# One-Pot Approach for C–C Bond Formation through Ruthenium-Amido Complex Catalyzed Tandem Aldol Reaction/Hydrogenation

Haifeng Sun, Deju Ye, Hualiang Jiang, Kaixian Chen, Hong Liu*

The Center for Drug Discovery and Design, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, 201203, P. R. of China
Fax +86(21)50807088; E-mail: hliu@mail.shcnc.ac.cn

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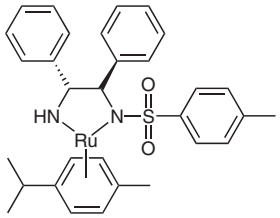
**Abstract:** A one-pot novel and efficient approach was developed for the α-alkylation of various nitriles with carbonyl compounds using ruthenium-amido complex catalyst **1**. The C–C bond was formed through aldol reaction followed by hydrogenation with triethylamine–formic acid (TEAF) and **1**. Moderate to high yields were obtained, and a variety of functional groups were tolerated, including nitro and chloro groups, and a furan ring.

**Key words:** ruthenium-amido complex, tandem reaction, aldol reaction, hydrogenation, C–C bond




**1**

**Figure 1** Ruthenium-amido complex **1**

Two-carbon homologation is a very important transformation in organic chemistry. The numerous methods[1] available mostly involve redox functional group transformations rather than carbon–carbon bond formation. In this regard, the development of two-carbon homologation through carbon–carbon bond formation using organocatalytic tandem methodology can provide an expedient access to homologated products from simple starting materials.

Of the various types of tandem reactions, an aldol reaction combined with a simultaneous catalytic hydrogenation for the formation of C–C bond is of importance, and several studies with different catalysts have been reported.[2] Recently, ruthenium/Hydrotalcites[3] (HTs) catalyzed direct α-alkylation of nitriles with primary alcohols was demonstrated for the effective synthesis of α-alkylated nitriles, which are important building blocks of various biologically active compounds.[4] However, this catalyst system usually required high reaction temperature and was only limited to arylacetonitriles as substrates. Ruthenium-amido complexes,[5] which have sufficient Brønsted basicities to deprotonate hydrogen donors, were found to efficiently catalyze asymmetric Michael addition of 1,3-dicarbonyl compounds to cyclic enones, nitroalkenes, and azodicarboxylates[6], and have been applied to the reduction of various activated olefins.[7] Herein we report a ruthenium-amido complex catalyst, {Ru[(*R*,*R*)-Tsdpen](η$^6$-*p*-cymene), Figure 1}, for the one-pot formation of C–C bond from various nitriles and aldehydes through tandem aldol reaction/hydrogenation.

Initially we found that the reaction of various aldehydes with ethyl cyanoacetate could efficiently proceed using ruthenium amido complex, Ru[(*R*,*R*)-Tsdpen](η$^6$-*p*-cymene) (**1**) as a catalyst via tandem aldol reaction/hydrogenation reaction. *p*-Nitrobenzaldehyde (**2a**) and ethyl cyanoacetate (**3a**) were used as model substrates to optimize the reaction conditions, including various solvent, reaction time, reaction temperatures, and different amounts of catalyst (Table 1). As illustrated in Table 1, the preliminary survey was carried out in toluene at 40 °C for 24 hours. The one-pot reaction provides good result using 0.05 equivalent catalyst (90%, Table 1, entry 1). The nature of solvent was found to have a pronounced impact on the process. Moderate yields were observed when we selected tetrahydrofuran, acetonitrile, and dichloromethane as solvent (Table 1, entries 2, 3, and 4). *tert*-Butyl alcohol was proved to be better than toluene as a solvent and the reaction time was shortened to 12 hours (98%, Table 1, entry 5). There is no significant change in yield when the reaction temperature was down to room temperature while the reaction time had to be prolonged to 24 hours (Table 1, entry 6). The yields of reaction were decreased and the reaction times were longer when the concentration of the catalyst **1** was lower (0.02, 0.01 equiv) (Table 1, entries 7 and 8). This indicated that the optimization of aldol/hydrogenation conditions by increasing the amount of **1** and reaction temperature may be more necessary. To our knowledge, this is the first report of tandem aldol/hydrogenation catalyzed by a ruthenium-amido complex. The reaction proceeded as follows: treatment of *p*-nitrobenzaldehyde and ethyl cyanoacetate with 0.05 equivalent of **1** gave an olefin product, which was successively reduced by **1** and TEAF that was directly added to the reaction solution.

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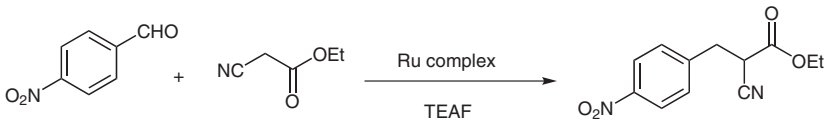
**Table 1** Optimization of Reaction Conditions Using *p*-Nitrobenzaldehyde and Ethyl Cyanoacetate[a]



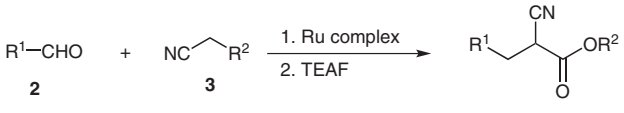

**2a** **3a** **5a**

| Entry | Solvent | Ru complex (equiv) | Temp (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | toluene | 0.05 | 40 | 24 | 90 |
| 2 | THF | 0.05 | 40 | 48 | 54 |
| 3 | MeCN | 0.05 | 40 | 48 | 65 |
| 4 | $CH_2Cl_2$ | 0.05 | 40 | 48 | 45 |
| 5 | *t*-BuOH | 0.05 | 40 | 12 | 98 |
| 6 | *t*-BuOH | 0.05 | r. t. | 24 | 95 |
| 7 | *t*-BuOH | 0.02 | 40 | 48 | 89 |
| 8 | *t*-BuOH | 0.01 | 40 | 48 | 56 |

[a] Reaction conditions: aldehyde **2a** (0.3 mmol), nitrile **3a** (0.3 mmol), solvent (6 mL), $Et_3N$ (0.2 mL)–formic acid (0.2 mL).
[b] Isolated yields.

After determining the optimized conditions, we examined the generality of the process as summarized in Table 2. It was found that the method was applicable to a broad range of various substituted aldehydes, including aromatic, aliphatic, and heterocyclic aldehydes. The results indicated that the electronic effects on the reaction were not significant. Aldehydes containing various electron-withdrawing and electron-donating substituents were used under the optimal reaction conditions (Table 2, entries 1–6), although those containing electron-donating group such as *p*-SMe, *o*-OMe and *m*-Cl gave moderate products yields (Table 2, entries 4–6). No obvious steric effects were observed and the reactions with *para*-, *ortho*-, and *meta*-substituted benzaldehydes proceeded in good yields (Table 2, entries 1–3), while 3,4,5-trimethoxybenzaldehyde gave lower yield (Table 2, entry 7). In further experiments for establishing the scope of this method, we selected heteroaryl aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde as reactants and the yields were also found to be good (Table 2, entries 8 and 9). Furthermore, alkyl aldehyde 3-phenylpropanal and the ketone cyclohexanone were relatively less reactive under the same conditions (Table 2, entries 11 and 12). At the same time, the scope of the process with respect to the variation of steric influence of cyanoacetates was investigated (Table 2). As shown, here also the products were obtained in good yields (Table 2, entries 13–16). Unfortunately we could not get chiral products even though we adopted a chiral ruthenium-amino complex as catalyst and also attempted to use some sterically hindred cyanoacetates as reactants.

**Table 2** α-Alkylation of Various Nitriles with Carbonyl Compounds Using the Ruthenium Complex




**2** **3** **5a–q**

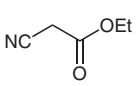
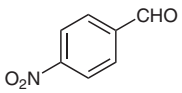
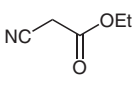
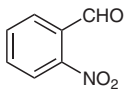
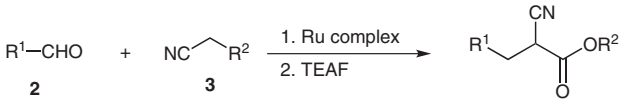
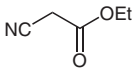
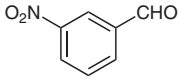
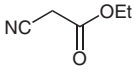
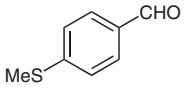
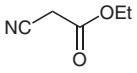
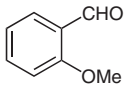
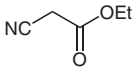
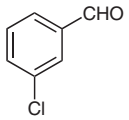
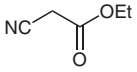
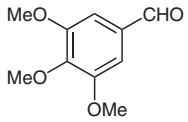
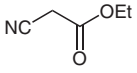
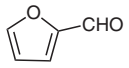
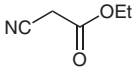
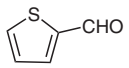
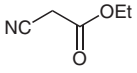
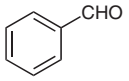
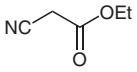
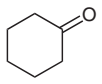
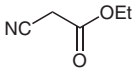
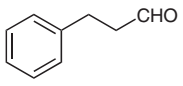
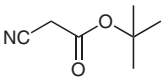
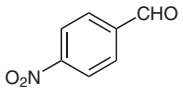
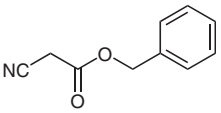
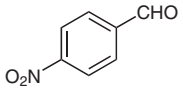
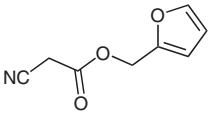
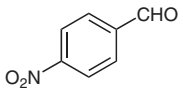
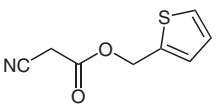
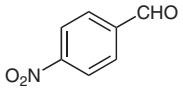
| Entry | Donor | Acceptor | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  |  | 12 | **5a** | 98 |
| 2 |  |  | 12 | **5b** | 91 |

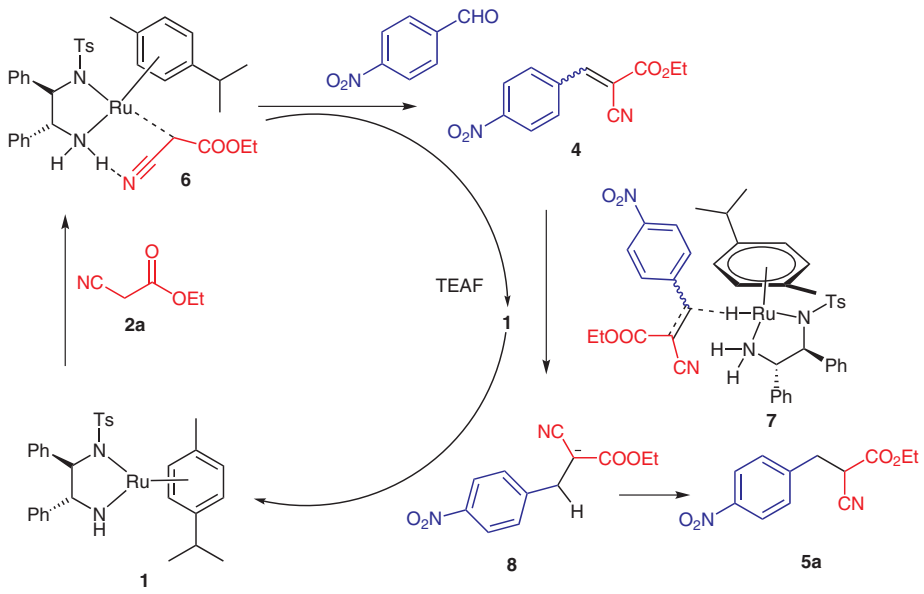
**Table 2** α-Alkylation of Various Nitriles with Carbonyl Compounds Using the Ruthenium Complex (continued)




**5a–q**

| Entry | Donor | Acceptor | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 3 |  |  | 12 | **5c** | 94 |
| 4 |  |  | 24 | **5d** | 80 |
| 5 |  |  | 24 | **5e** | 83 |
| 6 |  |  | 24 | **5f** | 84 |
| 7[b] |  |  | 24 | **5g** | 60 |
| 8 |  |  | 12 | **5h** | 92 |
| 9 |  |  | 12 | **5i** | 83 |
| 10 |  |  | 12 | **5j** | 87 |
| 11[b] |  |  | 48 | **5k** | trace |
| 12[b] |  |  | 48 | **5l** | 49 |
| 13 |  |  | 12 | **5m** | 92 |
| 14 |  |  | 12 | **5n** | 90 |
| 15 |  |  | 12 | **5o** | 91 |
| 16 |  |  | 12 | **5p** | 88 |

[a] Isolated yields.
[b] Reaction temperature = 60 °C.




**Scheme 1** Proposed mechanism for the tandem aldol reaction/hydrogenation

We propose a reaction mechanism for the transformation in Scheme 1. The studies recently reported[6a,b] imply that the reaction of the amido complex **1** with aldol donors may proceed to give the C-bound Ru cyanoacetate intermediate **6**, which further reacts with aldehydes to give an olefin product **4**. Successively, the transfer hydrogenation of C=C bond was completed by ruthenium-amido complex **7** with a hydrogen source to give the final product **5a** (Scheme 1). Considering the characteristics of activated olefins and the hydridic amido-ruthenium complex (RuH), which is a coordinately saturated complex, the reduction of the polarized α,β-unsaturated compounds is proposed to proceed in a stepwise conjugate reduction procedure. After a RuH conjugate addition to the α-carbon of the C=C bond (asymmetry generated step), the intermediate **8** might eliminate from the metal complex and subsequently catches another proton rapidly from the excess $Et_3NH^+$ in the reaction mixture.[6,7] Thus, no asymmetric induction could be generated in the α-carbon center of **5a**.

In conclusion, we have demonstrated a catalyst of ruthenium-amido complex for the one-pot synthesis of α-alkylated nitriles from the reaction of various nitriles with aldehydes through aldol/hydrogenation reaction. This work presents the first successful application of ruthenium-amido complex **1** with an M/NH bifunctional unit to catalytic aldol/hydrogenation reaction, and we are now working on the expansion of the scope of the reaction.

The reagents (chemicals) were purchased from commercial sources, and used without further purification. Analytical TLC was done using plates coated with HSGF 254 silica gel (0.15–0.20 mm thickness). All products were characterized by their NMR and MS spectra. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a 300 MHz instrument. Chemical shifts were reported in δ (ppm) downfield from TMS. Low- and high-resolution mass spectra (LRMS and HRMS) were recorded on a Finnigan MAT-95 LCQ-DECA spectrometer.

**Ruthenium-Amido Complex-Catalyzed Tandem Aldol Reaction/Hydrogenation; General Procedure**

Aldehyde **2** (0.3 mmol), nitrile **3** (0.3 mmol), and the catalyst **1** (0.05 equiv) were dissolved in *t*-BuOH (6 mL) and the mixture was stirred at 40 °C for 10 h. Then $Et_3N$ (0.2 mL) and formic acid (0.2 mL) were directly added to the reaction mixture and stirred for another 2 h. After completion of the reaction, the solvent was evaporated and the crude products **5a–p** were purified by column chromatography on silica gel using PE–EtOAc (6:1) as eluent (Table 2).

**Ethyl 2-Cyano-3-(4-nitrophenyl)propanoate (5a)**

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.299 (t, *J* = 7.2 Hz, 3 H), 3.36 (m, 2 H), 3.67–3.82 (m, 1 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 7.47 (d, *J* = 8.7 Hz, 2 H), 8.22 (d, *J* = 8.7 Hz, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.7, 34.7, 38.6, 63.2, 115.5, 123.8, 130.1, 142.6, 147.3, 164.7.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{11}N_2O_4$ $[M - H]^-$: 247.0719; found: 247.0706.

**Ethyl 2-Cyano-3-(2-nitrophenyl)propanoate (5b)**

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.31 (m, 3 H), 3.26–3.31 (m, 1 H), 3.67–3.73 (m, 1 H), 4.10–4.14 (m, 1 H), 4.25–4.30 (m, 2 H), 7.50–7.59 (m, 2 H), 7.62–8.7.66 (m, 1 H), 8.09–8.10 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 33.3, 38.1, 63.2, 115.9, 125.5, 129.3, 130.7, 133.6, 133.9, 165.1.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{11}N_2O_4$ $[M - H]^-$: 247.0719; found: 247.0705.

**Ethyl 2-Cyano-3-(3-nitrophenyl)propanoate (5c)**

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3 H), 3.27–3.34 (m, 1 H), 3.68–3.75 (m, 1 H), 4.10–4.16 (m, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 7.50–8.11 (m, 4 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 13.9, 34.8, 39.0, 63.3, 115.5, 122.9, 124.0, 129.9, 135.4, 137.1, 148.3, 164.8.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{11}N_2O_4$ $[M - H]^-$: 247.0719; found: 247.0718.

**Ethyl 2-Cyano-3-[4-(methylthio)phenyl]propanoate (5d)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H), 3.12–3.28 (m, 2 H), 3.67–3.72 (m, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 7.18–7.27 (m, 4 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.8, 15.5, 35.0, 39.5, 62.9, 116.0, 126.6, 129.4, 131.8, 138.0, 165.3.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{14}NO_2S$ [M – H]$^-$: 248.0745; found: 247.0765.

**Ethyl 2-Cyano-3-(2-methoxyphenyl)propanoate (5e)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 3.08–3.15 (m, 1 H), 3.86 (s, 3 H), 3.33–3.40 (m, 1 H), 4.20–4.27 (q, *J* = 7.2 Hz, 2 H), 7.53–8.20 (m, 4 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 31.5, 37.3, 55.2, 62.6, 110.3, 116.5, 120.6, 123.5, 129.7, 131.1, 157.3, 165.9.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{15}NO_3$ [M – H]$^-$: 232.1038; found: 232.1042.

**Ethyl 3-(3-Chlorophenyl)-2-cyanopropanoate (5f)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H), 3.14–3.30 (m, 2 H), 3.70–3.75 (m, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 7.19–7.20 (m, 1 H), 7.29–7.30 (m, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 35.1, 39.2, 63.0, 115.7, 127.2, 127.9, 129.1, 130.1, 134.5, 137.1, 165.1.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{11}ClNO_2$ [M – H]$^-$: 236.0478; found: 236.0457.

**Ethyl 2-Cyano-3-(3,4,5-trimethoxyphenyl)propanoate (5g)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 3.09–3.20 (m, 2 H), 3.68–3.73 (m, 1 H), 3.83 (s, 3 H, $CH_3$), 3.86 (s, 6 H, $CH_3$), 4.26 (q, *J* = 7.2 Hz, 2 H), 6.49 (s, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 36.0, 39.7, 56.0, 60.7, 62.9, 105.8, 116.2, 130.8, 137.3, 153.2, 165.4.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}NO_5$ [M – H]$^-$: 292.1185; found: 292.1180.

**Ethyl 2-Cyano-3-(furan-2-yl)propanoate (5h)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3 H, $CH_3$), 3.23–3.36 (m, 2 H), 3.81–3.86 (m, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 6.25–6.26 (m, 1 H), 6.32–6.34 (m, 1 H), 7.37 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.8, 28.4, 37.0, 63.0, 108.3, 110.5, 115.8, 142.5, 148.8, 165.1.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{11}NO_3$ [M – H]$^-$: 192.0661; found: 192.0645.

**Ethyl 2-Cyano-3-(thiophen-2-yl)propanoate (5i)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.3 (t, *J* = 6.9 Hz, 3 H), 3.4–3.5 (m, 2 H), 3.75–3.77 (m, 1 H), 4.24–4.31 (q, *J* = 6.9 Hz, 2 H), 6.97–7.00, 7.22–7.24 (m, 1 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 29.8, 39.8, 63.1, 115.9, 125.3, 127.2, 127.3, 136.6, 165.0.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{10}NO_2S$ [M – H]$^-$: 208.0432; found: 208.0447.

**Ethyl 2-Cyano-3-phenylpropanoate (5j)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 3.16–3.32 (m, 2 H), 3.90–3.74 (m, 1 H), 4.20–4.27 (q, *J* = 7.2 Hz, 2 H), 7.26–7.38 (m, 5 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 13.9, 35.7, 39.6, 62.9, 116.1, 127.7, 128.8, 129.0, 135.2, 165.5.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{12}NO_2$ [M – H]$^-$: 202.0868; found: 202.0849.

**Ethyl 2-Cyano-5-phenylpentanoate (5l)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.27–1.34 (m, 3 H), 1.81–1.98 (m, 3 H), 2.66–2.71 (m, 2 H), 3.45–3.50 (m, 2 H), 3.66–3.69 (m, 1 H), 4.22–4.30 (m, 2 H), 7.31–7.32 (m, 5 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.0, 28.3, 29.241, 34.91, 37.4, 62.8, 116.4, 128.5, 128.5, 140.7, 166.0.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}NO_2$ [M – H]$^-$: 230.1249; found: 230.1243.

***tert*-Butyl 2-Cyano-3-(4-nitrophenyl)propanoate (5m)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 3.68–3.73 (m, 1 H), 3.25–3.38 (m, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H), 8.21 (d, *J* = 8.7 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 27.6, 34.9, 39.6, 84.9, 115.9, 123.9, 130.1, 142.8, 147.4, 163.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}N_2O_4$ [M – H]$^-$; 275.1032; found: 275.1032.

**Benzyl 2-Cyano-3-(4-nitrophenyl)propanoate (5n)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.82–3.84 (m, 1 H), 3.32–3.35 (m, 2 H), 5.22 (s, 2 H), 7.30–7.39 (m, 7 H), 8.10–8.14 (d, *J* = 8.7 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 35.0, 38.8, 68.8, 115.3, 124.0, 128.7, 128.7, 129.0, 130.1, 134.1, 142.1, 147.5, 164.6.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}N_2O_4$ [M – H]$^-$: 309.0875; found: 309.0871.

**Furan-2-ylmethyl 2-Cyano-3-(4-nitrophenyl)propanoate (5o)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.28 (m, 2 H), 3.82–3.88 (m, 1 H), 5.18 (m, 2 H), 6.38–6.39 (m, 1 H), 6.46–6.49 (m, 1 H), 7.38–7.48 (m, 3 H), 8.14–8.17 (d, *J* = 6.4 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 34.8, 38.7, 59.9, 110.7, 112.0, 115.2, 123.8, 130.0, 142.2, 143.7, 147.3, 164.5.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{11}N_2O_5$ [M – H]$^-$: 299.0668; found: 299.0665.

**Thiophen-2-ylmethyl 2-Cyano-3-(4-nitrophenyl)propanoate (5p)**
$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.17–3.34 (m, 2 H), 3.81–3.85 (m, 1 H), 5.36 (m, 2 H), 6.97–7.01 (m, 1 H), 7.10–7.11 (m, 1 H), 7.34–7.37 (m, 3 H), 8.10–8.12 (d, *J* = 6.3 Hz, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 35.0, 38.7, 62.5, 115.205, 124.0, 127.0, 127.9, 129.7, 130.1, 135.7, 142.0, 147.5, 164.6.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{11}N_2O_4S$ [M – H]$^-$: 315.0440; found: 315.0437.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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