenanthroline)-palladium (II) together in acetonitrile in any convenient vial of appropriate size. There is no need of inert atmosphere protection. *N*,*N*-Dichloro-*p*-toluenesulfonamide, the nitrogen/chlorine source, was readily prepared by the treatment of *p*-toluenesulfonamide with commercial bleach and followed by CH_3COOH acidification.[7,8a] Unlike *N*,*N*-dichloro-*o*-nitrobenzenesulfonamide, which has been proven to be stable at room temperature for several months,[8b] *N*,*N*-dichloro-*p*-toluenesulfonamide must be kept in a refrigerator under dry conditions shortly after use.

An excess amount of *p*-$TsNCl_2$ (1.2 equiv.) proved to be necessary for complete consumption of the olefin starting materials, which is monitored by TLC. Less than 8 mol% of catalyst gave incomplete conversion even in a prolonged reaction period. The concentration of cinnamates can be decreased by at least 30%, which is in contrast to the *o*-$NsNCl_2$-based system where substrate concentration is critical for the catalytic cycle.[8b] In $Cu(OTf)_2$-catalyzed reaction, it was shown that yields were slightly increased by using 4 Å molecular sieves.[8a] However, this enhancement was not observed in the present dichloro-(1,10-phenanthroline)-palladium (II)-catalyzed aminohalogenation reaction.

The examination of the results listed in Table 1 reveals that cinnamic esters with either electron-donating or electron-withdrawing groups on their aromatic rings can be subjected to this new system. But for electron-withdrawing cinnamate (entry 8), at least 2 equiv. of $TsNCl_2$ is needed to furnish the reaction. The reaction also takes a longer time (48 h) to give the lowest chemical yield of 56% among 8 cases we examined. For all these cases, α,β-regioselectivity has been completely controlled. The regiochemistry was confirmed by mass spectroscopic analysis in which two major species, $[ArCHCl]^+$ and $[TsNHCHCOOMe]^+$, were clearly identified. Furthermore, excellent *anti*/*syn* stereoselectivity has been achieved for most examples of Table 1. Only in case 4 was modest stereoselectivity (*anti*/*syn*=10:1) obtained. The *anti*/*syn* stereoselectivity was unambiguously determined by the conversion of product **1** to a known sample,[8a] which can further confirm the regiochemistry assignment. It was also found that 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)-ruthenium (II) resulted in similar regio- and stereoselectivity except lower yields which are 20–30% lower than those of dichloro-(1,10-phenanthroline)-palladium (II)-catalyzed examples.



Scheme 3.

In earlier aminochlorination reactions of simple olefins with *N*-monochloro-*p*-toluenesulfonamide or *N*,*N*-dichloro-*p*-toluenesulfonamide as the nitrogen and chlorine sources, both bridged chloronium ion mechanisms and radical mechanisms were suggested.[7,9] To give a reasonable explanation for regio- and stereoselectivity for this new metal–ligand-catalyzed aminochlorination, we would like to suggest an alternative novel mechanism which involves the formation of a novel *N*-tosyl *N*-chloro aziridinium intermediate (Scheme 3).[8b] This hypothesis has been supported by the preliminary results of the α,β-differentiated diamination process we discovered recently,[10] although *N*,*N*-dichloro-*p*-nitrobenzenesulfonamide instead of *N*,*N*-dichloro-*p*-toluenesulfonamide was employed as the nitrogen source. Our latest study revealed that similar diamination can be achieved by reacting cyclohexene with *N*,*N*-dichloro-*p*-toluenesulfonamide in acetonitrile solution.

At the initial step of this mechanism, the palladium metal center of dichloro-(1,10-phenanthroline)-palladium (II) coordinates to *N*-chlorine instead of the oxygen motif of *N*,*N*-dichloro-*p*-toluenesulfonamide. This interaction weakens the N–Cl bond, which is necessary to remove the chlorine anion to form a 'Ns–$N^{\delta+}$–Cl' type of electrophilic species for subsequent electrophilic addition. The Pd-associated 'Cl^-' nearby the carbonium reactive site acts as the nucleophile to open the three-member ring of *N*-tosyl *N*-chloro aziridinium intermediate. The S_N2 mechanism of this aziridinium ring opening is responsible for the high *anti* stereoselectivty. The regioselectivity can be explained by the fact that the β-position of the aziridinium intermediate has more positive charge than the α-position because of the stabilization effect from the β-phenyl ring.

In conclusion, the first metal–ligand catalyzed regioselective and stereoselective aminochlorination of alkyl cinnamates has been established by using the less hygroscopic catalyst, dichloro-(1,10-phenanthroline)-palladium (II). The new system makes it possible to find an asymmetric aminohalogenation reaction if a metal–ligand complex is associated in the key olefin electrophilic addition step.[11] A novel mechanism of electrophilic amination of olefins to form *N*-tosyl *N*-chloro aziridinium intermediate was proposed. This important intermediate will find many applications in organic synthesis by reacting with a variety of other nucleophiles.

3. Experimental

3.1. General

All reactions were conducted without inert gas protection. Acetonitrile (HPLC grade) was purchased from Aldrich Chemical Co. and directly utilized without further drying and distillation. Other commercial chemicals were also used without purification and their stoichiometries were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on E. Merck silica gel 60 (230–400 mesh). High-resolution mass spectral analysis was conducted by the URC mass spectrometry facility of the University of California at Riverside.

The representative procedure is demonstrated by the dichloro-(1,10-phenanthroline)-palladium (II)-catalyzed aminochlorination reaction of methyl *trans*-cinnamate with *N*,*N*-dichloro-*p*-toluenesulfonamide as described in Scheme 2. Into a dry vial was added methyl cinnamate (81.0 mg, 0.50 mmol) and acetonitrile (1.5 mL). The reaction vial was immersed in a room temperature bath, and loaded with $\mathrm{TsNCl_2}$ (144 mg, 0.60 mmol, 1.20 equiv.) and dichloro-(1,10-phenanthroline)-palladium (II) (14.3 mg, 8 mol%). The resulting solution in the capped vial was stirred at room temperature for 22 h without inert gas protection. The reaction was finally quenched by dropwise addition of saturated aqueous $\mathrm{Na_2S_2O_3}$ solution (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with 10% aqueous ammonia chloride and brine, dried over anhydrous magnesium sulfate and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 1:3, v/v) provided *trans* methyl 3-chloro-2-(*p*-toluenesulfonamido)-3-phenylpropionate **1** (0.123 g, 81% yield) as white solid. Mp 142–144°C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.75 (d, J=9.93 Hz, 1H), 7.24–7.52 (m, 9H), 5.04 (d, J=10.3 Hz, 1H), 4.29 (t, J=10.3 Hz, 1H), 3.35 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 169.3, 142.8, 137.3, 136.7, 129.4, 128.9, 128.5, 128.2, 126.3, 61.1, 60, 52.0, 21.0. HRMS (DCI) *m*/*z* ($\mathrm{M^+ + NH_4^+}$) found 385.0986, calcd for $\mathrm{C_{17}H_{22}ClN_2O_4S}$ 385.0988.

3.1.1. Compound 2. White solid (266 mg, 70% yield); mp 143–145°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.74 (d, J=10 Hz, 1H), 7.06–7.50 (m, 8H), 4.99 (d, J=10.4 Hz, 1H), 4.25 (t, J=10 Hz, 1H), 3.35 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 169.5, 142.7, 138.5, 137.4, 133.7, 129.3, 129.0, 128.0, 126.3, 61.2, 60.2, 52.0, 21.0, 20.8. HRMS (DCI) *m*/*z* ($\mathrm{M^+ + NH_4^+}$) found 399.1141, calcd for $\mathrm{C_{18}H_{25}ClN_2O_4S}$ 399.1145.

3.1.2. Compound 3. White solid (285 mg, 75% yield); mp 132–134°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.77 (d, J=10 Hz, 1H), 7.20–7.58 (m, 8H), 5.22 (d, J=10.7 Hz, 1H), 4.48 (t, J=10.4 Hz, 1H), 3.31 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 169.5, 143.0, 137.3, 136.7, 134.6, 129.3, 130.7, 129.4, 128.8, 126.5, 126.4, 126.3, 59.8, 56.4, 52.0, 21.0, 18.6; HRMS (DCI) *m*/*z* ($\mathrm{M^+ + NH_4^+}$) found 399.1148, calcd for $\mathrm{C_{18}H_{25}ClN_2O_4S}$ 399.1145.

3.1.3. Compound 5. Colorless oil (331 mg, 82% yield); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.80 (d, J=9.6 Hz, 1H), 7.21–7.39 (m, 8H), 5.05 (d, J=10.4 Hz, 1H), 4.26 (dd, J=10.4, 9.6 Hz, 1H), 3.32 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 169.3, 142.7, 137.4, 135.6, 133.7, 130.0, 129.3, 128.4, 126.2, 61.2, 59.0, 52.2, 21.0.

3.1.4. Compound 6. White solid (249 mg, 62% yield); mp 136–138°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.91 (d, J=10 Hz, 1H), 7.30–7.53 (m, 8H), 5.42 (d, J=10 Hz, 1H), 4.64 (t, J=10 Hz, 1H), 3.35 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 168.9, 143.0, 137.3, 133.6, 133.3, 130.8, 129.9, 129.4, 127.5, 126.4, 126.3, 59.2, 56.1, 52.1, 21.0.

3.1.5. Compound 7. Colorless oil (344 mg, 77% yield); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.80 (d, J=9.8 Hz, 1H), 7.21–7.46 (m, 8H), 5.03 (d, J=12.0 Hz, 1H), 4.25 (dd, J=12.0, 9.8 Hz, 1H), 3.35 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 169.3, 142.8, 137.3, 136.0, 131.3, 131.0, 130.2, 130.0, 129.3, 129.2, 126.3, 126.2, 122.4, 61.2, 59.0, 52.2, 21.1.

3.1.6. Compound 8. Colorless oil (239 mg, 56% yield); ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.84 (d, J=8.0 Hz, 1H), 8.3 (m, 2H), 8.14 (m, 1H), 7.57 (m, 1H), 7.35 (d, J=8.0 Hz, 2H), 7.17 (d, J=8.0 Hz, 2H), 5.25 (d, J=10.0 Hz, 1H), 4.31 (dd, J=10.0, 8.0 Hz, 1H), 3.92 (m, 2H), 3.34 (s, 1H), 2.30 (s, 1H), 1.07 (t, J=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ 168.6, 147.3, 142.8, 138.8, 137.5, 135.0, 130.1, 129.3, 126.1, 123.8, 123.2, 61.4, 61.3, 58.5, 20.9, 13.7.

Acknowledgements

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11. About 10% ee was observed for case 1 of Table 1 when 20 mol% of the complex of 2,2′-methylenebis[(4*S*)-4-phenyl-2-oxazolidine]–MgI_2 was utilized as the catalyst.