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Novel imidazolination reaction of alkenes provides an easy access to new α,β-differentiated 1,2-vicinal diamines

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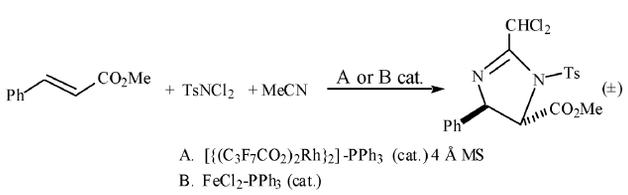
α,β-Differentiated 1,2-vicinal diamines have been efficiently synthesized by using new electrophilic imidazolination reaction of alkenes. The hydrolysis of imidazolines was performed by treatment with 6 M HCl in THF at 70 °C without epimerization. Eight examples were examined to give good to excellent yields (87–96%).

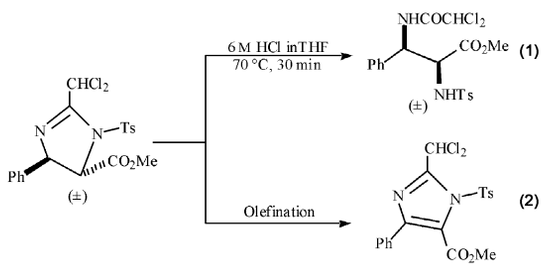
Introduction

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] α,β-Unsaturated carboxylate-derived diamines can mimic both α- and β-amino acids for peptide and protein studies. In fact, α,β-diamino acids have already been utilized for the design and synthesis of the anti-cancer drugs, taxol and taxotere.[3] The replacement of the hydroxyl group with the amine functionality can enhance the aqueous solubility of these drugs while the hydrogen bonding environment is retained. Enantiomerically pure diamines have been employed as chiral auxiliaries and ligands for asymmetric synthesis and catalysis.[4–6] Recently, we have discovered two new diamination reactions of olefins which are electrophilic and oxidative.[7,8] The first diamination of alkyl cinnamates was carried out in a tandem manner by using *N*,*N*-dichloro-2-nitrobenzenesulfonamide (2-$NsNCl_2$) and acetonitrile as the nitrogen sources without the use of any metal catalysts to give *anti*-alkyl-N^{α}-Ns,N^{β}-Ac-diaminophenylpropionates.[7] The second diamination of olefins was achieved by using *N*,*N*-dichloro-*p*-toluenesulfonamide (4-$TsNCl_2$) and acetonitrile as the nitrogen sources with the aid of the complex dirhodium(II) tetra(heptafluorobutyrate)[8a] or iron(III) chloride[8b] and triphenylphosphine as the catalysts. This reaction directly afforded imidazoline derivatives which are functionalized on position 3 (Scheme 1).



Scheme 1 Diamination of olefins for imidazoline synthesis

To make this new reaction more useful, we intend to convert the resulting imidazolines into other important compounds. For example, they can be hydrolyzed to give 1,2-vicinal α,β-diffrentiated diamino esters. They can conceivably be converted into 4,5-multifunctionalized imidazoles through olefination or converted into 4,5-multifunctionalized imidazolidines through reduction (Scheme 2). In this paper, we report our results of the application of olefin imidazolination to the synthesis of 1,2-vicinal diamines *via* an overall two-step procedure (Scheme 2, eqn. (1)) with the results collected in Table 1.



Scheme 2 Novel synthesis of diamines and imidazoles from imidazolines

Results and discussion

So far, only few known methods have appeared in the literature regarding the use of imidazolines for the synthesis of 1,2-vicinal diamines. In 1996,[4f] Hayashi and coworkers reported an imidazoline-based diamine synthesis by using the aldol reaction of imines with isocyanoacetate in the presence of transition metal catalysts. Almost at the same time, Corey and Kuhnle developed another imidazoline-based diamine synthesis starting from intramolecular coupling of bis-hydrobenzamide to form amarine.[4b] The ring-opening was conducted through reductive hydrolysis. A recent paper appeared for the synthesis of imidazolines *via* a three-component reaction (imine, CO and acid chloride),[9] although the resulting imidazolines have not, as yet, been converted into diamino acids. The above imidazoline syntheses were based on carbon–carbon bond formations. There are a few other olefin-derived imidazoline syntheses reported. However, they needed multiple steps *via* independent formation of aziridines or special haloamines.[10]

In comparison, our novel synthesis of diamines (for esters and ketones) only needs two steps starting from readily available and inexpensive olefins. More importantly, the products are functionalized and protected with different groups on their α- and β-positions, and therefore, can be selectively cleaved under different conditions. Two amine moieties of the products are also derived from inexpensive and readily available nitrogen sources, *p*-toluenesulfonamide and acetonitrile.

It should be noted that the resulting α,β-diamino ketones can be directly utilized for the synthesis of β,γ-diamino alcohols. A very recent synthesis for these diamino alcohols has been reported by Mangeney and coworkers.[11] This synthesis was achieved by adding the lithiated *N*-benzyl-*N*-*tert*-butylaminoacetonitrile to aldehydes to initially give β-hydroxy-α-aminonitriles, followed by a two-step procedure involving the addition of Grignard reagent and reduction.

Similar to known procedures for imidazoline hydrolysis, it is very convenient to carry out the reaction simply by adding 6 M

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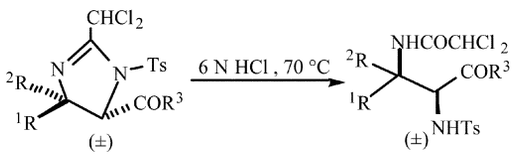
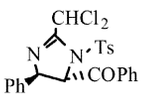
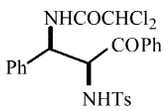
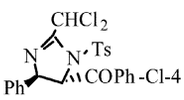
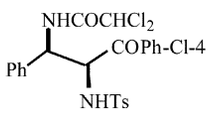
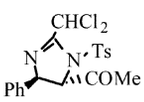
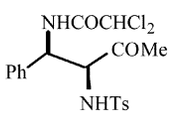
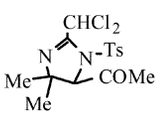
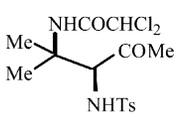
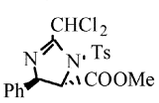
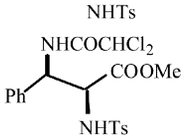
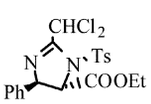
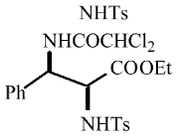
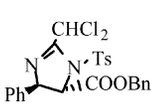
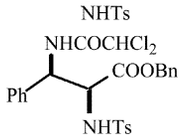
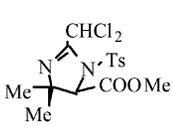
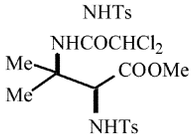
Table 1 Results of the new synthesis of 1,2-vicinal diamines



Entry	Substrate[a]	Product (±)[b]		Yield[c] (%)
1			**1**	96
2			**2**	88
3			**3**	91
4			**4**	92
5			**5**	92
6			**6**	87
7			**7**	93
8			**8**	94

[a] Synthesized by following the procedure in ref. 8 [b] No epimerization was observed. [c] Purified yields.

HCl in to a THF solution of the imidazoline starting materials. The reaction can be completed within 30 min at 70 °C. There was no epimerization observed during the acidic hydrolysis period. The reaction can also proceed at 50 °C to give similar chemical yields but it needed at least 1 h for completion. For entries 3 and 4 of Table 1, the imidazoline substrates showed poor solubility in THF; $CHCl_3$ was therefore used instead to achieve excellent yields (93 and 94%, respectively). We also found that the hydrolysis can proceed at room temperature, but needs much longer time (more than 24 h).

As indicated in Table 1, the synthesis of the imidazolines derived from both α,β-unsaturated esters and ketones worked very well under the simple conditions to give high yields. There is no significant difference between these two types of imidazolines (esters and ketones) regarding reaction rates and chemical yields. All products were obtained as white solids for the eight cases which we examined, and can be easily purified by recrystalization or column chromatography.

In conclusion, a novel two-step synthesis of vicinal diamines has been developed through hydrolysis of imidazolines resulting from imidazolination of α,β-unsaturated ketones or esters. The synthesis can be conducted by using inexpensive initial starting materials such as olefins, acetonitrile and *p*-toluenesulfonamide and commercial bleach to give crystalline products, which made purification convenient.

Experimental

NMR spectra were recorded at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR on a Varian 500 MHz NMR spectrometer. $CDCl_3$ was the only solvent used for the NMR analysis with TMS as the internal standard. Chemical shifts are reported downfield from TMS (0.00 ppm) for ^{1}H NMR and in the scale relative to $CDCl_3$ (77.0 ppm) for ^{13}C NMR. High-resolution mass spectral analysis was conducted by the Mass Spectrometry laboratory of the Scripps Research Institute. Column chromatography was performed with silica gel Merck 60 (230–400 mesh).

Representative procedure for the preparation of the 1,2-vicinal diamine products (Table 1, entry 5)

Into a vial containing the imidazoline derivative (63 mg, 0.14 mmol) was added THF (2 mL) and 6 M HCl (1 mL). The resulting mixture was stirred at 70 °C for 30 min and then cooled to room temperature. EtOAc (3 mL) was added to the

reaction mixture and the two phases were separated. The aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phase was washed with brine and water, and dried with anhydrous sodium sulfate. Purification by flash chromatography (acetone–hexane, 1/6 v/v) provided pure product **5** as a white solid (60 mg, 92% yield).

1. Isolated as a white solid, mp 168–170 °C. IR: 1686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.53–7.58 (m, 2H), 7.48–7.53 (m, 3H), 7.30–7.35 (m, 2H), 7.20–7.30 (m, 6H), 7.00–7.08 (m, 2H), 5.90–5.96 (d, J = 9.0 Hz, 1H), 5.88 (s, 1H), 5.22–5.28 (dd, J = 7.8, 5.5 Hz, 1H), 5.16–5.22 (dd, J = 9.0 5.5 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.0, 163.8, 143.9, 136.2, 136.1, 134.2, 134.1, 129.7, 129.0, 128.7, 128.3, 127.1, 126.9, 66.1, 60.3, 55.7, 21.4. HRMS (MALDI-FTMS): calc. for $C_{24}H_{22}N_2O_4Cl_2S$: *m/z* 505.075 (MH^+), found: 505.0736.

2. Isolated as a white solid, mp 189–191 °C. IR: 1687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.52–7.57 (m, 2H), 7.39–7.43 (m, 2H), 7.21–7.30 (m, 8H), 7.01–7.09 (m, 2H), 5.89 (s, 1H), 5.82–5.88 (d, J = 9.0 Hz, 1H), 5.18–5.26 (dd, J = 8.0, 6.0 Hz, 1H), 5.06–5.14 (dd, J = 9.0, 6.0 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 164.0, 144.1, 140.7, 136.1, 136.0, 132.6, 129.7, 129.6, 129.1, 129.0, 128.8, 127.0, 126.9, 66.1, 60.2, 55.8, 21.4. HRMS (MALDI-FTMS): calc. for $C_{24}H_{21}N_2O_4Cl_3S$: *m/z* 561.018 (MNa^+), found 561.0181.

3. Isolated as a white solid, mp 185–187 °C. IR: 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.57–7.64 (m, 2H), 7.29–7.40 (m, 4H), 7.22–7.29 (m, 4H), 5.89 (s, 1H), 5.58–5.68 (d, J = 9.0 Hz, 1H), 5.12–5.22 (dd, J = 8.0, 6.0 Hz, 1H), 4.24–4.34 (dd, J = 9.0, 6.0 Hz, 1H), 2.41 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 164.1, 144.2, 136.3, 136.1, 129.9, 129.3, 128.9, 127.0, 126.9, 66.1, 65.1, 54.9, 28.5, 21.6.

4. Isolated as a white solid, mp 105–107 °C. IR: 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66–7.73 (m, 2H), 7.28–7.34 (m, 2H), 6.52 (s, 1H), 5.84–5.96 (m, 2H), 4.42–4.52 (d, J = 9.0 Hz, 1H), 2.42 (s, 3H), 1.89 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.7, 164.2, 144.1, 136.3, 129.9, 127.4, 66.6, 64.4, 56.3, 30.5, 23.9, 23.7, 21.5. HRMS (MALDI-FTMS): calc. for $C_{15}H_{20}N_2O_4Cl_2S$: *m/z* 417.0413 (MNa^+), found 417.0429.

5. Isolated as a white solid, mp 184–186 °C. IR: 1743, 1340 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62–7.69 (m, 2H), 7.40–7.44 (d, J = 8.5 Hz, 1H), 7.30–7.37 (m, 3H), 7.27–7.30 (m, 2H), 7.19–7.25 (m, 2H), 5.93 (s, 1H), 5.30–5.40 (m, 1H), 5.20–5.30 (dd, J = 8.5, 5.5 Hz, 1H), 4.30–4.40 (dd, J = 9.0, 5.5 Hz, 1H), 3.47 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 163.7, 144.1, 136.3, 135.5, 129.8, 129.0, 128.8, 127.2, 126.8, 66.2, 59.3, 55.7, 53.0, 21.5. HRMS (MALDI-FTMS): calc. for $C_{19}H_{20}N_2O_5Cl_2S$: *m/z* 481.0362 (MNa^+), found 505.0736.

6. Isolated as a white solid, mp 200–202 °C. IR: 1735, 1339 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.64–7.71 (m, 2H), 7.44–7.53 (d, J = 8.0 Hz, 1H), 7.31–7.38 (m, 3H), 7.27–7.31 (m, 2H), 7.22–7.25 (m, 2H), 5.92 (s, 1H), 5.18–5.30 (m, 2H), 4.26–4.36 (dd, J = 9.0, 5.5 Hz, 1H), 3.86–3.96 (q, J = 7.0 Hz, 2H), 2.41 (s, 3H), 0.60–1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 163.6, 144.1, 136.3, 135.5, 129.8, 129.0, 128.8, 127.2, 126.9, 66.2, 62.6, 59.3, 55.8, 21.5, 13.7.

7. Isolated as a white solid, mp 176–178 °C. IR: 1738, 1341 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62–7.68 (m, 2H), 7.40–7.46 (d, J = 9.0 Hz, 1H), 7.24–7.38 (m, 6H), 7.20–7.24 (m, 2H), 7.12–7.18 (m, 2H), 7.08–7.12 (m, 2H), 5.88 (s, 1H), 5.28–5.32 (d, J = 9.0 Hz, 1H), 5.22–5.28 (dd, J = 9.0, 5.5 Hz, 1H), 4.86 (m, 2H), 4.32–4.40 (dd, J = 9.0, 6.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 163.6, 144.0, 136.3, 135.3, 133.9, 129.8, 129.0, 128.9, 128.8, 128.7, 128.6, 127.1, 126.9, 68.3, 66.1, 59.2, 55.8, 21.6.

8. Isolated as a white solid, mp 133–135 °C. IR: 1750, 1364 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.80–7.86 (m, 2H), 7.36–7.42 (m, 2H), 7.05 (s, 1H), 4.33 (s, 1H), 3.68 (s, 3H), 2.46 (s, 3H), 1.26 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 153.4, 145.7, 134.3, 130.1, 127.8, 71.0, 69.5, 61.4, 52.3, 29.3, 23.1, 21.7. HRMS (MALDI-FTMS): calc. for $C_{15}H_{20}N_2O_5Cl_2S$: 433.0362 (MNa^+), found 433.0361.

Acknowledgements

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