CHAPTER 4

Asymmetric Synthesis of Rasagiline and NHC-catalyzed Esterification of Aromatic Aldehydes
Section I:
Enantioselective Synthesis of Rasagiline an anti-Parkinson Drug

4.1.1 Introduction and Pharmacology

Neurodegenerative diseases are the third cause of death among aged population all over the world. Parkinson's disease (PD) named after the English doctor James Parkinson is the most common neurodegenerative disorder and manifests as rigidity, resting tremor and posture instability. PD is a degenerative disorder of the central nervous system, resulting from the death of cells that use dopamine to transmit their signals, resulting in decreased synaptic signal strength and concomitant symptomology. It is generally characterized by insufficient formation and activity of dopamine produced within substantia nigra, a region of the midbrain. Modern treatments are effective at managing the early stages of the disease, mainly through the use of dopamine agonists. As the disease progresses and dopaminergic neurons continue to be lost, these drugs eventually become ineffective at treating the symptoms and at the same time produce a complication called dyskinesia, marked by involuntary writhing movements.

![Rasagiline (1)](image)

**Fig. 1:** Structure of anti-Parkinson drug, rasagiline (1)

The existing therapies are still well-below the expectations for the advanced stages of the disease. Therefore, there is a need for novel therapeutic drug to ameliorate the
pathophysiological process of the disease. It is well-established that human cells contain two forms of monoamine oxidase (MAO) type A and type B. In the brain, MAO type B is far more prevalent and is responsible for the breakdown of dopamine after its release into the synapse. Since PD is generally regarded as a dopamine deficiency-disorder, there is a need for drugs, which can correct dopamine deficiency. In this regard, rasagiline (1) (Fig. 1) (Azilect®, Teva Pharmaceutical Industries Ltd., Israel), an irreversible MAO B inhibitor, was approved first in Israel (January 2005), followed by European agency (February 2005) and by US federal drug administration (May 2006) for the treatment of idiopathic PD as monotherapy or as adjunct therapy with L-dopa in advanced cases. Rasagiline (1) presents a very significant and selective activity concerning monoamine oxidase B inhibition. It is selective for MAO B over MAO A by a factor of fourteen. By inhibiting the breakdown of dopamine in the synapse, rasagiline (1) permits the signaling neurons to re-absorb more of dopamine. Structure activity studies show that its neuroprotective efficacy is strongly related to the propargylamino group. Very recently studies have revealed that rasagiline salts decrease human melanoma tumor growth in vivo, proving its potential as multi-target drug candidature for melanoma and PD.

4.1.2 Review of Literature

Literature search revealed that there are only few reports available on the synthesis of rasagiline (1) and its analogs. A short description on the reported synthesis of rasagiline (1) is presented below.

Moussa’s approach (1991)

Moussa et al. have reported the synthesis of rasagiline (1) by using high-performance liquid chromatography for the separation of racemic mixture as the key technique.
Thus, indanone 2 was treated with hydroxyl amine under basic condition to provide 1-indanone oxime 3. Hydrogenation of oxime 3 using Raney Ni afforded racemic mixture of primary amine (±)-4 in 87% yield. Propargylation of amine (±)-4 gave racemic mixture of rasagiline (±)-5, from which (+)-rasagiline (1) was isolated by resolving the racemic mixture on a Chiracel OJ (cellulose tris[p-methylbenzoate]) preparative HPLC column (Scheme 1).

![Chemical structure](image)

Scheme 1: (i) NH$_2$OH.HCl, H$_2$O, 50% aq. NaOH, C$_2$H$_5$OH, reflux, 15 min, 98%; (ii) Raney Ni, H$_2$ (80 psi), 16% aq. NH$_3$, CH$_3$OH, 25 °C, 25 h, 87%; (iii) K$_2$CO$_3$, propargyl chloride, CH$_3$CN, 60 °C, 16 h, 56%; (iv) Chiral HPLC separation.

**Davies’ approach (2006)**¹³

Davies et al. have achieved the synthesis of (+)-rasagiline (1) using catalytic enantio-selective C-H amination as the key step. Thus, sulfonamide 8 was obtained via enantioselective amination of indane 6 in trifluorotoluene with newly developed catalyst i.e. Rh$_2$(S-TCPATAD)$_4$ (7) (2 mol%), PhI(OAc)$_2$, MgO and NsNH$_2$ as amine source in 95% yield and 94% ee. Alkylation of sulfonamide 8 with propargyl bromide forming nosyl protected rasagiline 9, followed by the removal of nosyl group under Fukuyama’s protocol, afforded rasagiline (1) (Scheme 2).
**Scheme 2:** (i) Rh₂(S-TCPTAD)₄ (7), PhI(OAc)₂, trifluorotoluene, NsNH₂, MgO, 23 °C, 3 h, 95%; (ii) propargyl bromide, K₂CO₃, CH₃CN, 60 °C, 16 h, 75%; (iii) HSCH₂CH₂OH, DBU, DMF, 25 °C, 1 h, 64%.

**Boulton’s approach (2009)**

Boulton et al. have developed a useful synthetic method for the synthesis of (+)-rasagiline (1) using chiral ketone reduction as the key step.

**Scheme 3:** (i) RuCl(p-cymene)((S,S)-Ts-DPEN)(10), HCOOH, Et₃N, CH₂Cl₂, 30 °C, 21 h, 96%; (ii) (CH₃SO₂)O, Et₃N, CH₂Cl₂, -20 °C, 45 min; (iii) propargyl amine, CH₂Cl₂, 25 °C, 12 h, 68% (over two steps).
Thus, chiral reduction of 1-indanone 2 in the presence of an optically active Ru-catalyst \(\text{RuCl}(p\text{-cymene})[(S,S)-\text{Ts-DPEN}]\) gave the corresponding \((S)\)-indanol 11 in 96% yield with 98% ee. Mesylation of the hydroxyl moiety of indanol 11 provided mesylate 12, which on subsequent benzylic SN\(_2\) substitution with propargyl amine afforded rasagiline (1) (Scheme 3).

**Praveen’s approach (2010)**\(^{15}\)

Praveen *et al.* have reported the synthesis of rasagiline (1) by employing classical resolution, for the separation of racemic mixture as the key step. Indanone 2 was thus condensed with propargyl amine to afford indanylimine 13. Reduction of imine 13 with NaBH\(_4\) afforded racemic mixture of rasagiline (\(\pm\))-5, from which (+)-rasagiline (1) was isolated by resolving the racemic mixture in the presence of tartaric acid as the chiral resolving agent (Scheme 4).

**Tatendra’s approach (2011)**\(^{16}\)

Tatendra *et al.* have developed a useful synthetic method for the synthesis of rasagiline (1) commencing from chiral starting material. Reaction of \((S)\)-indanol 11 with \(p\)-TsCl (14) in presence of triethylbenzylammonium chloride (TEBA) as PTC
and NaOH afforded tosylate 15, in 92% yield, which on treatment with propargyl amine in presence of TEBA under reflux conditions gave rasagiline (1) (Scheme 5).

![Scheme 5](image)

**Scheme 5**: (i) TEBA, NaOH, H₂O, toluene, 25 °C, 2 h, 92%; (ii) propargyl amine, toluene, TEBAC, iPrOH, H₂O, reflux, 20 h, 79%.

### 4.1.3 Present work

#### 4.1.3.1 Objective

From the above discussion, it is evident that only few reports are available for the synthesis of rasagiline (1). However, some of the reported methods suffer from certain drawbacks such as use of chiral starting materials, chiral resolving agents, expensive separation methods, exotic reagents, etc. Significant commercial interest in the synthesis of rasagiline (1) is evident from the large number of patents filed for its synthesis. In this context, a more practical method that introduces chirality into the molecule using organocatalyst is highly desirable. This section describes an elegant synthetic route to the synthesis of rasagiline (1) using proline-catalyzed Mannich reaction of acetaldehyde as the key step.

Retro-synthetic analysis of rasagiline (1) reveals that amine 20 could be visualized as the key intermediate. The amino derivative 20 could be obtained by means of the Wolff-Kishner reduction of indanone 19, which could in turn be obtained by performing Friedel-Crafts acylation of the β-amino acid 18. The required β-amino acid 18 could be readily prepared from imine 16 (Fig. 2).
Fig. 2: Retrosynthetic analysis of rasagiline (1)

4.1.4 Results and Discussion

The complete synthetic sequence for rasagiline (1) is shown in Scheme 6, wherein proline-catalyzed Mannich reaction of acetaldehyde constitutes a key step for the introduction of chirality in the molecule.

Scheme 6: (i) CH₃CHO, D-proline (20 mol%), CH₃CN, 0 °C, 3 h, 62%; (ii) NaClO₂, NaH₂PO₄, tert-BuOH:H₂O (5:1), 25 °C, 30 min, 93%; (iii) CISO₃H, CH₂Cl₂, 25 °C, 2 h, then (Boc)₂O, Et₃N, cat. DMAP, CH₂Cl₂, 25 °C, 3 h, 83%; (iv) NH₂NH₂:H₂O, KOH, diethylene glycol, reflux, 4 h, 88%; (v) NaH, propargyl bromide, DMF, 25 °C, 4 h, 81%; (vi) 37% aq. HCl, dioxane, 25 °C, 30 min, 97%.
The present synthesis of rasagiline (1) started from Boc-protected benzaldimine 16, which on Mannich reaction with acetaldehyde (D-proline, CH$_3$CN, 0 °C)\textsuperscript{18} afforded β-aminoaldehyde 17 in 62% yield and 98% ee. The formation of β-aminoaldehyde 17 was confirmed from its $^1$H NMR spectrum, which showed typical proton signals at δ 9.73 (t, $J = 1.7$ Hz, 1H) and δ 2.83-2.96 (m, 2H) corresponding to aldehydic and homo benzylidyne methylene protons respectively. This was further ascertained by the presence of two characteristic carbon signals at δ 199.8 and 193.3 in its $^{13}$C NMR spectrum corresponding to carbamate and aldehydic carbonyl carbons respectively (Fig. 3).

Fig. 3: $^1$H and $^{13}$C NMR spectra of β-aminoaldehyde 17
The Pinnick oxidation of β-aminoaldehyde 17 with NaClO₂ and NaH₂PO₄ gave the corresponding β-aminocarboxylic acid 18 in 93% yield.¹⁹ The formation of carboxylic acid 18 was confirmed from its ¹H NMR spectrum, which showed two characteristic proton signals at δ 2.67 (br s, 1H) and 2.86 (br s, 1H) corresponding to homo benzylic methylene protons, while its ¹³C NMR spectrum showed a typical carbon signal at δ 170.1 due to the presence of carboxylic acid carbonyl carbon (Fig. 4). Its IR spectrum displayed a characteristic strong absorption band at 1707 cm⁻¹ indicating the presence of carboxylic acid group.

**Fig. 4:** ¹H and ¹³C NMR spectra of carboxylic acid 18
The indanone 19 was obtained by the Friedel-Crafts’ intramolecular acylation\(^ {20} \) of \( \beta \)-amino acid 18 on reaction with ClSO\(_3\)H, followed by the protection of primary amine \([\text{Boc}]_2\text{O}, \text{Et}_3\text{N}, \text{cat. DMAP}]\). Indanone 19 was confirmed from its \(^1\text{H}\) NMR spectrum, which showed two characteristic doublet of doublets at \( \delta \) 2.45 (dd, \( J = 3.2, 19.2 \) Hz, 1H) and 3.16 (dd, \( J = 7.6, 19.2 \) Hz, 1H), corresponding to the diastereotopic methylene protons, while its \(^{13}\text{C}\) NMR spectrum showed a characteristic carbon signal at \( \delta \) 202.9 due to ketone carbonyl carbon (Fig. 5).

![Fig. 5: \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra of indanone 19]
The formation of indanone 19 was also confirmed from its IR spectrum, which displayed a strong absorption band at 1712 cm\(^{-1}\) indicating the presence of ketone functional group. The optical purity of 19 was determined to be 98% ee from chiral HPLC analysis (Chiralcel AD-H, n-hexane/iPrOH, 90:10, 0.5 mL/min) retention time 14.36 (99.08%) and 19.88 (0.92%) (Fig. 6).

![IR spectrum and HPLC chromatogram of indanone 19](image)

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**Fig. 6:** IR spectrum and HPLC chromatogram of indanone 19
Wolff-Kishner reduction of indanone 19 with NH₂NH₂·H₂O and KOH afforded carbamate 20 in 88% yield.²¹ The formation of carbamate 20 was established from its ¹H NMR spectrum, which showed two characteristic proton signals at δ 2.74-3.03 (m, 2H) and 5.17 (d, J = 7.7 Hz, 1H) due to benzylic protons, while its ¹³C NMR spectrum displayed the disappearance of carbon signal at δ 202.9 corresponding to the ketone carbonyl carbon, confirming the reduction of ketone group (Fig. 7).

![Carbamate 20](image)

**Fig. 7:** ¹H and ¹³C NMR spectra of carbamate 20
Alkylation of carbamate 20 was achieved with propargyl bromide under basic conditions to afford the protected rasagiline 21 in 81% yield. The formation of protected rasagiline 21 was confirmed from its $^1$H NMR spectrum, which showed three typical proton signals at δ 2.96-3.10 (m, 1H), 3.32-3.63 (m, 1H) and 3.82-4.16 (m, 1H) corresponding to terminal alkyne and diastereotopic methylene protons attached to alkyne respectively. Its $^{13}$C NMR spectrum showed two characteristic carbon signals at δ 61.1 and 69.6 corresponding to alkyne carbons (Fig. 8).

Fig. 8: $^1$H and $^{13}$C NMR spectra of protected rasagiline 21
Finally, deprotection of the Boc protecting group with 37% aq. HCl in dioxane furnished rasagiline (1) in 97% yield and 98% ee, \([\alpha]^{D}_{25} +19.4 \ (c \ 0.5, \ CHCl_3)\) [lit.\(^{13}\) \([\alpha]^{D}_{25} +18.8 \ (c \ 1.7, \ CHCl_3)\)]. The \(^1\)H NMR spectrum of rasagiline (1) showed two typical proton signals at \(\delta 2.23 \ (t, \ J = 2.4 \ Hz, \ 1H)\) and 3.52 (t, \(J = 2.4 \ Hz, \ 2H)\) corresponding to benzylic methine and diastereotopic methylene protons attached to alkyne respectively.

![Fig. 9: \(^1\)H and \(^{13}\)C NMR spectra of rasagiline (1)](image)
Its $^{13}$C NMR spectrum showed characteristic carbon signals at $\delta$ 61.8, 71.5 and 82.4 corresponding to benzylic methine and alkyne carbons respectively (Fig. 9). The spectral data of rasagiline (1) were in complete agreement with the reported values.$^{22}$

**4.1.5 Conclusion**

In conclusion, we have achieved the asymmetric synthesis of rasagiline (1) (33% overall yield, 98% ee) using proline-catalyzed Mannich reaction, Friedel-Crafts acylation and Wolff–Kishner reduction as the key steps. The utilization of organocatalyst for introduction of chirality into the molecule and the high enantiomeric excess obtained in this method render our approach a good alternative to the known methods.

**4.1.6 Experimental Section**

(R)-tert-Butyl (3-oxo-1-phenylpropyl)carbamate (17)

To a stirred solution of benzaldehyde-derived N-Boc-imine 16 (2.870 g, 14 mmol) and redistilled acetaldehyde (3.9 mL, 70 mmol) in CH$_3$CN (150 mL) at 0 °C was added D-proline (0.320 g, 20 mol%) and the mixture was stirred further at 0 °C for 3 h. After the completion of reaction (monitored by TLC), it was quenched with water and extracted with Et$_2$O (3 x 100 mL). The combined organic layers were washed with brine, dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give the crude aldehyde, which was purified by column chromatography over silica gel using pet. ether:EtOAc (85:15) as eluent, to afford $\beta$-amino aldehyde 17 (2.16 g).

**Yield:** 62%; yellow solid; **mp:** 90-93 °C, (lit.$^{23}$ mp: 92-93.5 °C); [$\alpha$]$^D_{25}$ +29.6 (c 1.7, CHCl$_3$); lit.$^{23}$ [$\alpha$]$^D_{25}$ +29.0 (c 1.4, CHCl$_3$); **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 720, 1024, 1052,
1258, 1371, 1394, 1479, 1513, 1692, 2979, 3346; \textbf{\textsuperscript{1}H NMR} (200 MHz, CDCl\textsubscript{3}): \(\delta\) 1.41 (s, 9H), 2.83-2.96 (m, 2H), 4.87 (br s, 1H), 5.17 (br s, 1H), 7.26-7.34 (m, 5H), 9.73 (t, \(J = 1.7 \text{ Hz}, \) 1H); \textbf{\textsuperscript{13}C NMR} (50 MHz, CDCl\textsubscript{3}): \(\delta\) 28.3, 39.9, 49.9, 79.9, 126.3, 127.7, 128.8, 135.2, 155.0, 193.3, 199.8; \textbf{Analysis:} \(C_{14}H_{19}NO_{3}\) requires C, 67.45; H, 7.68; N, 5.62; found: C, 67.26; H, 7.53; N, 5.49%.

\(\textit{R}\)-3-((\textit{tert}-Butoxycarbonyl)amino)-3-phenylpropanoic acid (18)

NaH\textsubscript{2}PO\textsubscript{4} (3.37 g, 24.4 mmol) and NaClO\textsubscript{2} (1.502 g, 24.4 mmol) were added to a solution of \(\beta\)-amino aldehyde 17 (2.02 g, 8.14 mmol) in \textit{tert}-BuOH:H\textsubscript{2}O (45:9 mL) at 25 °C and the mixture allowed to stir for 30 min. After TLC showed the complete disappearance of starting material, it was diluted with EtOAc (100 mL) and dried over anhyd. Na\textsubscript{2}SO\textsubscript{4} and concentrated to give the crude acid, which was purified by column chromatography over silica gel using pet. ether:EtOAc (60:40) as eluent, to afford carboxylic acid 18 (2.01 g).

\textbf{Yield:} 93%; colorless solid; \textbf{mp:} 126-129 °C; \([\alpha]^{D}_{25}\) +40.1 (c 1.2, CHCl\textsubscript{3}); \textbf{IR} (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \(\nu_{\text{max}}\) 758, 1029, 1046, 1215, 1420, 1507, 1707, 2400, 2980, 3019; \textbf{\textsuperscript{1}H NMR} (200 MHz, CDCl\textsubscript{3}): \(\delta\) 1.40 (s, 9H), 2.67 (br s, 1H), 2.86 (br s, 1H), 4.85 (br s, 1H), 5.09 (br s, 1H), 7.27-7.36 (m, 5H); \textbf{\textsuperscript{13}C NMR} (50 MHz, CDCl\textsubscript{3}): \(\delta\) 28.2, 40.6, 53.7, 80.1, 126.2, 127.4, 128.5, 145.9, 154.8, 170.1; \textbf{Analysis:} \(C_{14}H_{19}NO_{4}\) requires C, 63.38; H, 7.22; N, 5.28; found: C, 63.16; H, 7.11; N, 5.21%.

\(\textit{R}\)-\textit{tert}-Butyl (3-oxo-2,3-dihydro-1H-indenyl)carbamate (19)

To a solution of carboxylic acid 18 (2 g, 7.5 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (40 mL) was added ClSO\textsubscript{3}H (2.5 mL, 37.5 mmol). The reaction mixture was stirred at 25 °C for 2 h, and quenched with saturated solution of NaHCO\textsubscript{3}, extracted with Et\textsubscript{2}O (3 × 50 mL). The combined organic phases were dried over anhyd. Na\textsubscript{2}SO\textsubscript{4} and concentrated under
reduced pressure to afford the crude product, which was directly used for the next step without purification.

To a stirred solution of crude amine in CH$_2$Cl$_2$ (40 mL) and Et$_3$N (3.2 mL, 22.5 mmol) was added catalytic amount of DMAP (0.091 g, 0.75 mmol). After stirring for 5 min at 0 ºC, (Boc)$_2$O (3.27 g, 15.0 mmol) was added drop-wise and the reaction mixture was allowed to stir for another 3 h. After the completion of the reaction, it was extracted with Et$_2$O (3 × 50 mL), washed with water, brine and dried over anhyd. Na$_2$SO$_4$ and concentrated to give the crude ketone, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (85:15) to furnish indanone 19 (1.54 g).

**Yield:** 83%; colorless solid; **mp:** 104-106 ºC; [α]$^D_{25}$ -14.6 (c 0.8, CHCl$_3$); 98% ee from chiral HPLC analysis (Chiralcel AD-H, n-hexane/ iPrOH, 90:10, 0.5 mL/min) retention time 14.36 (99.08%) and 19.88 (0.92%); **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 751, 1045, 1163, 1276, 1393, 1500, 1604, 1712, 2400, 2933, 2981, 2981, 3019, 3440; **$^1$H NMR** (200 MHz, CDCl$_3$): $\delta$ 1.46 (s, 9H), 2.45 (dd, $J$ = 3.2, 19.2 Hz, 1H), 3.16 (dd, $J$ = 7.6, 19.2 Hz, 1H), 5.00 (d, $J$ = 8.4 Hz, 1H), 5.34 (br s, 1H), 7.41-7.48 (m, 1H), 7.63 (d, $J$ = 3.8 Hz, 2H), 7.70 (d, $J$ = 7.6 Hz, 1H); **$^{13}$C NMR** (50 MHz, CDCl$_3$): $\delta$ 28.4, 44.9, 48.7, 79.8, 123.2, 125.9, 128.9, 135.1, 136.6, 154.3, 155.6, 202.9; **Analysis:** C$_{14}$H$_{17}$NO$_3$ requires C, 68.00; H, 6.93; N, 5.66; found: C, 67.94; H, 6.73; N, 5.46%.

**(R)-tert-Butyl (2,3-dihydro-1H-indenyl)carbamate (20)**

To a stirred solution of indanone 19 (1.632 g, 6.6 mmol) and NH$_2$NH$_2$.H$_2$O (1.668 g, 33 mmol) in diethylene glycol (40 mL) was added KOH pellets (1.847 g, 33 mmol). The resulting solution was refluxed for 4 h. After TLC showed the complete disappearance of starting material, the reaction mixture was diluted with H$_2$O, extracted with EtOAc (3 x 50 mL) and dried over anhyd. Na$_2$SO$_4$ and concentrated to
give the crude carbamate, which was purified by column chromatography over silica gel using pet. ether:EtOAc (85:15) as eluent, to afford carbamate 20 (1.355 g).

**Yield:** 88%; colorless gum; \([\alpha]^{D}_{25} +24.3 \) (c 1, CHCl\(_3\)); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 768, 849, 928, 1024, 1050, 1168, 1215, 1421, 1505, 1706, 2400, 2979, 3019; **\(^1\)H NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 1.48 (s, 9H), 1.68-1.87 (m, 1H), 2.49-2.65 (m, 1H), 2.74-3.03 (m, 2H), 4.70 (d, \(J = 7.3\) Hz, 1H), 5.17 (d, \(J = 7.7\) Hz, 1H), 7.15-7.20 (m, 3H), 7.27-7.32 (m, 1H); **\(^{13}\)C NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 28.4, 30.0, 34.3, 55.1, 79.1, 123.9, 124.6, 126.6, 127.7, 142.9, 143.5, 155.5; **Analysis:** C\(_{14}\)H\(_{19}\)NO\(_2\) requires C, 72.07; H, 8.21; N, 6.00; found: C, 72.01; H, 8.14; N, 5.87%.

\((R)-\text{tert-Butyl (2,3-dihydro-1H-indenyl)(prop-2-yn-1-yl)carbamate (21)}\)

To a stirred solution of carbamate 21 (0.500 g, 2.14 mmol) and NaH (0.098 g, 60% w/w, 2.35 mmol) in dry DMF (5 mL) was added propargyl bromide (80% solution in toluene, 286 µL, 2.57 mmol) at 25 °C and the mixture was stirred under nitrogen atmosphere for 4 h. The reaction was quenched with H\(_2\)O and the resulting mixture was extracted with EtOAc (3 x 10 mL), washed with saturated aq. NH\(_4\)Cl (5 mL) and brine solution (5 mL). The organic layers were separated, dried over anhyd. Na\(_2\)SO\(_4\), and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (95:05) as an eluent to give protected rasagiline 21 (0.470 g).

**Yield:** 81%; yellow oil; \([\alpha]^{D}_{25} -14.4 \) (c 0.7, CHCl\(_3\)); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 669, 716, 929, 1159, 1215, 1330, 1405, 1439, 1456, 1477, 1521, 1687, 2126, 2400, 2935, 2980, 3019, 3308; **\(^1\)H NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 1.50 (br s, 9H), 2.07 (br s, 1H), 2.22 (br s, 1H), 2.36-2.52 (m, 1H), 2.75-2.91 (m, 1H), 2.96-3.10 (m, 1H); 3.32-3.63 (m, 1H), 3.82-4.16 (m, 1H), 5.45-5.82 (m, 1H), 7.16-7.21 (m, 4H); **\(^{13}\)C NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 27.6, 28.3, 30.0, 30.1, 61.1, 69.6, 80.3, 123.9, 124.8, 126.5, 127.7, 141.7,
143.7, 155.2; **Analysis**: C_{17}H_{21}NO_{2} requires C, 75.25; H, 7.80; N, 5.26; found: C, 75.03; H, 7.56, N, 5.14%.

**(R)-Indanyl-prop-2-ynyl-amine [rasagiline] (1)**

To a solution of protected rasagiline 21 (0.300 g, 1.1 mmol) in dioxane (5 mL) was added 37% aq. HCl in H_{2}O (0.5 mL) and the mixture stirred for 30 min at 25 °C. The reaction mixture was quenched with sat. NaHCO_{3}. Dioxane was evaporated and the residue was extracted with EtOAc (3 × 10 mL) and the combined organic phases were dried over anhyd. Na_{2}SO_{4} and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (70:30) to give rasagiline 1 (0.182 g).

**Yield**: 97%; yellow solid; **mp**: 146-149 °C, (lit. 13 **mp**: 148 °C); [α]_{D}^{25}+19.4 (c 0.5, CHCl_{3}); lit. 13 [α]_{D}^{25}+18.8 (c 1.7, CHCl_{3}); **IR** (CHCl_{3}, cm^{-1}): \( \nu_{\max} \) 649, 1088, 1161, 1215, 1349, 1456, 2400, 2848, 2929, 3281; **\(^{1}\)H NMR** (400 MHz, CDCl_{3}): \( \delta \) 1.69 (br s, 1H), 1.84-1.92 (m, 1H), 2.23 (t, \( J = 2.4 \) Hz, 1H), 2.36-2.45 (m, 1H), 2.79-2.87 (m, 1H), 3.01-3.09 (m, 1H); 3.52 (t, \( J = 2.4 \) Hz, 2H), 4.42 (t, \( J = 6.2 \) Hz, 1H), 7.16-7.24 (m, 3H), 7.34 (d, \( J = 5.9 \) Hz, 1H); **\(^{13}\)C NMR** (100 MHz, CDCl_{3}): \( \delta \) 30.5, 33.3, 36.1, 61.8, 71.5, 82.4, 124.3, 124.9, 126.3, 127.7, 143.8, 144.4; **Analysis**: C_{12}H_{13}N requires C, 84.17; H, 7.65; N, 8.18; found: C, 84.13; H, 7.57; N, 8.12%.}

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Section II:
N-Heterocyclic Carbene-Catalyzed Esterification of Aromatic Aldehydes with Alcohols under Aerobic Condition

4.2.1 Introduction

The direct transformation of aldehydes to the corresponding esters with alcohols under mild conditions is often required in organic synthesis, especially in the synthesis of natural products. For example: Lee et al. have utilized intramolecular oxidative esterification of ω-hydroxy aldehyde 22 as the key step in their synthesis of cytotoxic (+)-dactylolide (24) (Fig. 10).  

![Chemical structures](image)

**Fig. 10**: Oxidative esterification of aldehyde in the synthesis of (+)-dactylolide (24)

Further esterification processes are widespread in the industrial synthesis of a variety of end-products such as fragrances, monomers, plasticizers, etc, many of which are
classified as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemicals targets are prominent, and often require more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. Aromatic esters are also important and useful structural elements finding tremendous applications in wide range of fields encompassing solvents, lubricants, plasticizing agents, perfumes, pharmaceuticals, agrochemicals, etc.\textsuperscript{26} The conventional methods for the synthesis of carboxylic esters from aldehydes involve oxidation of aldehydes to carboxylic acids followed by esterification with alcohols catalyzed by acids. In contrast, the direct method of conversion of aldehydes to carboxylic esters holds considerable promise in organic synthesis as it minimizes the number of steps.

**4.2.2 Review of Literature**

Literature search revealed that there are several methods available for the direct transformation of aldehydes into the corresponding esters. Direct transformation of aldehydes into esters has been achieved using a variety of reagents such as V\textsubscript{2}O\textsubscript{5}/H\textsubscript{2}O\textsubscript{2},\textsuperscript{27} oxone\textsuperscript{®},\textsuperscript{28} pyridinium hydrobromide perbromide,\textsuperscript{29} acetone cyano hydriins,\textsuperscript{30} (NaIO\textsubscript{4})/LiBr,\textsuperscript{31} I\textsubscript{2},\textsuperscript{32} TBHP,\textsuperscript{33} and electrochemical methods.\textsuperscript{34} Recently, N-Heterocyclic carbenes (NHCs)-catalyzed oxidative esterification of aldehydes with alcohols,\textsuperscript{35} alkyl halides\textsuperscript{36} and boronic acids\textsuperscript{37} has also been reported. Some of the recent developments on this transformation are discussed below.

**Gopinath’s approach (2000)\textsuperscript{27}**

In Gopinath’s approach, aldehydes \textsuperscript{25}, in the presence of methanol, undergo oxidative transformation to the corresponding esters \textsuperscript{26} upon treatment with catalytic amounts of V\textsubscript{2}O\textsubscript{5} in combination with 30\% aq. H\textsubscript{2}O\textsubscript{2} as oxidant (Scheme 7).
Esterification

Scheme 7: (i) V$_2$O$_5$ (cat.), 30% aq. H$_2$O$_2$, CH$_3$OH, 80 °C, 0.5-6 h, 83-100%.

**Traivs’ approach (2003)**

Travis et al. have developed a highly efficient, mild, and simple protocol for the oxidation of aldehydes 25 to the corresponding carboxylic acids utilizing oxone as the sole oxidant. Direct conversion of aldehydes 25 in alcoholic solvents to their corresponding ester products 26 has also been reported. These reactions may prove to be valuable alternatives to traditional metal-mediated oxidations, however, it uses more than stoichiometric amounts of oxone (Scheme 8).

Scheme 8: (i) Oxone, CH$_3$OH, 18 h, 25 °C, 9-98%.

**Onami’s approach (2004)**

In this approach, the direct esterification of aldehydes with alcohols was carried out with pyridinium hydrobromide perbromide (PHPB) in water at 25 °C. A variety of aldehydes 25 were converted to their corresponding esters 26. Further, a variety of...
aliphatic alcohols were also converted to the corresponding Tishchenko-like dimeric esters in good yields under the same reaction conditions (Scheme 9).

![Scheme 9: PHPB, CH₃OH, H₂O, 25 °C, 40-87 h, 70-94%.

Sudalai’s approach (2005), (2007)³⁰,³¹

Sudalai et al. have described a simple procedure for the conversion of electron-deficient aldehydes 25 into the corresponding esters 26 on reaction with methanol in excellent yields mediated by acetone cyanohydrin and base (Scheme 10).

![Scheme 10: (i) acetone cyanohydrin (5 mmol), Et₃N, CH₃OH, 25 °C, 2 h, 60-92%.

In yet another approach, these authors have converted aromatic aldehydes 25 directly to the corresponding aromatic esters 26 in high yields on treatment with CH₃OH using sodium metaperiodate (NaIO₄)/LiBr as oxidant under acidic medium (Scheme 11).
Scheme 11: (i) LiBr, NaIO₄, conc. H₂SO₄, CH₃OH, 25 °C, 18 h, 78-98%.

Budhewar’s approach (2006)³²

Budhewar et al. have developed a simple and mild procedure for the facile, direct oxidative methyl esterification of aldehydes 25 using molecular I₂ in combination with PhI(OAc)₂ in methanol (Scheme 12).

Scheme 12: (i) I₂, PhI(OAc)₂, CH₃OH, 25 °C, 10-14 h, 67-89%.

Li’s approach (2007)³³

Li et al. have developed an oxidative esterification reaction between aldehydes 25 and alcohols 27 catalyzed by a combination of Cu(ClO₄)₂·6H₂O and InBr₃ using TBHP as an oxidant (Scheme 13).

Scheme 13: (i) Cu(ClO₄)₂·6H₂O, InBr₃, TBHP, 100 °C, 16 h, 42-91%.
Connon’s approach (2008)$^{35e}$

Connon et al. have developed a novel method of direct esterification of aldehydes with methanol using thiazolium NHC (28) as a catalyst and azobenzene as an oxidant in THF. Aromatic aldehydes 25 were thus converted to their corresponding esters 26 in moderate to good yields (Scheme 14).

\[
\text{R} = \text{OCH}_3, \text{CH}_3, \text{Cl}, \text{H}, \text{etc.}
\]

**Scheme 14:** (i) NHC (28) (5 mol%), PhN=NPh, CH$_3$OH, THF, Et$_3$N, 25 to 60 °C, 24-48 h, 16-97%.

Scheidt’s approach (2008)$^{35f}$

Scheidt et al. have described NHC-catalyzed oxidation of unactivated aldehydes to the corresponding carboxylic esters. Thus the reaction of unactivated aldehydes 29 with alcohols 27 in the presence of triazolium NHC catalyst (30) and oxidant MnO$_2$ provided esters 31 in high yields (Scheme 15).

\[
\text{R} = \text{aryl, alkyl, heteroaryl} \quad \text{R}^1 = \text{CH}_3, \text{'Pr}, \text{etc.}
\]

**Scheme 15:** (i) NHC (30) (10 mol%), DBU, MnO$_2$, CH$_2$Cl$_2$, 25 °C, 0.5-3 h, 56-98%.
**Xin’s approach (2011)**<sup>36a</sup>

Xin et al. have developed an oxidative esterification reaction between aldehydes 25 and alkyl halides 33 catalyzed by imidazolium NHC (32) and molecular oxygen as an oxidant in THF at 50 °C that gave carboxylic esters in good yields (Scheme 16).

**Scheme 16:** (i) NHC (32) (10 mol%), DBU, O<sub>2</sub>, THF, 50 °C, 24-72 h, 25-90%.

**Arde’s approach (2011)**<sup>37a</sup>

Arde et al. have developed an useful method of imidazolidine NHC (35) catalyzed aerobic oxidation of aromatic aldehydes 25 with boronic acids 34. Aromatic aldehydes 25 were thus converted into their corresponding esters 26 in good yields (Scheme 17).

**Scheme 17:** (i) NHC (35) (10 mol%), Cs<sub>2</sub>CO<sub>3</sub>, O<sub>2</sub>, toluene, 25 °C, 3-48 h, 25-99%.
Boydston’s approach (2012)$^{34}$

This methodology involves thiazolium NHC (36) catalyzed anodic oxidation of aldehydes 25 to the corresponding carboxylic esters 26 on reaction with alcohols 27 (Scheme 18). The electrochemical approach assumes the formation of electroactive intermediates that react with alcohol to provide esters.

\[
\begin{align*}
\text{R} = \text{CH}_3, \text{CN}, \\
\text{Br, etc.} & \quad \text{R}^1 = \text{Bn,}^{3} \text{Pr, etc.}
\end{align*}
\]

**Scheme 18:** (i) NHC (36) (10 mol%), DBU, TBAB, CH$_3$CN, graphite anode, Pt cathode, +0.1 V vs. Ag/AgNO$_3$, 2-56 h, 45-98%.

Delany’s approach (2013)$^{35j}$

This methodology employs an additive-free mild protocol for triazolium NHC (37)-catalyzed direct esterification of aldehydes 25 with CH$_3$OH using O$_2$ as oxidant. No other stoichiometric oxidants or catalysts for O$_2$ activation were required (Scheme 19).

\[
\begin{align*}
\text{R} = \text{OCH}_3, \text{CH}_3, \\
\text{Cl, H, etc.} & \quad \text{R}^1 = \text{Meso-N-S}_{\text{BF}_4}
\end{align*}
\]

**Scheme 19:** (i) NHC (37) (15 mol%), DBU, THF:CH$_3$OH (1:1), O$_2$, 25 °C, 12-92 h, 15-94%.
4.2.3 Present Work

4.2.3.1 Objective

Although several reports for transformation of aldehydes to the corresponding esters in the presence of alcohols has been reported, there are certain drawbacks associated with them such as (i) heavy metals (Pd, Mn, Fe, etc) as oxidants; (ii) harsh reaction conditions; (iii) excess use of bases and alcohols/halides; (iv) use of more than stoichiometric amounts of oxidants and (v) effective for a limited range of substrates. In this regard, an organocatalytic additive-free mild protocol for oxidative esterification of aldehydes is highly desirable. This section describes NHC-catalyzed direct esterification of aromatic aldehydes with a variety of alcohols under aerobic condition using catalytic amount of DBU. On a similar line Delany et al. have reported,\(^{35}\) entitled “NHC-catalysed aerobic aldehyde esterifications with alcohols: no additives or cocatalysts required” (see Scheme 19) using triazolium NHC (37) as a new catalyst several months after our publication. Since the method involves NHC as catalyst, a brief account of NHC catalyst is described below.

4.2.3.2 N-Heterocyclic Carbene Catalysis

Proline, a naturally available amino acid, has been studied extensively as organocatalyst for reactions occurring through enamine as well as iminium ion as intermediates.\(^{38}\) In the last two decades, N-heterocyclic carbenes (NHC) have emerged as an important and powerful class of organocatalysts with tremendous applications in a variety of synthetic transformations and are receiving much attention as proline, because of their unique electronic properties. Fig. 11 shows the presence of a carbene moiety stabilized by two adjacent \(\pi\)-donating atoms in NHC. The unsaturation in the backbone makes this an aromatic system, so that the carbene \(\pi\)-orbital is available to act as a \(\pi\)-acid. The ability of NHCs to act as both electron
Esterification

donors and acceptors permits them to serve as organocatalysts in a variety of coupling
reactions.\textsuperscript{39}

\begin{center}
\textbf{Fig. 11}: Stabilization of $N$-heterocyclic carbenes
\end{center}

NHC can provide catalytic access to acyl anion equivalents, an umpolung strategy in
which organic molecules react in an inverse manner compared to their innate polarity-
driven reactivity.\textsuperscript{40}

\begin{center}
\textbf{Fig. 12}: Intermediates in NHC-organocatalysis
\end{center}
The majority of organocatalyzed transformations that are proceeding through umpolung are mediated by NHC. They have a number of modes of activation for a given substrate, like (i) acyl anion, (ii) hydroacylation, (iii) homoenoate, and (iv) rebound catalysis, in which it forms four important intermediates namely (i) Breslow intermediate, (ii) enolate, (iii) homoenoate and (iv) acylazolium and α,β-unsaturated acylazolium (Fig. 12). The most prominent intermediate in NHC catalysis is Breslow intermediate. It is assumed that the azolium precatalyst is deprotonated in the reaction mixture to afford a nucleophilic carbene. Addition to an aldehyde followed by proton transfers affords an enamine type intermediate, referred to as the Breslow intermediate, in which the originally electrophilic carbon atom of the aldehyde has gained nucleophilic character. It can then attack a second molecule of aldehyde to furnish the benzoin product or a Michael acceptor to afford a Stetter product.

Breslow intermediates also occur in biosynthesis; for example, 2-oxoacid dehydrogenases such as pyruvate dehydrogenase, use thiamine pyrophosphate (TPP) as a carbene cofactor (Fig. 13). Decarboxylation is achieved by the reaction of carbene with pyruvate to give, that after CO₂ elimination provides Breslow intermediate. Under aerobic conditions, enaminol opens the dithiolane ring of a lipoyl group in a nucleophilic reaction to give an acetyl lipoamide thioester, which on transacylation with coenzyme A (CoASH) using enzymes eventually provides acetyl coenzyme A (CoASAc). Importantly, most published NHC-catalyzed processes mimic the reactivity of the naturally-occurring enaminol of 2-oxoacid dehydrogenases and react via umpoled aldehydes. For anaerobic condition nature has developed an alternative reaction pathway for formation of CoASAc. Pyruvate ferredoxin oxidoreductase (PFOR), catalyses the decarboxylation of pyruvate to form
CoASAc via Breslow intermediate 42, which reacts as a single electron-transfer reductant and the two electrons obtained during the turnover are transferred to ferredoxine. Electron transfer from the electron-rich enaminol 42 to a \([Fe_4S_4]^{2+}\) cluster leads to radical cation 43. Renewed electron transfer in the presence of CoASH eventually provides CoASAc.

**Fig. 13**: TPP-mediated enzymatic transformation of pyruvate to CoASAc
4.2.4 Results and Discussion

The fact that Breslow intermediates can behave as single electron transfer reagents inspired us to develop catalytic processes for oxidative esterification of aldehydes, that proceeds via oxidation of enaminol intermediates. The major challenge in the oxidation of aldehydes using NHC is the identification of mild oxidant, with the following characteristics (i) it is compatible with the carbene catalyst; (ii) avoids the formation of carboxylic acid by-products and (iii) shows high functional group compatibility. We envisaged that molecular O₂ should be an ideal oxidant for this purpose based on its nature of reactivity, low cost, and environment-friendly characteristics. Fig. 14 shows some of the NHC precatalysts that were examined for the oxidative esterification of aldehydes using molecular O₂ as oxidant.

![NHC precatalysts](attachment:image.png)

**Fig. 14:** N-Heterocyclic carbene precatalysts screened for the oxidative esterification of aromatic aldehydes

In a preliminary study, when 4-nitrobenzaldehyde 50f was subjected to oxidative esterification with MeOH (1 equiv) in the presence of NHC 44 (10 mol%) and DBU (20 mol%) as base in THF under N₂ atmosphere at 25 °C, no trace of ester 51f was
formed. When the same experiment was conducted in open air, **51f** was indeed isolated in low yields (45%). However, a dramatic increase in yield (70%) was realized when the experiment was carried out under O₂ atmosphere (O₂ balloon, 1 atm). Out of several NHC catalysts screened, imidazolium salt **44** showed higher catalytic activity, providing the desired product **51f** in 70% yield.

**Table 1**: Oxidative esterification of 4-nitrobenzaldehyde: optimization studies

<table>
<thead>
<tr>
<th>entry</th>
<th>NHC catalysts (10 mol%)</th>
<th>base (20 mol%)</th>
<th>solvent</th>
<th>yield of <strong>51f</strong> (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No catalyst</td>
<td>DBU</td>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>DBU</td>
<td>THF</td>
<td>76 (45)c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBU</td>
<td>CH₂Cl₂</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBU</td>
<td>CH₃CN</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBU</td>
<td>DMSO</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBU</td>
<td>toluene</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Et₃N</td>
<td>THF</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nBuLi</td>
<td>THF</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KtOBu</td>
<td>THF</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>DBU</td>
<td>THF</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>DBU</td>
<td>THF</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>DBU</td>
<td>THF</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>1e</td>
<td>DBU</td>
<td>THF</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>1f</td>
<td>DBU</td>
<td>THF</td>
<td>26</td>
</tr>
</tbody>
</table>

a Reaction conditions: 4-nitrobenzaldehyde (5 mmol), methanol (6 mmol), NHC catalyst (10 mol%), base (20 mol%), 25 °C, O₂ (1 atm), 4h. b Isolated yield after column chromatographic purification. c under open air.
When NHC catalyst loading was increased from 10 mol% up to 20 mol%, there was neither improvement in the yield of ester formed nor reduction in the time required for completion of the reaction. Additionally, increasing the temperature from 25 °C to 50 °C had deleterious effect in the yield, which may be due to the formation of unwanted acid by-product. Surprisingly, increasing the amount of alcohol from 1 equiv to 1.2 equiv resulted in improved yield (76%) of the ester formed. However, a further systematic increase in the amount of alcohol (from 1.2 up to 3 equiv) had no effect on yield improvement. Among several solvents and bases screened for the reaction, THF and DBU were found to be the effective solvent and base (Table 1).

With the optimized conditions (aldehyde (1 equiv), MeOH (1.2 equiv), NHC 44 (10 mol%), DBU (20 mol%), O₂, and THF at 25 °C) in hand, we then turned our attention to a variety of aromatic aldehydes 50a-p as substrates having both electron-donating and -withdrawing groups in order to gauge the scope and generality of the reaction. The results of such studies are presented in Table 2. As can be seen, several aromatic aldehydes underwent oxidative esterification with methanol smoothly under mild conditions in moderate to good yields. Remarkably, substrates with electron-withdrawing groups showed higher reactivity as compared to electron-releasing substituents. Heteroaromatic aldehydes such as 3-pyridine carboxaldehyde 50o also gave the corresponding ester in 76% yield, which are otherwise difficult to obtain under acid-catalysed esterifications due to salt formation of aldehyde 50o. It is noteworthy that, 4-(methylthio)benzaldehyde 50e, was not over-oxidized under our reaction condition. In the case of cinnamaldehyde, an inseparable mixture of saturated and unsaturated methyl esters were obtained, while aliphatic aldehydes failed to undergo this reaction, which may be a limitation.
Table 2: Oxidative esterification of aryl aldehydes: substrate scope

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates, Ar ((50a-p))</th>
<th>time (h)</th>
<th>yield of (51a-p) (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>(m)-tolualdehyde</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>b</td>
<td>4-OMe-benzaldehyde</td>
<td>30</td>
<td>72</td>
</tr>
<tr>
<td>c</td>
<td>3,4-(OMe)(_2)-benzaldehyde</td>
<td>36</td>
<td>70</td>
</tr>
<tr>
<td>d</td>
<td>3,4,5-(OMe)(_3)-benzaldehyde</td>
<td>36</td>
<td>65</td>
</tr>
<tr>
<td>e</td>
<td>4-SMe-benzaldehyde</td>
<td>28</td>
<td>68</td>
</tr>
<tr>
<td>f</td>
<td>4-NO(_2)-benzaldehyde</td>
<td>4</td>
<td>76</td>
</tr>
<tr>
<td>g</td>
<td>3- NO(_2)-benzaldehyde</td>
<td>10</td>
<td>82</td>
</tr>
<tr>
<td>h</td>
<td>4-Br-benzaldehyde</td>
<td>14</td>
<td>78</td>
</tr>
<tr>
<td>i</td>
<td>3- Br-benzaldehyde</td>
<td>18</td>
<td>72</td>
</tr>
<tr>
<td>j</td>
<td>4-Cl-benzaldehyde</td>
<td>18</td>
<td>79</td>
</tr>
<tr>
<td>k</td>
<td>3-Cl-benzaldehyde</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td>l</td>
<td>4-F-benzaldehyde</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>m</td>
<td>4-CF(_3)-benzaldehyde</td>
<td>7</td>
<td>69</td>
</tr>
<tr>
<td>n</td>
<td>4-CN-benzaldehyde</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>o</td>
<td>3-pyridinecarboxaldehyde</td>
<td>20</td>
<td>76</td>
</tr>
<tr>
<td>p</td>
<td>furfural</td>
<td>24</td>
<td>63</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: aldehyde (5 mmol), methanol (6 mmol), NHC 44 (10 mol%), DBU (20 mol%), 25 \(^\circ\)C, \(O_2\) (1 atm). \(^b\)isolated yield after column chromatographic purification.
A wide range of alcohols were then examined for oxidative esterification with 4-nitrobenzaldehyde as the substrate; the results are summarized in Table 3. Both primary and secondary alcohols including allylic, propargylic and benzylic alcohols underwent this reaction to give the corresponding esters in excellent yields.

**Table 3: Oxidative esterification of 4-nitrobenzaldehyde: alcohol scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol components</th>
<th>time (h)</th>
<th>yield of ester %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ethanol</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>2-propanol</td>
<td>7</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>benzyl alcohol</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>allyl alcohol</td>
<td>4</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>propargyl alcohol</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>(S)-tetrahydrofuran-3-ol</td>
<td>16</td>
<td>66 (99% ee)</td>
</tr>
</tbody>
</table>

*Reaction conditions: 4-nitrobenzaldehyde (5 mmol), alcohol (6 mmol), NHC 44 (10 mol%), DBU (20 mol%), 25 °C, O₂ (1 atm). *b*isolated yield after column chromatographic purification; *c* the (R)-isomer gave the corresponding ester in 64% yields and 99% ee.

The formation of all ester products were confirmed unambiguously from their corresponding ¹H, ¹³C NMR and IR spectral data.

**Example 1:** The ¹H NMR spectrum of methyl 4-cyanobenzoate (51n) showed a typical singlet at δ 3.96 (s, 3H) corresponding to methoxyl protons (−OCH₃), while other signals at δ 7.75 (d, J = 8.6 Hz, 2H) and 8.14 (d, J = 8.6 Hz, 2H) correspond to aromatic protons. Its ¹³C NMR spectrum showed two characteristic carbon signals at δ 52.6 and 165.1 attributed to methoxyl carbon (−OCH₃) and ester carbonyl carbon.
Esterification

Its IR spectrum displayed two characteristic strong absorption frequencies at 1727 and 2229 cm$^{-1}$ indicating the presence of ester carbonyl and cyano functional groups respectively (Fig. 15).

**Fig. 15**: $^1$H, $^{13}$C NMR and IR spectra of methyl 4-cyanobenzoate (51n)
**Example 2:** The $^1$H NMR spectrum of allyl 4-nitrobenzoate (51t) showed two typical proton signals at $\delta$ 4.86 (d, $J = 5.8$ Hz, 2H) and 5.31-5.46 (m, 2H) corresponding to allylic methylene and terminal olefinic protons respectively, while its $^{13}$C NMR spectrum showed characteristic carbon signals at $\delta$ 119.0, 131.6 and 164.1 corresponding to olefinic and ester carbonyl carbons respectively (Fig. 16).

![NMR spectra of allyl 4-nitrobenzoate (51t)](image)

**Fig. 16:** $^1$H and $^{13}$C NMR spectra of allyl 4-nitrobenzoate (51t)

In order to gain insight into the mechanistic details of the reaction, the following experiments (see Scheme 20) were conducted: (i) for aldehyde 50f, no esterification
took place under N$_2$ atmosphere, while at the same time low yield (45%) was obtained under open air conditions, suggesting the necessity of O$_2$ for realizing higher yields; (ii) the esterification reaction between $p$-nitrobenzoic acid (52) and methanol did not proceed under the reaction conditions, suggesting the absence of carboxylic acid as the intermediate; (iii) when (S)-tetrahydrofuran-3-ol 53 was used as alcohol partner, retention of configuration was indeed obtained in ester 51v, thereby confirming the incorporation of alcohol oxygen into ester moiety; (iv) when 1 equivalent of sodium methoxide (54) was used as alcohol component, the corresponding methyl ester 51f was obtained in 46% yield, suggesting the possibility of alkoxide anion formation as the intermediate (Scheme 20).

Scheme 20: A series of control experiments for mechanistic details
Based on the above results and literature precedents,\textsuperscript{37, 50} we have proposed a catalytic cycle in which peroxo anion II,\textsuperscript{37} formed from reaction between Breslow intermediate I and O\textsubscript{2}, has been depicted as the key intermediate in the esterification process. This on decomposition results in the formation of acyl intermediate III.\textsuperscript{37b} Subsequently, alkoxide ion\textsuperscript{50} formed from alcohol reacts with III to give the corresponding ester with the liberation of NHC (Scheme 21).

**Scheme 21**: Probable mechanistic pathway for the oxidative esterification of aromatic aldehydes

### 4.2.5 Conclusion

A simple organocatalytic procedure for the direct oxidative esterification of aromatic aldehydes with alcohols employing NHC as catalyst and oxygen as oxidant at ambient conditions has been developed. The reaction is simple to carry out and the products are obtained in high yields and purity from stoichiometric amount of alcohol and catalytic amount of organic base.
4.2.6 Experimental Section

General experimental procedure for esterification of aromatic aldehydes

To a flame-dried round bottom flask equipped with a magnetic stir bar was added imidazolium salt 44 (0.170 g, 10 mol%), DBU (0.15 mL, 20 mol%) and THF (10 mL) in that order. The contents were evacuated and covered with molecular O₂ in balloon. The resultant reaction mixture was kept stirring at 25 °C for 45 min. To this mixture was added aromatic aldehydes 50a-p (5 mmol) and alcohol (6 mmol) successively. It was allowed to stir at 25 °C. After completion of the reaction (monitored by TLC), THF was evaporated, H₂O (50 mL) added and the mixture extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over anhyd. Na₂SO₄ concentrated to give crude ester, which was purified by silica gel-packed column chromatography to obtain pure esters, 51a-w.

Methyl 3-methylbenzoate (51a)

**Yield:** 78%; colorless gum; **IR** (CHCl₃, cm⁻¹): νmax 684, 815, 897, 976, 1043, 1166, 1239, 1381, 1607, 1682, 1722, 1873, 2496; **¹H NMR** (200 MHz, CDCl₃): δ 2.41 (s, 3H), 3.91 (s, 3H), 7.30-7.34 (m, 2H), 7.81-7.85 (m, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 21.2, 51.8, 126.7, 128.1, 130.0, 133.5, 137.9, 166.9; **Analysis:** C₉H₁₀O₂ requires C, 71.98; H, 6.71; found: C, 71.83; H, 6.59%.

Methyl 4-methoxybenzoate (51b)

**Yield:** 72%; colorless solid; **mp:** 49-51 °C, (lit.³² **mp:** 49 °C); **IR** (CHCl₃, cm⁻¹): νmax 770, 848, 1029, 1103, 1168, 1256, 1280, 1317, 1434, 1458, 1606, 1716, 2953; **¹H NMR** (200 MHz, CDCl₃): δ 3.86 (s, 3H), 3.88 (s, 3H), 6.90 (d, J = 8.9 Hz, 2H), 7.98 (d, J = 8.9 Hz, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 51.7, 55.2, 113.5, 122.6, 131.5, 163.2, 166.5; **Analysis:** C₉H₁₀O₃ requires C, 65.05; H, 6.07; found: C, 64.91; H, 5.93%.
Methyl 3,4-dimethoxybenzoate (51c)

**Yield:** 70%; colorless solid; **mp:** 59-61 °C, (lit.\(^{32}\) mp: 60 °C); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 764, 1133, 1271, 1294, 1434, 1514, 1600, 1714; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.89 (s, 3H), 3.93 (s, 6H), 6.87 (d, \(J = 8.4\) Hz, 1H), 7.53 (d, \(J = 1.9\) Hz, 1H), 7.66 (dd, \(J = 1.9, 8.4\) Hz, 1H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 51.8, 55.8, 110.2, 111.9, 122.6, 123.5, 148.6, 152.9, 166.6; **Analysis:** C\(_{10}\)H\(_{12}\)O\(_4\) requires C, 61.22; H, 6.16; found: C, 61.09; H, 6.12%.

Methyl 3,4,5-trimethoxybenzoate (51d)

**Yield:** 65%; colorless solid; **mp:** 82-85 °C, (lit.\(^{32}\) mp: 82 °C); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 761, 1132, 1229, 1342, 1413, 1465, 1591, 1719; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.90 (s, 3H), 3.91 (s, 9H), 7.28 (s, 2H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 52.1, 56.1, 60.7, 106.7, 125.0, 142.1, 152.9, 166.4; **Analysis:** C\(_{11}\)H\(_{14}\)O\(_5\) requires C, 58.40; H, 6.24; found: C, 58.31; H, 6.12%.

Methyl 4-(methylthio)benzoate (51e)

**Yield:** 68%; colorless gum; **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 759, 1116, 1245, 1298, 1382, 1402, 1708; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 2.51 (s, 3H), 3.89 (s, 3H), 7.23 (d, \(J = 8.6\) Hz, 2H), 7.91 (d, \(J = 8.6\) Hz, 2H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 14.7, 51.8, 124.8, 126.3, 129.8, 145.3, 166.5; **Analysis:** C\(_9\)H\(_{10}\)O\(_2\)S requires C, 59.32; H, 5.53; found: C, 59.18; H, 5.41%.

Methyl 4-nitrobenzoate (51f)

**Yield:** 76%; colorless solid; **mp:** 94-96 °C, (lit.\(^{32}\) mp: 96 °C); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 722, 818, 1076, 1104, 1136, 1262, 1298, 1338, 1536, 1618, 1719; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.98 (s, 3H), 8.21 (d, \(J = 8.6\) Hz, 2H), 8.30 (d, \(J = 8.6\) Hz, 2H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 14.7, 51.8, 124.8, 126.3, 129.8, 145.3, 166.5; **Analysis:** C\(_8\)H\(_7\)NO\(_4\) requires C, 53.04; H, 3.89; N, 7.73; found: C, 52.92; H, 3.76; N, 7.62%.
Methyl 3-nitrobenzoate (51g)

**Yield:** 82%; colorless solid; **mp:** 78-80 °C, (lit.\(^{32}\) mp: 78 °C); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 719, 823, 1072, 1100, 1133, 1266, 1292, 1350, 1528, 1615, 1722; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.99 (s, 3H), 7.61-7.69 (m, 1H), 8.34-8.44 (m, 2H), 8.81-8.87 (m, 1H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 52.6, 124.4, 127.2, 129.5, 131.8, 135.1, 148.2, 164.6; **Analysis:** C\(_8\)H\(_7\)NO\(_4\) requires C, 53.04; H, 3.89; N, 7.73%; found: C, 52.96; H, 3.81; N, 7.67%.

Methyl 4-bromobenzoate (51h)

**Yield:** 78%; colorless solid; **mp:** 77-80 °C, (lit.\(^{32}\) mp: 79 °C); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 758, 847, 1157, 1276, 1397, 1590, 1716; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.92 (s, 3H), 7.57 (d, \(J = 10\) Hz, 2H), 7.89 (d, \(J = 10\) Hz, 2H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 52.1, 127.9, 129.0, 131.0, 131.6, 166.0; **Analysis:** C\(_8\)H\(_7\)BrO\(_2\) requires C, 44.68; H, 3.28; found: C, 44.59; H, 3.12%.

Methyl 3-bromobenzoate (51i)

**Yield:** 72%; colorless gum; **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 718, 746, 1067, 1121, 1260, 1293, 1436, 1571, 1727; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.92 (s, 3H), 7.26-7.35 (m, 1H), 7.63-7.71 (m, 1H), 7.93-7.99 (m, 1H), 8.12-8.18 (m, 1H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 52.2, 122.4, 128.0, 129.8, 132.0, 132.6, 135.7, 165.4; **Analysis:** C\(_8\)H\(_7\)BrO\(_2\) requires C, 44.68; H, 3.28; found: C, 44.53; H, 3.11%.

Methyl 4-chlorobenzoate (51j)

**Yield:** 79%; colorless gum; **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 760, 1015, 1091, 1115, 1434, 1488, 1596, 1725; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 3.92 (s, 3H), 7.41 (d, \(J = 8.6\) Hz, 2H), 7.97 (d, \(J = 8.6\) Hz, 2H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 52.1, 128.6, 131.0, 139.3, 165.9; **Analysis:** C\(_8\)H\(_7\)ClO\(_2\) requires C, 56.32; H, 4.14; found: C, 56.21; H, 4.03%.
Methyl 3-chlorobenzoate (51k)

**Yield:** 70%; colorless gum; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 748, 1126, 1259, 1283, 1295, 1437, 1728; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.92 (s, 3H), 7.32-7.40 (m, 1H), 7.48-7.54 (m, 1H), 7.88-7.94 (m, 1H), 7.97-8.02 (m, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 52.2, 127.6, 129.5, 131.8, 132.8, 134.5, 165.5; **Analysis:** C$_8$H$_7$ClO$_2$ requires C, 56.32; H, 4.14; found: C, 56.23; H, 4.06%.

Methyl 4-flurobenzoate (51l)

**Yield:** 76%; colorless gum; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 607, 767, 854, 1092, 1113, 1154, 1280, 1436, 1508, 1601, 1727; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.90 (s, 3H), 7.04-7.13 (m, 2H), 7.99-8.09 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 52.1, 115.4, 128.6, 131.0, 165.1, 166.1; **Analysis:** C$_8$H$_7$FO$_2$ requires C, 62.34; H, 4.58; found: C, 62.23; H, 4.39%.

Methyl 4-(trifluromethyl)benzoate (51m)

**Yield:** 69%; pale yellow liquid; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 775, 865, 1019, 1068, 1327, 1413, 1440, 1730, 2957; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.92 (s, 3H), 7.70 (d, $J = 8.2$ Hz, 2H), 8.14 (d, $J = 8.2$ Hz, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 52.3, 120.9, 125.2-125.4 (m), 126.3, 128.1, 129.9, 132.5-135.7 (m), 165.5; C$_9$H$_7$F$_3$O$_2$ requires C, 52.95; H, 3.46; found: C, 52.76; H, 3.33%.

Methyl 4-cyanobenzoate (51n)

**Yield:** 72%; colorless gum; **IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 763, 866, 960, 1019, 1108, 1181, 1289, 1315, 1440, 1727, 2229; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 3.96 (s, 3H), 7.75 (d, $J = 8.6$ Hz, 2H), 8.14 (d, $J = 8.6$ Hz, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 52.6, 116.5, 117.7, 130.1, 132.1, 133.9, 165.1; **Analysis:** C$_9$H$_7$NO$_2$ requires C, 67.07; H, 4.38; N, 8.69; found: C, 66.91; H, 4.26; N, 8.52%.
Methyl nicotinate (51o)

**Yield:** 76%; colorless liquid; **IR** (CHCl₃, cm⁻¹): υ_{max} 824, 959, 1072, 1292, 1350, 1436, 1528, 1615, 1722, 3045; **¹H NMR** (200 MHz, CDCl₃): δ 3.93 (s, 3H), 7.33-7.40 (m, 1H), 8.23-8.29 (m, 1H), 8.71-8.76 (m, 1H), 9.16-9.19 (m, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 52.3, 123.2, 126.0, 136.9, 150.8, 153.3, 165.5; **Analysis:** C₇H₇NO₂ requires C, 61.31; H, 5.14; N, 10.21; found: C, 61.26; H, 5.06; N, 10.12%.

Methyl furan-2-carboxylate (51p)

**Yield:** 63%; colorless liquid; **IR** (CHCl₃, cm⁻¹): υ_{max} 797, 1121, 1177, 1197, 1306, 1479, 1731, 3127, 3144; **¹H NMR** (200 MHz, CDCl₃): δ 3.90 (s, 3H), 6.50 (d, J = 3.8 Hz, 1H), 7.17 (d, J = 3.8 Hz, 1H), 7.57 (s, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ 52.0, 111.9, 118.0, 144.8, 146.5, 159.2; **Analysis:** C₆H₆O₃ requires C, 57.14; H, 4.80; found: C, 57.02; H, 4.69%.

Ethyl 4-nitrobenzoate (51q)

**Yield:** 80%; colorless solid; **mp:** 97-99 °C, (lit.³⁷a **mp:** 97-98 °C); **IR** (CHCl₃, cm⁻¹): υ_{max} 757, 872, 1103, 1277, 1320, 1352, 1528, 1724; **¹H NMR** (200 MHz, CDCl₃): δ 1.44 (t, J = 7.4 Hz, 3H), 4.43 (q, J = 7.4 Hz, 2H), 8.21 (d, J = 8.9 Hz, 2H), 8.30 (d, J = 8.9 Hz, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 14.2, 61.9, 123.5, 130.6, 135.8, 150.5, 164.4; **Analysis:** C₉H₉NO₄ requires C, 55.39; H, 4.65; N, 7.18; found: C, 55.21; H, 4.52; N, 7.01%.

Isopropyl 4-nitrobenzoate (51r)

**Yield:** 76%; colorless solid; **mp:** 105-108 °C, (lit.³⁷a **mp:** 105-106 °C); **IR** (CHCl₃, cm⁻¹): 717, 874, 1103, 1287, 1322, 1349, 1375, 1525, 1607, 1713; **¹H NMR** (200 MHz, CDCl₃): δ 1.39 (d, J = 6.4 Hz, 6H), 5.24-5.31 (m, 1H), 8.19 (d, J = 8.4 Hz, 2H), 8.27 (d, J = 8.4 Hz, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 21.8, 69.7, 123.4, 130.6,
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136.2, 150.4, 164.1; **Analysis**: C_{10}H_{11}NO_{4} requires C, 57.41; H, 5.30; N, 6.70; found: C, 57.30; H, 5.19; N, 6.54%.

**Benzyl 4-nitrobenzoate (51s)**

**Yield**: 80%; colorless solid; **mp**: 82-84 °C, (lit. \[^{37a}\] mp: 81-82 °C); **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 743, 1103, 1286, 1348, 1523, 1713; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 5.40 (s, 2H), 7.37-7.46 (m, 5H), 8.21-8.31 (m, 4H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 67.5, 123.5, 128.4, 128.6, 128.7, 130.7, 135.2, 135.4, 150.5, 164.3; **Analysis**: C\(_{14}\)H\(_{11}\)NO\(_4\) requires C, 65.37; H, 4.31; N, 5.44; found: C, 65.23; H, 4.21; N, 5.31%.

**Allyl 4-nitrobenzoate (51t)**

**Yield**: 76%; colorless oil; **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 720, 855, 933, 995, 1014, 1048, 1102, 1271, 1319, 1348, 1526, 1608, 1727; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 4.86 (d, \(J = 5.8\) Hz, 2H), 5.31-5.46 (m, 2H), 5.94-6.13 (m, 1H), 8.21 (d, \(J = 8.9\) Hz, 2H), 8.29 (d, \(J = 8.9\) Hz, 2H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 66.3, 119.0, 123.5, 130.7, 131.6, 135.5, 150.6, 164.1; **Analysis**: C\(_{10}\)H\(_9\)NO\(_4\) requires C, 57.97; H, 4.38; N, 6.76; found C, 57.78; H, 4.19; N, 6.59%.

**Prop-2-ynyl 4-nitrobenzoate (51u)**

**Yield**: 82%; yellow gum; **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 715, 875, 1124, 1286, 1322, 1350, 1527, 1608, 1728, 3290; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)): \(\delta\) 2.55 (t, \(J = 2.5\) Hz, 1H), 4.94 (d, \(J = 2.5\) Hz, 2H), 8.24 (d, \(J = 8.4\) Hz, 2H), 8.32 (d, \(J = 8.4\) Hz, 2H); \(^{13}\)C **NMR** (50 MHz, CDCl\(_3\)): \(\delta\) 53.2, 75.8, 123.6, 130.9, 134.7, 150.8, 163.8; **Analysis**: C\(_{10}\)H\(_7\)NO\(_4\) requires C, 58.54; H, 3.44; N, 6.83; found: C, 58.42; H, 3.29; N, 6.74%.

**(S)-Tetrahydrofuran-3-yl 4-nitrobenzoate (51v)**

**Yield**: 66%, colorless gum; [\(\alpha\)]\(_D\)^{25} = -31.24 (c 1.2, CH\(_2\)Cl\(_2\)); lit\[^{37a}\] [\(\alpha\)]\(_D\)^{25} = +31.26 (c 1.0, CH\(_2\)Cl\(_2\)) for the corresponding \((R)\)-enantiomer; **IR** (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 720, 878, 1086, 1106, 1120, 1529, 1604, 1718, 2877, 2933, 3076; \(^1\)H **NMR** (200 MHz, CDCl\(_3\)):
δ 2.14-2.21 (m, 1H), 2.29-2.43 (m, 1H), 3.91-4.07 (m, 4H), 5.57-5.60 (m, 1H), 8.21 (d, J = 8.8 Hz, 2H), 8.30 (d, J = 8.8 Hz, 2H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): δ 32.8, 66.9, 72.9, 76.4, 123.5, 130.7, 135.2, 150.7, 164.1; Analysis: C\(_{11}\)H\(_{11}\)NO\(_5\) requires C, 55.70; H, 4.67; N, 5.90; found: C, 55.62; H, 4.51; N, 5.79%.

\((R)\)-Tetrahydrofuran-3-yl 4-nitrobenzoate (51w)

Yield: 64%; colorless gum; [\(\alpha\)]\(_{D}\)\(^{25}\) +31.24 (c 1.2, CH\(_2\)Cl\(_2\); lit\(^{37a}\) [\(\alpha\)]\(_{D}\)\(^{25}\) +31.26 (c 1.0, CH\(_2\)Cl\(_2\)); IR (CHCl\(_3\), cm\(^{-1}\)): \(\nu_{\text{max}}\) 721, 879, 1084, 1105, 1122, 1528, 1604, 1718, 2877, 2933, 3076; \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): δ 2.14-2.20 (m, 1H), 2.30-2.35 (m, 1H), 3.91-3.93 (m, 1H), 3.98-4.03 (m, 3H), 5.55-5.58 (m, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): δ 32.8, 66.9, 72.9, 76.4, 123.5, 130.7, 135.2, 150.7, 164.1; Analysis: C\(_{11}\)H\(_{11}\)NO\(_5\) requires C, 55.70; H, 4.67; N, 5.90; found: C, 55.60; H, 4.49; N, 5.76%.

### 4.2.7 References


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**Chapter IV**

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