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Graphical Abstract

From Isonitrile to Nitrile via Ketenimine Intermediate: Palladium-catalyzed 1,1-Carbocyanation of Allyl Carbonate by α-Isocyanoacetate

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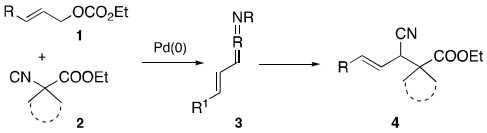

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From Isonitrile to Nitrile via Ketenimine Intermediate: Palladium-catalyzed 1,1-Carbocyanation of Allyl Carbonate by α-Isocyanoacetate

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ABSTRACT

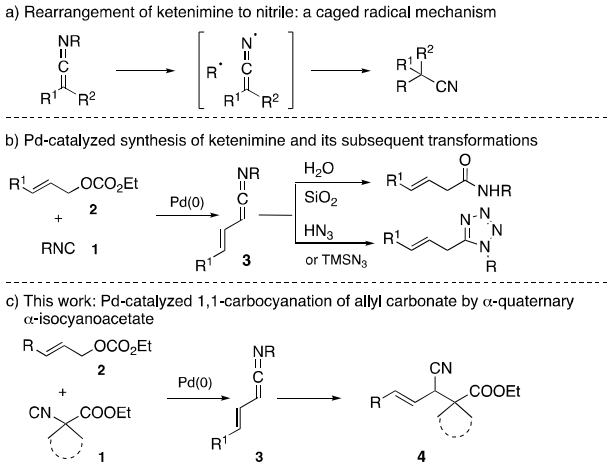
A palladium-catalyzed 1,1-carbocyanation of allyl carbonate by α-quaternary α-isocyanoacetate was developed. Formation of ketenimine followed by homolysis of the C-N bond and recombination of the resulting caged radical pair was proposed to account for the formation of the unusual coupling product, the β-cyano-γ,δ-unsaturated ester.

1. Introduction

Ketenimines are an important class of reactive species which show very rich chemistry and are well exploited in organic synthesis.[1-3] One particular type of reaction is the isomerization of ketenimines to nitriles via a formal 1,3-alkyl migration process. Homolytic cleavage of the C-N bond followed by recombination of the resulting caged radical pair through C-C bond formation accounts for this formal 1,3-rearrangement process (Scheme 1a).[4]

In connection with our interest in exploiting the diverse reactivities of isocyanides,[5] we recently reported palladium-catalyzed reactions of isocyanides **1** with allyl carbonates **2** (Scheme 1b),[6] propargyl carbonates[7] and α-haloketones.[8] All these reactions produced ketenimine intermediates **3** that can be isolated or be in situ converted to β,γ-unsaturated amides and diverse heterocycles. Concurrently, the groups of Yang,[9] Wu and Jian[10] reported similar transformations involving the in situ generated ketenimine intermediates.

Exploring the application scope of the reaction shown in Scheme 1b, we replaced the simple isonitrile by α-quaternary-α-isocyanoacetate. Interestingly, the reaction produced a new product that was identified as β-cyano-γ,δ-unsaturated ester (Scheme 1c). Since such a 1,1-carbocyanation of a C_{sp}^3 carbon is,



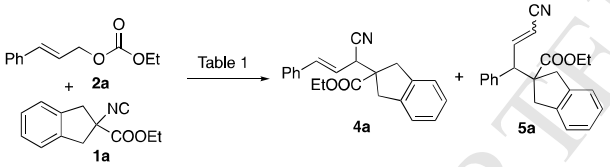
Scheme 1. Pd-catalyzed synthesis of ketenimine and its subsequent transformations.

to the best of knowledge, unprecedented, we set out to examine this reaction in detail. We report herein that the Pd-catalyzed reaction of α-quaternary-α-isocyanoacetates **1** with allyl carbonates **2** represents indeed a general way to access β-cyano-γ,δ-unsaturated esters **4**. Mechanistic studies suggested that the reaction went through a ketenimine intermediate **3** which underwent homolytic cleavage of the C-N bond followed by recombination of the resulting caged radical pair to afford the observed product.

2. Results and discussion

The reaction of ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate (**1a**)[11,12] with cinnamyl ethyl carbonate (**2a**) was chosen as a benchmark reaction (Table 1). Under the conditions optimized previously for the synthesis of ketenimines (1.0 mol% of $Pd(OAc)_2$, THF, 50 °C),[6] **4a** was isolated in 46% yield (entry 1). Addition of Et_3N (2.0 equiv) decreased yield of **4a** to 12% (entry 2), while adding other bases (K_2CO_3, K_3PO_4, KTFA, *t*BuOK, DBU) or acid (AcOH) led to the complete degradation. Among ligands screened (dppp, DPEPhos, XantPhos, XPhos, DavePhos, PhDavephos, *t*BuDavePhos, (*S*)-*t*BuPHOX, tri-*t*-butylphosphonium tetrafluoroborate, 1,10-phenanthroline), DavePhos was the most effective to give the desired product **4a** in 34% isolated yield (entry 3). Various solvents were next examined (DCE, MeCN, dioxane, toluene, THF, DMF, EtOH) and DCE was found to give a slightly better yield of **4a** (entries 3,4). Using DCE as solvent, in the presence of DavePhos or *t*BuDavePhos, similar yields were obtained (entries 4,5). Increasing (80 °C) or decreasing (rt) the temperature afforded the desired product with lower yields (entries 6,7). With these results in hand, the influence of palladium sources was reinvestigated and $Pd(PPh_3)_4$ turned out to be the catalyst of choice affording **4a** in 60% yield (entry 8). Finally, the influence of the leaving group of the allylic species was examined. Using allyl *t*-butyl carbonate, acetate, allyl bromide and allyl chloride as reaction partners, the isocyanide **2a** was recovered. Finally, the optimum conditions consisted of performing the reaction of **1a** with **2a** in DCE (0.1 M), in the presence of $Pd(PPh_3)_4$ at 55 °C. Under these conditions, **4a** was isolated together with its regioisomer **5a** in 60% yield in a ratio of 4:1 (entry 8). The structure of **4a** was determined by X-ray crystallographic analysis.[13]

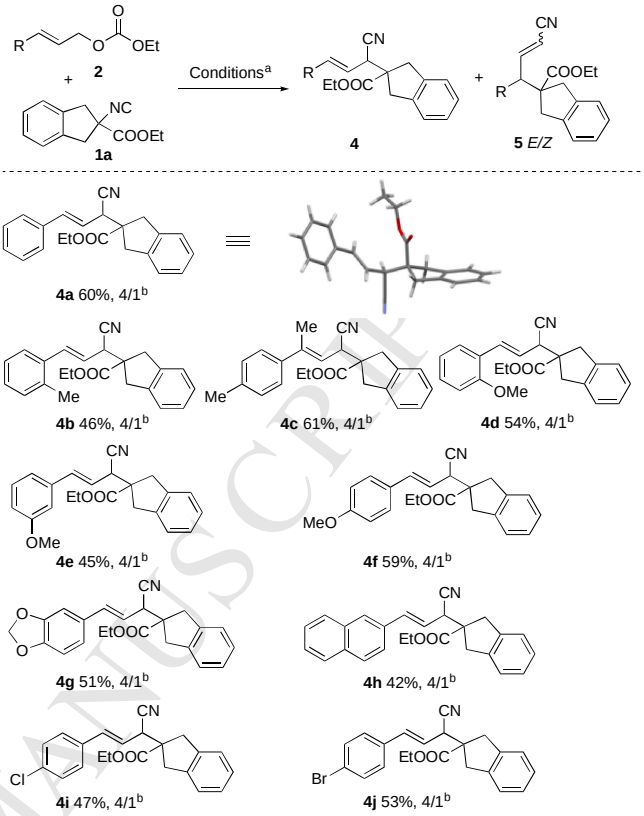
Table 1. Pd-catalyzed coupling reaction of allyl carbonate and isocyanide: Condition survey[a]



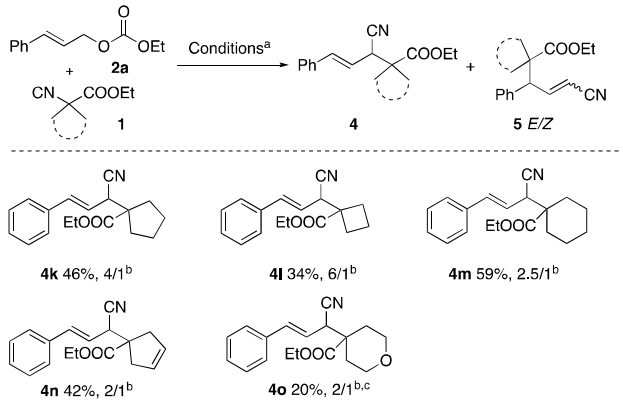
entry	Pd	ligand	solvent	base	yield(%)[b](**4a**/**5a**)
1	$Pd(OAc)_2$[c]	-	THF	-	46 (11:1)
2	$Pd(OAc)_2$	-	THF	Et_3N	12
3	$Pd(OAc)_2$	DavePhos	THF	-	34
4	$Pd(OAc)_2$	DavePhos	DCE	-	47
5	$Pd(OAc)_2$	*t*BuDavePhos	DCE	-	48
6	$Pd(OAc)_2$	*t*BuDavePhos	DCE	-	41[d]
7	$Pd(OAc)_2$	*t*BuDavePhos	DCE	-	40[e]
8	$Pd(PPh_3)_4$		DCE		60 (4/1)

[a] Reaction conditions: **1a** (0.11 mmol), **2a** (0.10 mmol), Pd catalyst (10 mol%), ligand (20 mol%), solvent (1.0 mL, *c* 0.1 M), 55 °C. [b] Isolated yield. [c] 1 mol% of catalyst. [d] Reaction was performed at 80 °C. [e] Reaction was performed at rt.

The scope of this novel 1,1-carbocyanation protocol was next examined varying firstly the structure of allyl carbonates **2** (Scheme 2). Reaction of isocyanide **1a** with cinnamyl ethyl carbonates **2** bearing an electron-withdrawing or donating substituent at different positions of the benzene ring participated in the reaction to give the desired products (**4a**-**4g, 4i**-**4j**) in good yields. (*E*)-Ethyl (3-(naphthalen-2-yl)allyl) carbonate was converted to the corresponding coupling product **4h** without event. It is worth noting that the aryl chloride and even aryl bromide was compatible to this Pd(0) catalyzed process.



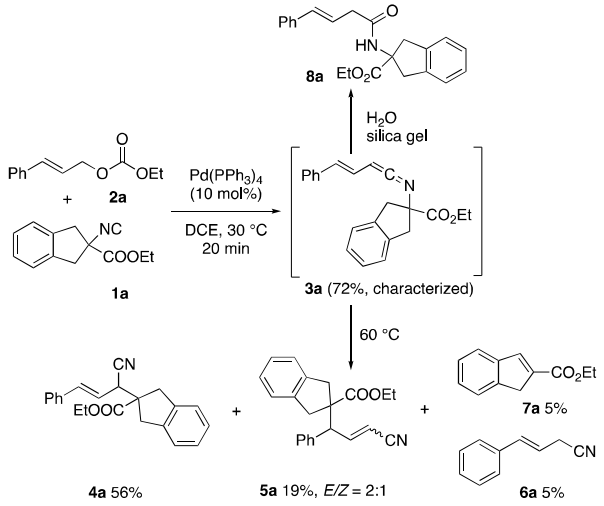
Scheme 2. Pd-catalyzed coupling reaction of allyl carbonate and isocyanide. [a] Reaction conditions: allyl carbonate **2** (0.10 mmol), isocyanide **1a** (0.11 mmol), $Pd(PPh_3)_4$ (10 mol%) in DCE (1.0 mL, *c* 0.1 M), 55 °C. [b] The ratio of **4**/**5**.



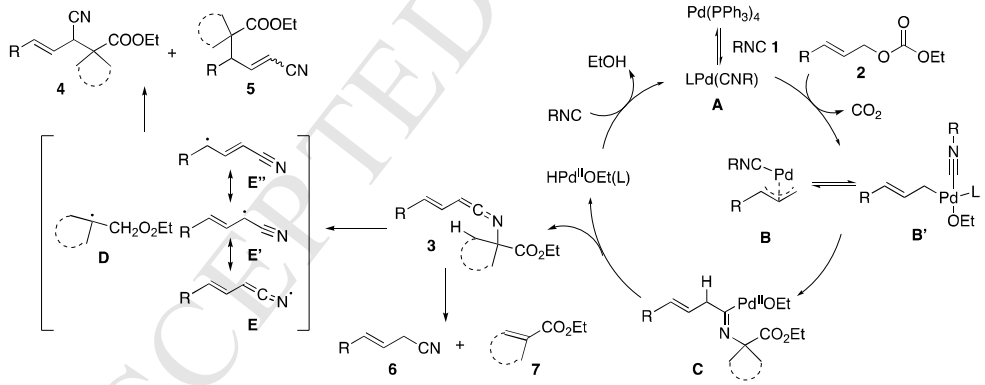
Scheme 3. Pd-catalyzed coupling reaction of allyl carbonate and isocyanide. [a] Reaction conditions: allyl carbonate **2a** (0.10 mmol), isocyanide **1** (0.11 mmol), $Pd(PPh_3)_4$ (10 mol%) in DCE (1.0 mL, *c* 0.1 M), 100 °C. [b] The ratio of **4**/**5**. [c] Reaction was performed at 55 °C.

The scope of the isocyanides was then examined. As shown in Scheme 3, the reaction of **2a** with ethyl 1-isocyanocyclopentane-1-carboxylate, ethyl 1-isocyanocyclobutane-1-carboxylate, or ethyl 1-isocyanocyclohexane-1-carboxylate proceeded smoothly providing the desired products **4k**-**4m**, respectively, in good yields. Ethyl 1-isocyanocyclopent-3-ene-1-carboxylate worked well, affording the desired product **4n**. Ethyl 4-cyanotetrahydro-2*H*-pyran-4-carboxylate participated also in the reaction, however, producing the product **4o** in lower yield (20%).

To get the mechanistic insight, following control experiments were carried out (Scheme 4). Performing the reaction of **1a** with **2a** at 30 °C for 20-30 min under otherwise standard conditions afforded the ketenimine **3a** in 72% NMR yield. Stirring a slurry of the crude mixture of **3a** in water in the presence of silica gel gave the corresponding carboxamide **8a**.[6] On the other hand, increasing the temperature of the above reaction mixture gradually to 60 °C, ketenimine **3a** was consumed with concurrent formation of **4a** and **5a**, indicating that **3a** could well be the intermediate of the present reaction. Two other products **6a**[14] and **7a**[15] were also isolated (See Supporting Information). Under standard conditions in the presence of TEMPO or BHT, the yield of the product **4a** was not significantly affected, and products resulting from the radical recombination with nitroxyl radical were not detected.



Scheme 4. Control experiments.



Scheme 5. Mechanistic hypothesis.

Based on these results, a possible reaction pathway is depicted in Scheme 5. Oxidative addition of allyl carbonate **2** to Pd(0) followed by decarboxylation would generate the π-allyl Pd complex **B** which is in equilibrium with the (η^1-allyl) Pd species **B'**. Migratory insertion from **B'** would generate the imidoylpalladium intermediate **C**.[16] β-Hydride elimination would furnish ketenimine **3** and $HPd^{II}L(OEt)$ species. The latter would, upon reductive elimination, regenerate the Pd(0) species **A**. On the other hand, C-N bond homolysis of ketenimine **3** would afford radical pairs **D** and **E**. The radical recombination of **D** and **E** via C-C bond formation afforded **4** and its regioisomer **5**. The fact that the products resulting from the dimerization of **D** and **E** and the minimum impact of TEMPO on the reaction outcome were also in line with the fact that the **D** and **E** were formed as a caged radical pair. The reverse ene reaction of ketenimine **3** via a six-membered transition state could account for the formation of minor products **6** and **7**.[17]

Conclusion

In conclusion, we developed a novel palladium-catalyzed 1,1-carbocyanation of allyl carbonate **2** by α,α-disubstituted α-isocyanoacetate **1**. Formation of ketenimine **3** followed by homolysis of the C-N bond and recombination of the resulting caged radical pair was proposed to account for the formation of the β-cyano-γ,δ-unsaturated ester **4**.

3. Experimental section

General procedure for the synthesis of 4

In a dry sealed tube was added the allyl carbonate **2** (0.1 mmol) and the isocyanide **1** (0.11 mmol) in dry DCE (1 mL) and the reaction mixture was stirred for 1 min before the addition of $Pd(PPh_3)_4$ (10 mol%). The reaction mixture was allowed to stir at 55 °C until complete consumption of the allyl carbonate (about 1 hour). Then, the reaction was cooled down to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: PE:EtOAc 10:1) to afford the products as a mixture of **4** and **5** (yellow oil). Compound **4** can be isolated by multiple elution on preparative TLC (eluent: PE:EtOAc 50:1).

*4.1. Ethyl (E)-2-(1-cyano-3-phenylallyl)-2,3-dihydro-1H-indene-2-carboxylate (**4a**)*

19.6 mg, 60% yield (from (*E*)-ethyl(3-phenylallyl) carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 - 7.24 (m, 3H), 7.23 - 7.17 (m, 6H), 6.73 (d, *J* = 15.7 Hz, 1H), 5.95 (dd, *J* = 15.7, 7.3 Hz, 1H), 4.32 - 4.19 (m, 2H), 3.92 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.67 (d, *J* = 16.8 Hz, 1H), 3.63 (d, *J* = 16.7 Hz, 1H), 3.32 (d, *J* = 16.6, 1H), 3.28 (d, *J* = 16.8, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 173.6, 140.0, 139.95, 136.1, 135.6, 128.8, 128.6, 127.4, 126.8, 124.5, 119.6, 118.4, 62.1, 56.3, 42.0, 40.9, 40.9, 14.3. IR υ (cm^{-1}): 2934 (br), 2357 (w), 2340 (w), 1729 (s), 1487 (w), 1461 (w), 1448 (w), 1302 (w), 1259 (w), 1201 (s), 1095 (w), 1073 (w), 1048 (w), 967 (m), 744 (s), 693 (m). HRMS (APPI) calcd for $C_{22}H_{22}NO_2^+$ [M+H$^+$] 332.1645; found 332.1637.

*4.2. Ethyl (E)-2-(1-cyano-3-(o-tolyl)allyl)-2,3-dihydro-1H-indene-2-carboxylate (**4b**)*

15.9 mg, 46 % yield (from (*E*)-ethyl (3-(*o*-tolyl)allyl) carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 4H), 7.18 - 7.07 (m, 3H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 15.6 Hz, 1H), 5.81 (dd, *J* = 15.6, 7.4 Hz, 1H), 4.31 - 4.18 (m, 2H), 3.94 (dd, *J* = 7.4, 1.3 Hz, 1H), 3.65 (d, *J* = 16.8 Hz, 1H), 3.58 (d, *J* = 16.4 Hz, 1H) 3.28 (d, *J* = 16.4 Hz, 1H), 3.24 (d, *J* = 16.8 Hz, 1H), 2.31 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 140.1, 140.0, 135.9, 135.0, 134.3, 130.4, 128.5, 127.4, 126.3, 126.3, 124.5, 121.0, 118.5, 62.1, 56.2, 42.3, 41.1, 40.8, 19.9, 14.3. IR υ (cm^{-1}): 2978 (br), 2358 (m), 2343 (m), 1730 (s), 1484 (w), 1460 (w), 1303 (w), 1258 (w), 1203 (m), 1048 (w), 967 (w), 744 (m), 636 (m), 628 (m), 615 (s). HRMS (ESI) calcd for $C_{23}H_{23}NO_2Na^+$ [M+Na$^+$] 368.1621; found 368.1626.

*4.3. Ethyl (E)-2-(1-cyano-3-(p-tolyl)but-2-en-1-yl)-2,3-dihydro-1H-indene-2-carboxylate (**4c**)*

22.0 mg, 61% yield (from (*E*)-ethyl (3-(*p*-tolyl)but-2-en-1-yl) carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 4H), 7.12-7.05 (m, 4H), 5.56 (dq, *J* = 9.9, 1.6 Hz, 1H), 4.28 - 4.18 (m, 2H), 4.00 (d, *J* = 9.9 Hz, 1H), 3.60 (d, *J* = 16.5 Hz, 1H), 3.59 (d, *J* = 16.0 Hz, 1H), 3.25 (d, *J* = 16.0 Hz, 1H), 3.22 (d, *J* = 16.8 Hz, 1H), 2.33 (s, 3H), 2.03 (d, *J* = 1.6 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 142.5, 140.2, 140.0, 139.3, 138.0, 129.2, 127.4, 127.3, 126.0, 124.7, 124.5, 119.0, 117.3, 62.0, 56.6, 41.0, 40.7, 37.4, 21.2, 16.9, 14.3. IR υ (cm^{-1}) : 2927 (br), 2364 (m), 2341 (w), 2330 (w), 1731 (s), 1513 (w), 1461 (m), 1305 (w), 1259 (m), 1196 (s), 1047 (w), 1023 (w), 814 (m), 742 (m), 652 (m). HRMS (ESI) calcd for $C_{24}H_{25}NO_2Na^+$ [M+Na$^+$] 382.1778; found 382.1768.

*4.4. Ethyl (E)-2-(1-cyano-3-(2-methoxyphenyl)allyl)-2,3-dihydro-1H-indene-2-carboxylate (**4d**)*

19.5 mg, 54 % yield (from (*E*)-ethyl (3-(2-methoxyphenyl)allyl) carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.17 (m, 5H), 7.07 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.00 (d, *J* = 15.8 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.97 (dd, *J* = 15.8, 7.7 Hz, 1H), 4.27 - 4.21 (m, 2H), 3.91 (dd, *J* = 7.7, 1.3 Hz, 1H), 3.81 (s, 3H), 3.62 (d, *J* = 16.8, 1H), 3.57 (d, *J* = 16.8, 1H), 3.28 (d, *J* = 16.8 Hz, 1H), 3.25 (d, *J* = 16.4 Hz, 1H),1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 157.0, 140.2, 140.1, 131.5, 129.7, 127.5, 127.3, 127.3, 124.7, 124.5, 124.5, 120.7, 120.0, 118.7, 110.9, 62.0, 56.4, 55.5, 42.5, 40.9, 40.8, 14.3. IR υ (cm^{-1}): 2942 (br), 2358 (w), 2340 (w), 1730 (s), 1598 (w), 1579 (w), 1488 (m), 1462 (m), 1437 (w), 1299 (m), 1202 (m), 1113 (w), 1095 (w), 1050 (m), 1026 (m), 970 (m), 861 (w), 750 (s), 758 (s), 784 (w), 794 (w), 802 (w), 672 (w), 686 (w). HRMS (ESI) calcd for $C_{23}H_{23}NO_3Na^+$ [M+Na$^+$] 384.1570; found 384.1580.

*4.5. Ethyl (E)-2-(1-cyano-3-(3-methoxyphenyl)allyl)-2,3-dihydro-1H-indene-2-carboxylate (**4e**)*

16.2 mg, 45% yield (from (*E*)-ethyl (3-(3-methoxyphenyl)allyl) carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 - 7.20 (m, 4H), 6.86 - 6.82 (m, 2H), 6.74 - 6.70 (m, 2H), 5.95 (dd, *J* = 15.6, 8.4 Hz, 1H), 4.29 - 4.24 (m, 2H), 3.94 (dd, *J* = 7.5, 1.4 Hz, 1H), 3.81 (s, 3H), 3.65 (d, *J* = 16.8 Hz, 1H), 3.60 (d, *J* = 16.8 Hz, 1H), 3.28 (d, *J* = 16.8 Hz, 2H), 3.26 (d, *J* = 16.4 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.9, 140.0, 140.0, 137.0, 136.0, 129.8, 127.4, 124.5, 124.5, 119.9, 119.4, 118.4, 114.4, 112.0, 62.1, 56.3, 55.4, 42.0, 41.0, 40.9, 14.3. IR υ (cm^{-1}): 2933 (w), 2023 (w), 1732 (s), 1599 (m), 1580 (m), 1488 (m), 1458 (m), 1434 (m), 1367 (w), 1292 (m), 1264 (s), 1200 (m), 1158 (m), 1169 (m), 1097 (w), 1046 (m), 969 (m), 864 (w), 799 (w), 778 (m), 759 (m), 749 (m), 690 (w), 680 (w), 654 (w). HRMS (ESI) calcd for $C_{23}H_{23}NO_3Na^+$ [M+Na$^+$] 384.1570; found 384.1577.

*4.6. Ethyl (E)-2-(1-cyano-3-(4-methoxyphenyl)allyl)-2,3-dihydro-1H-indene-2-carboxylate (**4f**)*

21.2 mg, 59% yield (from (*E*)-ethyl (3-(4-methoxyphenyl)allyl) carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 4H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 15.7 Hz, 1H), 5.80 (dd, *J* = 15.6, 8.4 Hz, 1H), 4.26 - 4.20 (m, 2H), 3.88 (dd, *J* = 7.5, 1.4 Hz, 1H), 3.80 (s, 3H), 3.61 (d, *J* = 16.4 Hz, 1H), 3.57 (d, *J* = 16.0 Hz, 1H), 3.25 (d, *J* = 16.4 Hz, 1H), 3.24 (d, *J* = 16.4 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 160.0, 140.1, 140.0, 135.6, 128.4, 128.1, 127.3, 124.5, 118.6, 117.2, 114.2, 114.2, 62.0, 56.4, 55.5, 42.1, 40.9, 14.3. IR υ (cm^{-1}): 2938 (br), 2363 (w), 2335 (w), 1730 (s), 1606 (m), 1511 (s), 1250 (s), 1176 (s), 1199 (m), 1302 (m), 1034 (m), 969 (m), 848 (w), 745 (m), 666 (w), 776 (w), 1094 (w), 1113 (w), 1367 (w), 1441 (w), 1462 (m), 1486 (w). HRMS (ESI) calcd for $C_{23}H_{24}NO_3^+$ [M+H$^+$] 362.1751; found 362.1758.

*4.7. Ethyl (E)-2-(3-(benzo[d][1,3]dioxol-5-yl)-1-cyanoallyl)-2,3-dihydro-1H-indene-2-carboxylate (**4g**)*

19.2 mg, 51% yield (from (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)allyl ethyl carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 4H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.69 - 6.66 (m, 2H), 6.61 (d, *J* = 15.4 Hz, 1H), 5.95 (s, 2H), 5.76 (dd, *J* = 15.6, 8.0 Hz, 1H), 4.27 - 4.19 (m, 2H), 3.88 (dd, *J* = 7.3, 1.2 Hz, 1H), 3.61 (d, *J* = 17.6 Hz, 1H), 3.56 (d, *J* = 17.2 Hz, 1H), 3.24 (d, *J* = 16.4, 1H), 3.22 (d, *J* = 16.4, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 148.2, 148.1, 140.1, 140.0, 135.7, 130.0, 127.4, 124.5, 121.8, 118.5, 117.7, 108.5, 106.0, 101.4, 62.0, 56.3, 42.0, 41.0, 40.9, 14.3. IR υ (cm^{-1}): 3031 (m), 2340 (m), 2162 (s), 2153 (m), 1802 (m), 1729 (s), 1504 (s), 1489 (s), 1446 (s), 1253 (s), 1204 (s), 1040 (s), 971 (s), 962 (m), 938 (s), 929 (s), 808 (s), 799 (m), 776 (s), 745 (s), 725 (s), 715 (m), 695 (s), 671 (m), 657 (s). HRMS (ESI) calcd for $C_{23}H_{22}NO_4^+$ [M+H$^+$] 376.1543 ; found 376.1556.

*4.8. Ethyl (E)-2-(1-cyano-3-(naphthalen-2-yl)allyl)-2,3-dihydro-1H-indene-2-carboxylate (**4h**)*

16.0 mg, 42% yield (from (*E*)-ethyl (3-(naphthalen-2-yl)allyl) carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 - 7.74 (m, 3H), 7.58 (s, 1H), 7.51 - 7.42 (m, 2H), 7.34 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.20 (s, 4H), 6.88 (d, *J* = 15.7 Hz, 1H), 6.05 (dd, *J* = 16.0, 7.6 Hz, 1H), 4.30 - 4.22 (m, 2H), 3.98 (dd, *J* = 7.3, 1.4 Hz, 1H), 3.66 (d, *J* = 16.4 Hz, 1H), 3.60 (d, *J* = 16.8 Hz, 1H), 3.30 (d, *J* = 16.4 Hz, 1H), 3.27 (d, *J* = 16.4 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 140.1, 136.1, 133.5, 133.4, 133.0, 128.5, 128.3, 127.8, 127.4, 127.2, 126.6, 126.5, 124.5, 124.5, 123.5, 119.9, 118.5, 62.1, 56.4, 42.2, 41.1, 40.9, 14.3. IR υ (cm^{-1}): 3239 (m), 2361 (m), 2314 (br), 2154 (m), 2091

(w), 2042 (w), 2022 (s), 1967 (m), 1767 (m), 1728 (s), 1299 (m), 1271 (m), 1206 (br), 887 (m), 843 (m), 783 (s), 765 (s), 743 (s), 711 (s). HRMS (ESI) calcd for $C_{26}H_{24}NO_2^+$ [M+H$^+$] 382.1802 ; found 382.1804.

*4.9. Ethyl (E)-2-(3-(4-chlorophenyl)-1-cyanoallyl)-2,3-dihydro-1H-indene-2-carboxylate (**4i**)*

17.1 mg, 47% yield (from (*E*)-3-(4-chlorophenyl)allyl ethyl carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.19 (s, 4H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 15.7 Hz, 1H), 5.90 (dd, *J* = 15.7, 7.2 Hz, 1H), 4.27 - 4.21 (m, 2H), 3.91 (dd, *J* = 7.2, 0.8 Hz, 1H), 3.63 (d, *J* = 16.8 Hz, 1H), 3.57 (d, *J* = 16.4 Hz, 1H), 3.24 (d, *J* = 16.4 Hz, 1H), 3.22 (d, *J* = 16.4 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 140.0, 134.8, 134.5, 131.9, 128.3, 127.4, 124.5, 124.4, 122.6, 120.4, 118.2, 62.1, 56.2, 42.0, 41.1, 40.8, 14.3. IR υ (cm^{-1}): 2927 (br), 2341 (m), 1730 (s), 1490 (m), 1461 (m), 1305 (w), 1259 (w), 1196 (m), 1087 (w), 1047 (w), 1012 (w), 972 (w), 811 (w), 745 (m), 669 (m). HRMS (APPI) calcd for $C_{22}H_{21}ClNO_2^+$ [M+H$^+$] 366.1255; found 366.1254.

*4.10. Ethyl (E)-2-(3-(4-bromophenyl)-1-cyanoallyl)-2,3-dihydro-1H-indene-2-carboxylate (**4j**)*

21.8 mg, 53% yield (from (*E*)-3-(4-bromophenyl)allyl ethyl carbonate and ethyl 2-isocyano-2,3-dihydro-1*H*-indene-2-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.19 (s, 4H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 16.0 Hz, 1H), 5.92 (dd, *J* = 15.7, 7.2 Hz, 1H), 4.32-4.17 (m, 2H), 3.91 (dd, *J* = 7.2, 0.8 Hz, 1H), 3.63 (d, *J* = 16.8 Hz, 1H), 3.57 (d, *J* = 16.4 Hz, 1H), 3.24 (d, *J* = 16.8 Hz, 1H), 3.21 (d, *J* = 16.4 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 140.0, 134.7, 134.4, 134.1, 129.0, 128.0, 127.4, 124.5, 124.5, 120.3, 118.3, 62.1, 56.3, 42.0, 41.1, 40.8, 14.3. IR υ (cm^{-1}): 2924 (br), 2360 (m), 2341 (w), 1732 (s), 1492 (m), 1460 (m), 1445 (w), 1406 (w), 1367 (w), 1302 (m), 1256 (m), 1199 (m), 1090 (m), 1042 (w), 1014 (m), 969 (w), 807 (m), 769 (w), 742 (m), 669 (w). HRMS (APPI) calcd for $C_{22}H_{21}{}^{79}BrNO_2^+$ [M+H$^+$] 410.0750; found 410.0748.

*4.11. Ethyl (E)-1-(1-cyano-3-phenylallyl)cyclopentane-1-carboxylate (**4k**)*

13.0 mg, 46% yield (from (*E*)-ethyl(3-phenylallyl) carbonate and ethyl 1-isocyanocyclopentane-1-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.27 (m, 5H), 6.75 (dd, *J* = 15.8, 1.5 Hz, 1H), 6.00 (dd, *J* = 15.8, 6.9 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.97 (dd, *J* = 6.9, 1.5 Hz, 1H), 2.27 - 2.14 (m, 2H), 1.90 (m, 1H), 1.85 - 1.68 (m, 5H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 135.7, 135.6, 128.9, 128.6, 126.8, 120.4, 119.0, 61.6, 56.1, 42.4, 36.3, 33.5, 26.0, 25.8, 14.3. IR υ (cm^{-1}): 2959 (br), 2023 (m), 1448 (m), 1183 (br), 1032 (m), 969 (m), 756 (s), 696 (m), 667 (m), 1727 (s). HRMS (ESI) calcd for $C_{18}H_{21}NO_2Na^+$ [M+Na$^+$] 306.1465; found 306.1475.

*4.12. Ethyl (E)-1-(1-cyano-3-phenylallyl)cyclobutane-1-carboxylate (**4l**)*

10.0 mg, 34% yield (from (*E*)-ethyl(3-phenylallyl) carbonate and ethyl 1-isocyanocyclobutane-1-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.27 (m, 5H), 6.78 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.95 (d, *J* = 6.7 Hz, 1H), 2.59 - 2.45 (m, 2H), 2.38 - 2.22 (m, 2H), 2.12 - 2.00 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 135.7, 135.6, 128.9, 128.6, 126.8, 119.1, 118.5, 61.6, 49.3, 41.5, 29.4, 27.1, 15.6, 14.4. IR υ (cm^{-1}): 2952 (br), 2370 (m), 2177 (m), 2017 (m), 1970 (m), 2189 (m), 1730 (s), 1721 (s), 1650 (w), 1558 (w), 1542 (w), 1457 (m), 1206 (s), 1254 (m), 1266 (m), 718 (s), 965 (m), 808 (w), 1013 (m). HRMS (ESI) calcd for $C_{17}H_{19}NO_2Na^+$ [M+Na$^+$] 292.1308; found 292.1323.

*4.13. Ethyl (E)-1-(1-cyano-3-phenylallyl)cyclohexane-1-carboxylate (**4m**)*

17.4 mg, 59% yield (from (*E*)-ethyl(3-phenylallyl) carbonate and ethyl 1-isocyanocyclohexane-1-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 - 7.27 (m, 5H), 6.69 (d, *J* = 15.8 Hz, 1H), 5.98 (dd, *J* = 15.8, 7.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.64 (d, *J* = 7.4 Hz, 1H), 2.22 (d, *J* = 9.4 Hz, 2H), 1.75 - 1.61 (m, 4H), 1.53 - 1.40 (m, 4H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 135.9, 135.7, 128.9, 128.6, 126.8, 119.2, 118.1, 61.4, 50.3, 44.5, 33.3, 30.7, 25.4, 23.3, 23.0, 14.4. IR υ (cm^{-1}): 2940 (br), 2368 (w), 2329 (w), 2163 (m), 2152 (m), 2065 (w), 2009 (m), 1944 (w), 1733 (s), 1448 (m), 1214 (s), 1134 (s), 739 (m), 681 (s). HRMS (ESI) calcd for $C_{19}H_{23}NO_2Na^+$ [M+Na$^+$] 320.1621; found 320.1623.

*4.14. Ethyl (E)-1-(1-cyano-3-phenylallyl)cyclopent-3-ene-1-carboxylate (**4n**)*

12.0 mg, 42% yield (from (*E*)-ethyl(3-phenylallyl) carbonate and ethyl 1-isocyanocyclopent-3-ene-1-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 6.77 (dd, *J* = 15.7, 1.5 Hz, 1H), 5.99 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.66 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.92 (dd, *J* = 7.1, 1.5 Hz, 1H), 3.02 (d, *J* = 17.6 Hz, 1H), 2.97 (d, *J* = 17.2 Hz, 1H), 2.67 (d, *J* = 16.0 Hz, 1H), 2.61 (d, *J* = 15.2 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 136.0, 135.7, 135.6, 128.9, 128.6, 128.5, 128.3, 126.8, 119.6, 118.6, 61.9, 54.3, 42.4, 42.0, 41.0, 14.3. IR υ (cm^{-1}): 2973 (br), 2359 (s), 2326 (br), 2234 (w), 2160 (m), 2147 (m), 1990 (m), 1965 (m), 1955 (m), 1841 (w), 1733 (s), 1541 (m), 1509 (m), 1451 (m), 1264 (m), 1200 (s). HRMS (ESI) calcd for $C_{18}H_{19}NO_2Na^+$ [M+Na$^+$] 304.1313; found 304.1320.

*4.15. Ethyl (E)-4-(1-cyano-3-phenylallyl)tetrahydro-2H-pyran-4-carboxylate (**4o**)*

6.0 mg, 20% yield (from (*E*)-ethyl(3-phenylallyl) carbonate and ethyl 4-isocyanotetrahydro-2*H*-pyran-4-carboxylate), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.27 (m, 5H), 6.72 (dd, *J* = 15.7, 1.2 Hz, 1H), 5.96 (dd, *J* = 15.7, 7.4 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.98 - 3.89 (m, 2H), 3.65 (dd, *J* = 7.4, 1.3 Hz, 1H), 3.52 (dt, *J* = 12.0, 2.2 Hz, 1H), 3.42 (dt, *J* = 12.1, 2.1 Hz, 1H), 2.22 - 2.12 (m, 2H), 1.93 - 1.86 (m, 1H), 1.86 - 1.80 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 136.6, 135.4, 128.9, 128.9, 126.9, 118.1, 117.41, 65.2, 65.1, 61.9, 48.2, 44.4, 32.8, 31.0, 14.4. IR υ (cm^{-1}): 2959 (br), 2359 (w), 2341 (w), 2164 (s), 2153 (m), 2028 (w), 1967 (w), 1875 (w), 1804 (w), 1730 (s), 1216 (m), 1200 (m), 1031 (w), 1013 (w), 759 (s), 732 (m), 723 (m), 687 (m). HRMS (ESI) calcd for $C_{18}H_{21}NO_3Na^+$ [M+Na$^+$] 322.1414; found 322.1417.

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