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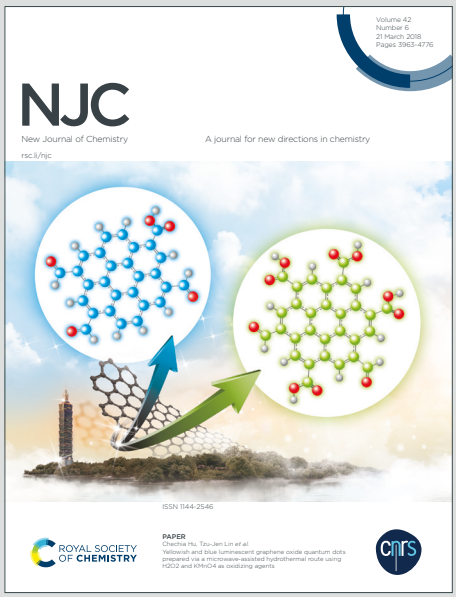

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Infrared spectroscopic detection of ketene formation from carbene and CO source: amide synthesis

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Abstract:

Synthesis and transformation of ketene into desired organic molecule is one of the methodologies widely used in synthetic organic chemistry, however there are only few reports available for the detection of ketenes (not free ketene but ketene complex of transition metal complexes) by using expensive techniques. Nevertheless, there is no report available to detect the ketene directly. In this regard we have developed a methodology to make amides via ketene formation by using diazo compounds, [$Co_2(CO)_8$] as a carbonyl source and suitable amines, and detected the ketene formation with the help of IR spectroscopy. The non-gaseous carbonyl source, [$Co_2(CO)_8$] mediated carbonylation of ethyl 2-diazo-2-phenylacetate produced ketene as key intermediate. The transformation of ketene to amide has been achieved by the nucleophilic addition of amine. We have also taken an effort to detect the formation of ketene intermediate from the reaction between ethyl 2-diazo-2-phenylacetate and [$Co_2(CO)_8$] in the absence of nucleophile. The IR spectroscopy revealed the formation of ketene followed by the transformation of ketene to amide by further addition of amine. The progress of the reaction has been monitored with function of time by using IR spectroscopy. Furthermore, all the newly synthesized amides have been fully characterized by using standard spectroscopic and analytical techniques.

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Introduction

The chemistry of ketene is a dynamic area of research in both synthetic and mechanistic aspects.[1] Ketenes are highly reactive, versatile intermediate for many organic transformations such as esters, amides, *β*-lactones, *β*-lactams.[1,2] The most prevalent methodology for the synthesis of ketene are thermolysis,[3]Wolf rearrangement,[4] dehydrogenation of acyl chloride,[5] and aza-Wittig reaction[6]. However all these methodologies suffer from their own limitations such as, narrow substrate scope along with the formation of undesired side products.[7] One of the prominent way of generation of ketene is carbonylation of carbene.[8] A large number of transition metal mediated generation of ketene from carbene using carbon monoxide has also been reported.[9] Bruin *et al*. reported a Rh-PNP complex which showed a stronger affinity towards binding ketene than any other metals.[7] Carbon monoxide mediated generation of ketene from carbene is one of the promising methods while other known methods suffer from their own drawbacks such as harsh reaction conditions, poor yield etc.[10] Transition metal catalyzed carbonylation of carbene precursors such as diazo compounds and tosylhydrazones using carbon monoxide is also been reported.[11] Wang *et al*. reported the generation of ketene through transition metal catalyzed carbonylation of carbene using CO gas and further reacted with nucleophiles to produce corresponding organic compounds and it has its own merits.[10-12]Nevertheless, handling of carbon monoxide is perilous owing to its toxicity and thus required adequate facilities.[13]

Metal carbonyls are good non-gaseous carbonyl source. Ungváry *et al*. reported dicobalt octacarbonyl as a non-gaseous CO-source for ketene generation by carbonylation of carbene generated from diazoacetate and the disadvantage of this method is one has to use equal molar concentration of metal carbonyl. The in situ generated ketene further can be scavenged by added nucleophiles or by N-substituted imines in a [2 + 2] cycloaddition reaction.[14-16]

In spite of its (ketene) greater utility, there is no reliable method to detect the formation of free ketene. The commonly used gravimetric, titrimetric and gas chromatography methods are not sound enough for trace analysis and highly decomposing compound like ketene;[17,18] Nevertheless the derivatized ketene could be detected by gas chromatography due to the increased stability.[19]The report for the spectrometric detection of the ketene dye, 1-acetyl-4-(4-nitrobenzylidene)-1,4-dihydropyridine which is formed by the addition of ketene with a 10:1 mixture of 4-(4-nitrobenzyl)-pyridine and 1-hydro-4-(4-nitrobenzyl)-pyridinium perchlorate could be interfered by the salts produced by the dyes.[20] A laser photolysis study with IR and UV-

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detection has been reported for the detection of ketene hydrate derived from diazoquinone.[21-23] Albeit, in all the cases ketene is detected in the derivatized form, however the ketene intermediate is not flourished as intrinsically.

Similarly, the mechanism involved in the metal catalyzed generation of ketene from diazo compounds is not clear. In the reaction mechanism, the formation of ketene is just inferred and not detected. Grotjahn *et al*. reported the first coordination of ketenes to *trans*-ClIr[P(^{i}Pr)$_3$]$_2$[24]; Hermann *et al*.[25] reported the synthesis and structures of η^2-ketene complexes by carbonylation of metallocarbenes (**Scheme 1**). Hoff *et al*. reported a mechanism involving metalloradical based conversion of diazo and CO to ketene and studied the carbonylation of diazoalkanes using $Cr_2(CO)_6(C_5R_5)_2$, (R=H, CH_3) and spectroscopically detected the formation of ketene along with two key intermediates in the reaction ($Cr(CO)_2$(ketene)(C_5R_5) and $Cr_2(CO)_5(C_5R_5)_2$).[26] Bruin *et al.* detected the formation of free phenyl ketene from β-lactam by ^{1}H NMR spectroscopy.[7] Ungvary *et al*. reported the mechanistic investigation of [$Co_2(CO)_8$] catalyzed carbonylation of ethyl diazoacetate. The reaction mechanism involves the formation of highly reactive ethoxycarbonyl ketene by intramolecular coupling of a carbonyl ligand with the ethoxycarbonyl carbene ligand.[27]

Scheme 1. Spectroscopically detected transition metal complex of ketene.

In continuation of our research in carbene related chemistry[28] and in aim to explore the chemistry of ketene, herein we reported the infrared spectroscopy supported detection of ketene. The transformation of ketene into amide is also been detected by IR spectroscopic technique.

Results and discussion

Recently we have reported the synthesis of amido esters through carbonylation of diazo compounds followed by nucleophilic addition reaction.[28e] In order to understand the mechanism of amide formation and to detect the ketene intermediate, we started our experiments with aliphatic amines (**Scheme 2)**. The aliphatic amines takes longer reaction time when compared to the aromatic amines therefore practically one can accomplish the ketene detection. And therefore we selected aliphatic amine as a nucleophile in order to detect the ketene using IR spectroscopy technique.

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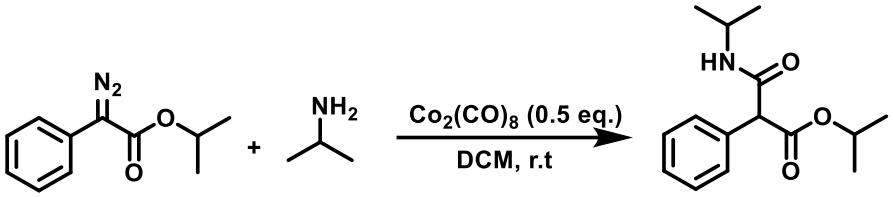
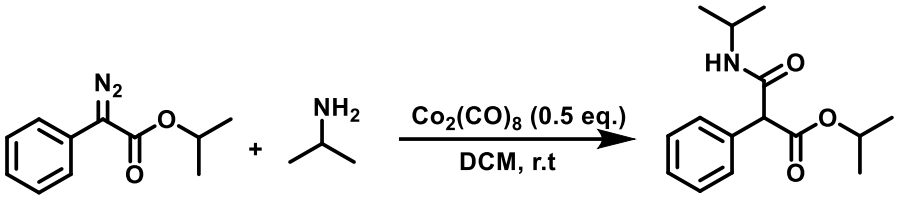


Scheme 2 Synthesis of amido esters through carbonylation of diazo compounds followed by nucleophilic addition reaction.

Table 1 Optimization of catalyst for aliphatic amine reaction with phenyldiazoester[a]



entry	metalcarbonyl[b]	time (h)	yield (%)[c]
1	$[Co_2(CO)_8]$	18	80
2	$[Fe_2(CO)_9]$	32	18
3	$[Mn_2(CO)_{10}]$	48	n.d

[a]All the reactions were carried out with 1 mmol of isopropyl amine and 1.1 mmol of phenyldiazoester in 5 mL of DCM in a Schlenk tube under dinitrogen atmosphere. [b]0.5 mmol of metal carbonyl was used. [c]Pure compound from column chromatography.

Initial screening did begin with metal carbonyls; the treatment of $[Co_2(CO)_8]$ (0.5 equiv., 0.5 mmol) with isopropyl amine (1 mmol) and isopropyl 2-diazo-2-phenylacetate (1.1 equiv., 1.10 mmol) using dichloromethane (5 mL) as the solvent yielded desired amido ester in 18 h with 87% yield (**Table 1, entry 1**). Replacement of $[Co_2(CO)_8]$ by $[Fe_2(CO)_9]$ and $[Mn_2(CO)_{10}]$ lead to longer reaction time and poor yield. The reaction with $[Fe_2(CO)_9]$ produced 18 % of amido ester in 32 h (**Table 1, entry 2**) and the reaction with $[Mn_2(CO)_{10}]$ did not produce expected product even after 48 h (**Table 1, entry 3**).

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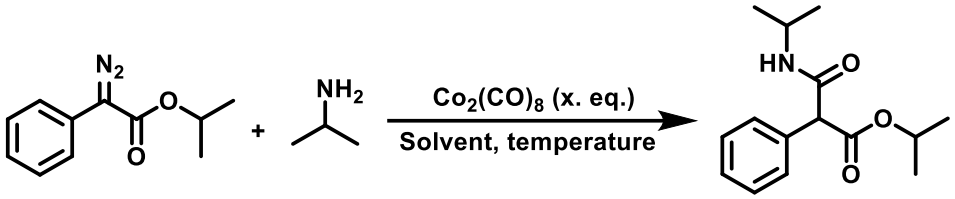
Table 2 Optimization of solvent, temperature and catalyst load[a]



entry	solvent	$[Co_2(CO)_8]$ (equiv)	time (h)	yield(%)[b]
1	DCM	0.5	18	80
2	Toluene	0.5	24	56
3	THF	0.5	24	34
4	CH_3OH	0.5	24	19
5	CH_3CN	0.5	24	n.d[c]
6	DCE	0.5	24	77
7	DCM	0.25	14	68
8	DCM	1.00	14	83
9	DCM	0.75	14	81
10	DCM	0.5	14	61[d]

[a]All the reactions were carried out with 1 mmol of isopropyl amine and 1.1 mmol of phenyldiazoester in 5 mL of solvent in a Schlenk tube under dinitrogen atmosphere. [b]Pure compound from column chromatography. [c]Expected product not detected. [d]Reaction carried out at 40 ºC.

With a suitable carbonyl source $[Co_2(CO)_8]$, we have carried out solvent screening. Toluene produced 56% of amido ester in 24 h (**Table 2, entry 2**) and THF produced 34% yield in 24 h (**Table 2, entry 3**). Methanol gave only 19% of desired amido ester along with trace amount of OH-addition product (**Table 2, entry 4**). In case of acetonitrile, expected product was not formed even after 48 h instead, carbene dimerization was taken place (**Table 2, entry 5**). DCE produced expected amido ester in 77% yield (**Table 2, entry 6**). Thus the solvent screening results revealed that the DCM is a better choice of solvent for the reaction. With DCM as an optimal solvent decreasing the $[Co_2(CO)_8]$ load to 0.25 equivalent reduced the yield to 68% (**Table 2, entry**

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7). Further increasing the catalyst load up to 0.75 and 1.0 equivalents produced the desired product in 81% and 83% yields, respectively (**Table 2, entry 9 and 8**). Since there is no significant change in the yield even by doubling the catalyst load, therefore 0.5 equivalent was decided as the optimal catalyst load. Raising the reaction temperature up to 40 ºC decreased the product yield along with increased carbene dimerization; therefore, the optimum reaction temperature was found to be room temperature.

The optimized condition was applied for the synthesis of amido esters using aliphatic amines as ketene scavenger. Keeping the isopropyl 2-diazo-2-phenylacetate as constant, aliphatic amines have been varied. As expected, all the aliphatic amines took longer time compared to the aromatic amines for completion of the reaction. Among all the aliphatic amines, methylamine produced less yield of 58%. *n*-propyl amine (**3d**) produced 82% amido ester and *iso*-propyl amine (**3a**) produced 80% of the product; likewise, *n*-butyl amine (**3c**) produced 81% yield and *tert*-butyl amine (**3b**) produced 75% yield. This might be attributed to the increase in the negative charge on the nitrogen atom of amine due to the +I effect of the alkyl group and bulkiness of the *tert*-butyl group. Dipropyl amine, cyclohexyl amine and dicyclohexyl amine produced 77, 82 and 85% yield, respectively (**3f – 3h**). Phenethylamine yielded 87% of the expected amido ester (**3i**) and 3,4-dimethoxy phenethylamine produced 84% yield (**3j**). 4-Fluorobenzylamine (**3k**), benzylamine (**3l**), 4-methoxy benzylamine (**3m**) and 4-methyl benzylamine (**3m**) produced 85, 92, 82 and 88% yields, respectively.

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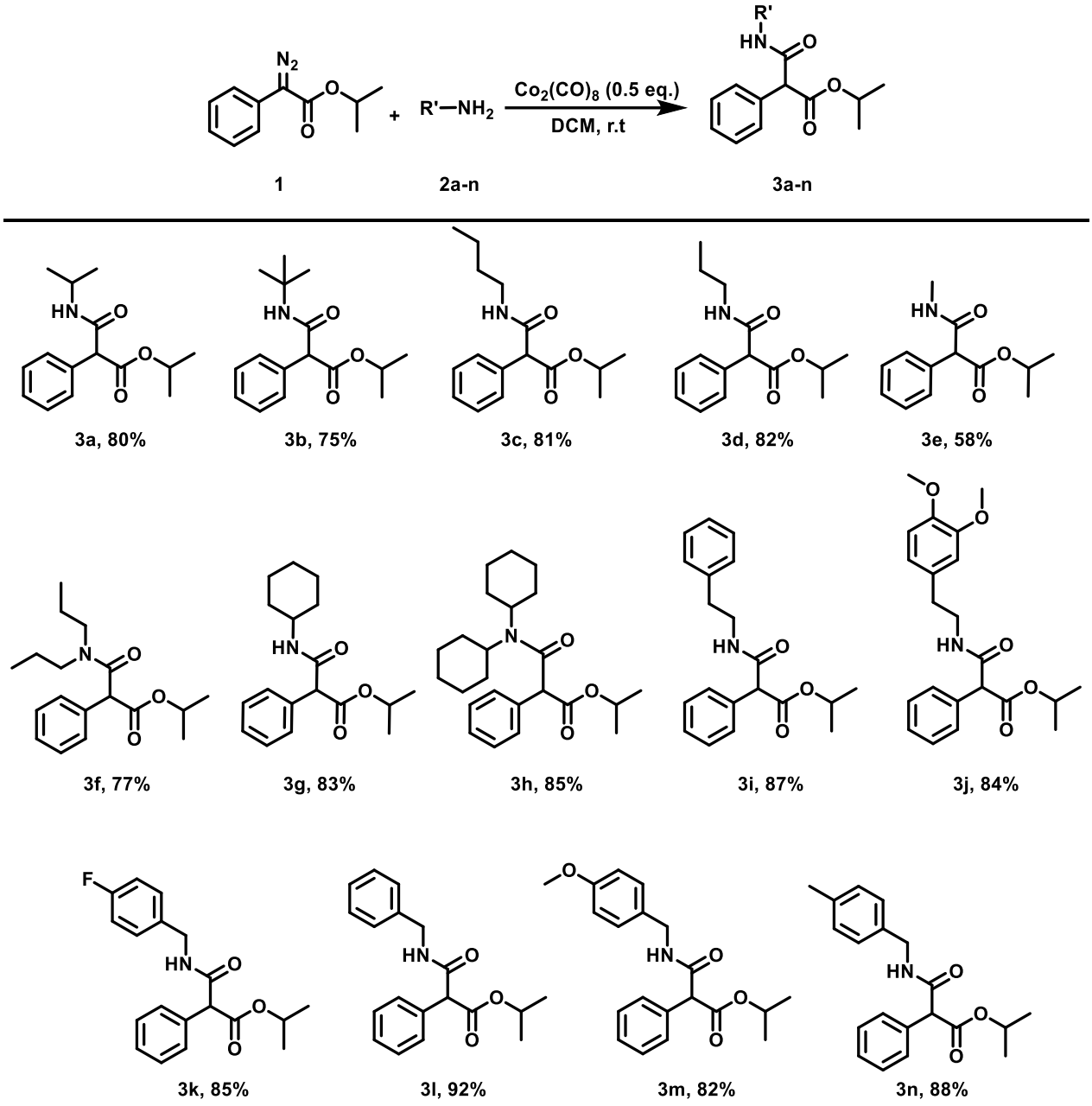
Scheme 3 Scope of amines for the synthesis of amido esters



Then the scope of diazoesters has been explored by changing different diazo esters. Among all the diazo esters screened, almost all of them produced good to better yields. As mentioned above, in this case also methylamine produced lesser yield (**6a**, **59%**). *n*-Butylamine produced 88 and 86% yields with 4-bromo substituted (**6b**) and ethylphenyldiazoacetate (**6c**), respectively. *iso*-

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Propylamine produced 71% and 68% yields with 4-bromo (**6d**) and 4-methyl substituted ethylphenyldiazoacetate (**6e**), respectively. Among all the benzyl amines, 4-bromo substituted ethylphenyldiazoacetate produced maximum yield of 94% (**6f**), methylphenyldiazoacetate (**6g**) and ethylphenyldiazoacetate (**6h**), produced 90% and 91% yields respectively. Both 2,4-dichloro (**6i**) and 4-fluoro (**6j**) substituted ethylphenyldiazoacetate yielded 88% of expected amido ester. In case of 4-methylbenzylamine, ethylphenyldiazoacetate (**6k**) gave 88% yield and methylphenyldiazoacetate (**6l**) produced 81% yield. 4-Methyl (**6m**) and 4-bromo (**6n**) substituted ethylphenyldiazoacetate yielded 89% and 83% of desired amido ester. Ethylphenyldiazoacetate gave 81% yield with 4-fluoro benzylamine (**6o**).

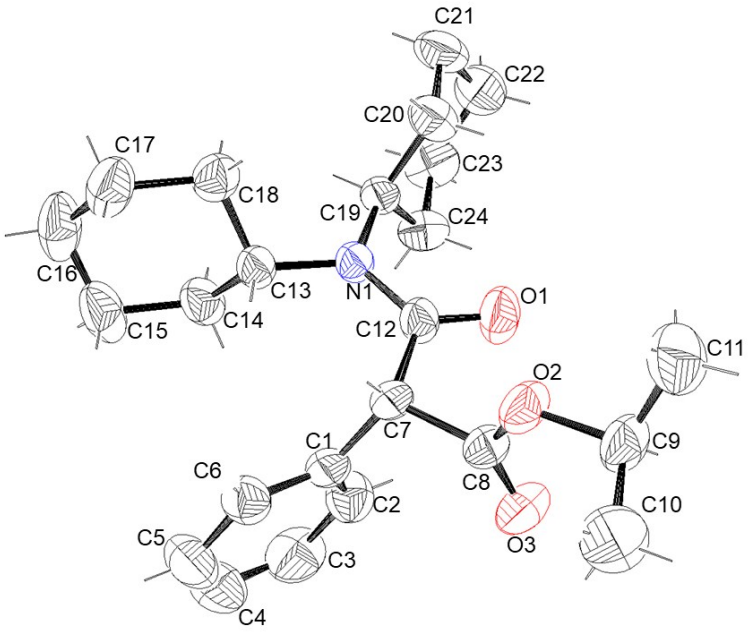

Fig. 1 Molecular structure of **3h** (hydrogen atoms are omitted for clarity). Thermal ellipsoids are set at 50 % probability (**CCDC:1948319**).

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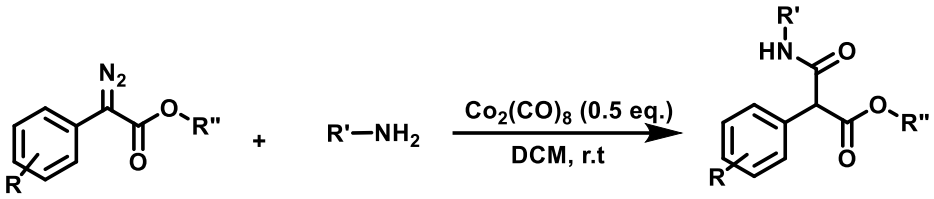
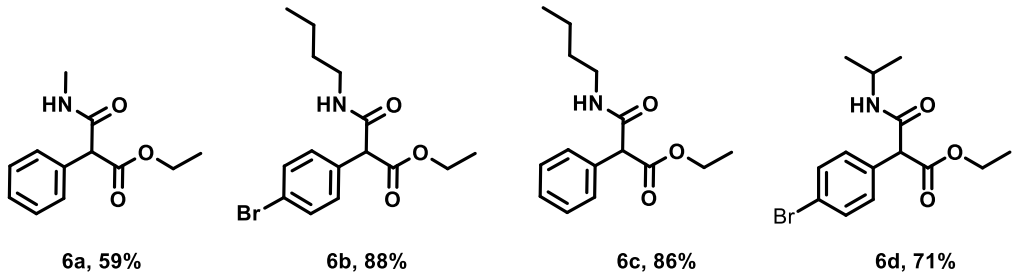
Scheme 4 Scope of diazo compounds for the synthesis of amido esters



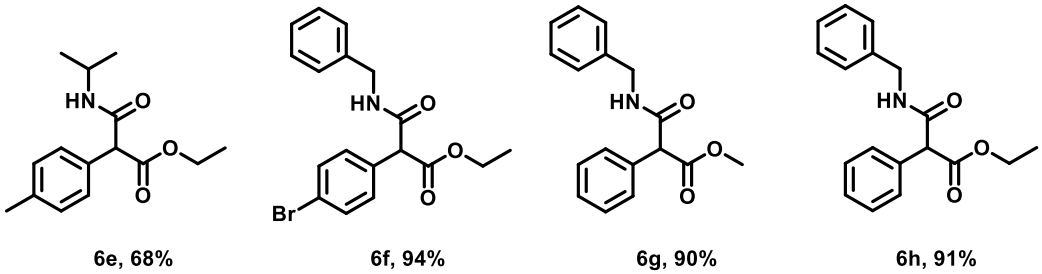
4a; R=H, R"=Et
4b; R=Me, R"=Et
4c; R=Br, R"=Et
4d; R=H, R"=Me
4e; R=2,4-Cl, R"=Et
4f; R=F, R"=Et

5a; R' = Me
5b; R' = *n*-Pr
5c; R' = *n*-Bu
5d; R' = *i*-Pr
5e; R' = Bn
5f; R' = 4-Me-Bn
5g; R' = 4-F-Bn

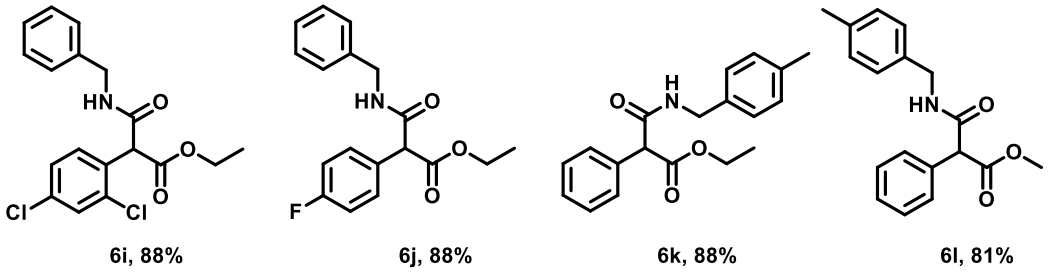
6a-o



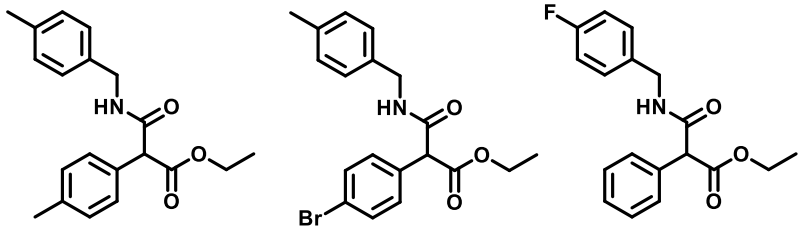
6a, 59% 6b, 88% 6c, 86% 6d, 71%



6e, 68% 6f, 94% 6g, 90% 6h, 91%



6i, 88% 6j, 88% 6k, 88% 6l, 81%



6m, 89% 6n, 83% 6o, 81%

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Detection of ketene intermediate using IR – spectroscopy

After exploring the substrate scope, in order to obtain more evidence for the formation of ketene pro-reactive intermediate, we used infrared spectroscopy technique. IR experiment has been carried out for the reaction of ethyl 2-diazo-2-phenylacetate with isopropylamine in the presence of [$Co_2(CO)_8$] and spectra has been recorded during the course of the reaction at various time intervals.

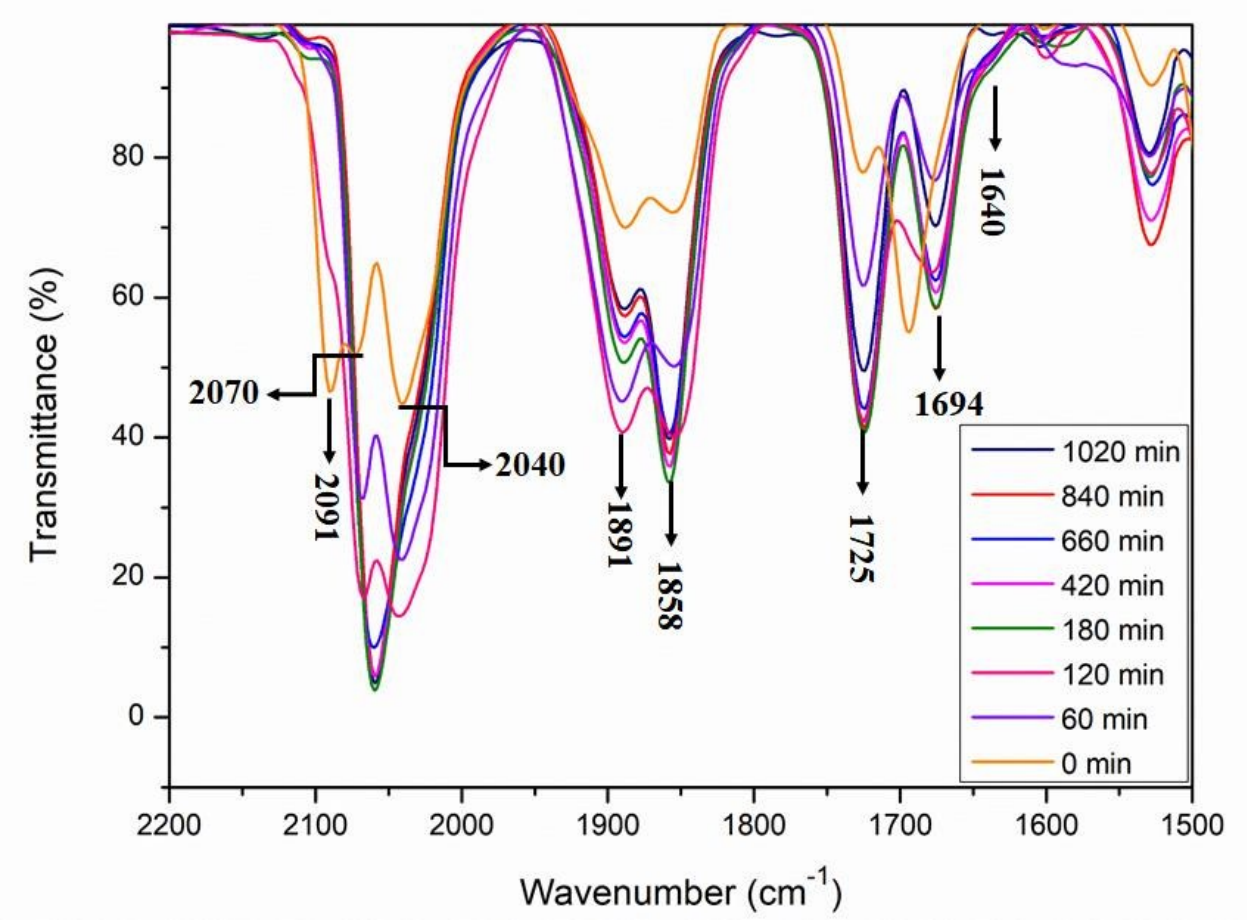

Fig. 2 FTIR spectra recorded during the course of the reaction of [$Co_2(CO)_8$] with ethyl-2-diazo-2-phenylacetate at 25 °C in DCM (in a sealed reaction tube fitted with septa). Band at 2091 cm^{-1} is assigned to N-N stretching of ethyl-2-diazo-2-phenylacetate; band at 1891cm^{-1} is assigned to C=O stretching of ketene and band at 1640 cm^{-1} assigned to C=O stretching of amide.

To get a clear knowledge about the formation of ketene intermediate, the reaction was started with ethyl 2-diazo-2-phenylacetate and [$Co_2(CO)_8$] without addition of nucleophile (amine). During the course of the reaction, the ketene formation has been detected by infrared

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spectroscopy. As depicted in **Figure 2**, at 0 minute, the observed bands at 2070, 2040 and 1858 cm^{-1} can be attributed to unreacted $[Co_2(CO)_8]$ (**Figure S1**) and a band at 2091 cm^{-1} can be attributed to unreacted diazo (N_2 vibration) compound (**Figure S2**). Over a period of time the vibrational band at 2091 cm^{-1} which is attributed to N=N stretching of diazo compound started decreasing gradually, with simultaneous increase in intensity of the vibrational band at1891 cm^{-1}owing to the formation of ketene ($R_2C=C=O$). To confirm the transformation of ketene into amide, isopropyl amine has been added at this stage. The appearance of a new IR band at 1640 cm^{-1}, which corresponds to the C=O stretching frequency confirmed the formation of amide (amide band). The IR spectra showed a periodic decrease in the intensity of diazo compound and ketene band with the simultaneous increase in the intensity of C=O stretching band of amide. After 17 hr, the IR band corresponding to the diazo almost disappeared and the band corresponding to amide intensified to the maximum.

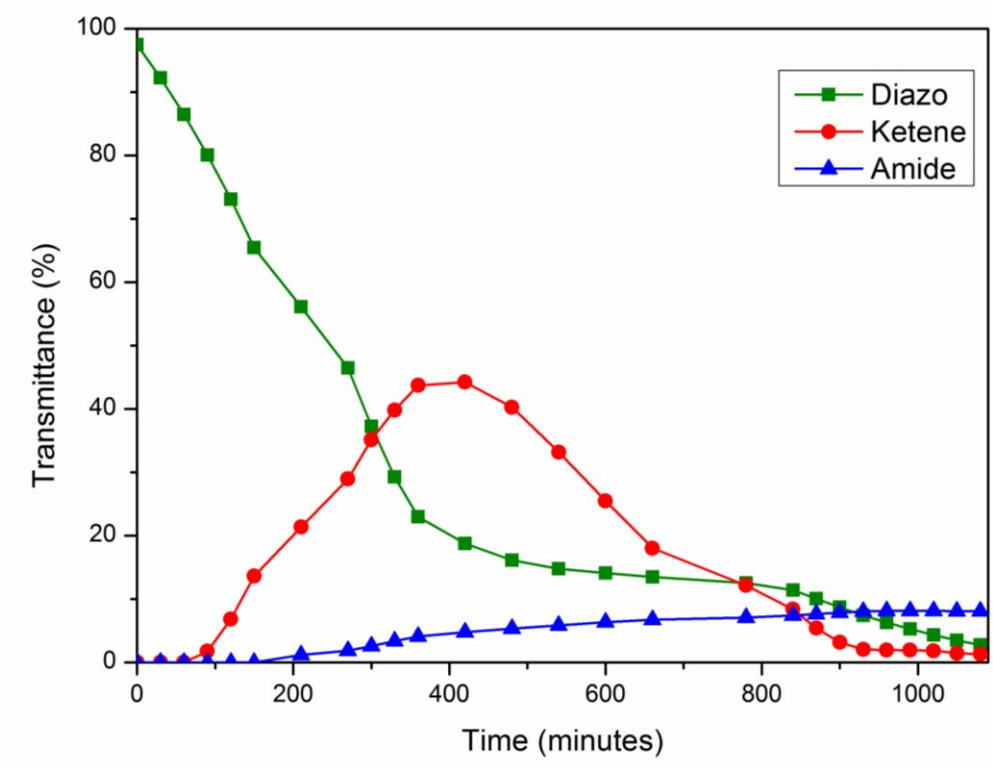

Fig. 3 Transmittance versus time plots for key species in reaction ofethyl-2-diazo-2-phenylacetate and $[Co_2(CO)_8]$. Transmittance bands of ethyl-2-diazo-2-phenylacetate at 2087 $cm^{-1}$and ketene at 1886 cm^{-1}.

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A transmittance versus time plot for the key species in the reaction is depicted in **Figure 3**. The graph shows a periodic decrease in the intensity of diazo and a gradual increase in the intensity of ketene band followed by decrease in the intensity with a simultaneous increase in the intensity of amide band (after addition of amine). Attempts have been made to characterize the metal carbonyl after the reaction however the results were not fruitful.

Conclusion

There are numerous reports for metal mediated ketene involved organic transformations. In all the cases, the formation of ketene is just inferred but not directly detected. Here we attempted to detect the ketene intermediate by using IR spectroscopy that formed during the course of formation of amide. The formation of amide from the reaction of carbene (generated from diazoester), amine and $[Co_2(CO)_8]$ was also been detected by infrared spectroscopy. The IR spectroscopic technique revealed the formation of ketene intermediate and further transformation of ketene into amide. The choice of aliphatic amine over aromatic amine made the ketene detection more viable due to the extended reaction time. All the newly synthesized amides have been fully characterized by using standard spectroscopic and analytical techniques. More research work related to carbene and ketene are under progress in our laboratory.

Experimental section

1. General Information. Unless and otherwise specified all the reactions were carried out with oven dried glassware under nitrogen atmosphere. All the solvents were distilled prior to use by using standard procedures. Dichloromethane was distilled from the CaH_2 and used. Amines were procured from Aldrich chemicals and used as received without any further purification. All the diazo compounds were prepared by following the standard literature procedures, characterized and confirmed by the spectral data.[21] TLC was performed on pre-coated silica gel 60 F254 on aluminum plates and UV light (254 nm). Column chromatography was performed on silica gel 100−200 mesh size. ^1H and ^{13}C NMR spectra were recorded on 400 MHz (^1H) and 100 MHz (^{13}C), Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references for ^1H NMR and ^{13}C NMR. HR-MS was recorded on UHD Q-TOF mass spectrometer. CCDC1948319 (for 3h) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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2. General procedure for IR control experiment:

The IR spectrum was recorded on a Perkin-Elmer spectrophotometer. A sealed reaction tube fitted with rubber septa was charged with [$Co_2(CO)_8$] (0.26 mmol), ethyldiazoacetate (0.52 mmol) and 5 mL of dichloromethane. The reaction was carried out at room temperature and IR spectrum was recorded for reaction mixture for every 30 min. DCM was used as background reference. After the observation of ketene band, isopropyl amine (0.57 mmol) was added to the reaction tube and the experiment was continued till the disappearance of N_2 stretching band of diazo compound.

3. General procedure for amine addition into ketene generated from diazo compounds (A). An oven dried 20 mL Schlenk flask was charged with amine (1 mmol) and [$Co_2(CO)_8$] (0.5 equiv.), then 5 mL of dichloromethane was added to the reaction mixture. Then a dichloromethane solution of diazo compound (1.1 mmol) was added dropwise to the reaction mixture and the reaction mixture was stirred at room temperature for 14 h. The completion of the reaction was monitored by TLC using appropriate mixture of hexane and ethyl acetate as an eluent. After completion of reaction, the reaction mixture was extracted with 15 mL (5 mL × 3) of diethyl ether. Then diethyl ether was evaporated under reduced pressure and the crude residue was purified using column chromatography on silica gel using hexane/ethyl acetate.

Isopropyl 3-(isopropylamino)-3-oxo-2-phenylpropanoate (3a). Prepared according to the general procedure A. Compound **3a** was isolated as a white solid in 80% yield (211 mg). Melting point: 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 5.2, 3.0 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.34 – 7.28 (m, 2H), 6.76 (t, J = 11.6 Hz, 1H), 5.04 (hept, J = 6.3 Hz, 1H), 4.43 (s, 1H), 4.07 (qt, J = 13.2, 6.6 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H), 1.16 (t, J = 6.6 Hz, 6H), 1.12 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.61, 166.48, 134.57, 129.05, 128.20, 77.48, 77.16, 76.84, 69.62, 58.82, 41.75, 22.59, 21.76, 21.52. IR (KBr) 3350, 3035, 2975, 2927, 2854, 1732, 1655, 1523, 1455, 1356, 1311, 1278, 1229, 1177, 1101, 1021, 972, 806, 742, 703, 605, 504 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{15}H_{22}NO_3$ m/z $[M + H]^+$: 264.1600; found: 264.1593.

Isopropyl 3-(tert-butylamino)-3-oxo-2-phenylpropanoate (3b). Prepared according to the general procedure A. Compound **3b** was isolated as a white solid in 75% yield (200 mg). Melting

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point: 135.8 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 5.0, 2.9 Hz, 1H), 7.37 (d, J = 1.3 Hz, 1H), 7.35 (d, J = 6.6 Hz, 1H), 7.34 – 7.32 (m, 1H), 7.32 – 7.27 (m, 1H), 6.73 (s, 1H, NH), 5.04 (hept, J = 6.3 Hz, 1H), 4.36 (s, 1H), 1.32 (s, 9H), 1.27 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.75, 166.42, 134.83, 129.02, 128.15, 77.48, 77.16, 76.84, 69.54, 59.70, 51.52, 28.67, 21.78, 21.54; IR (KBr) 3307, 3076, 2980, 2935, 1739, 1648, 1553, 1456, 1362, 1226, 1178, 1105, 966, 809, 711, 582 (cm^{-1}); HRMS calcd for $C_{16}H_{24}NO_3$ (ESI-MS) m/z $[M + H]^+$: 278.1756; found: 278.1755.

Isopropyl 3-(butylamino)-3-oxo-2-phenylpropanoate (3c). Prepared according to the general procedure A. Compound **3c** was isolated as a white solid in 81% yield (225 mg). Melting point: 121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dt, J = 3.6, 2.1 Hz, 2H), 7.35 (s, 1H), 7.31 (ddd, J = 11.9, 8.2, 5.4 Hz, 2H), 6.90 (s, 1H, NH), 5.05 (hept, J = 6.3 Hz, 1H), 4.46 (s, 1H), 3.25 (qd, J= 7.0, 1.0 Hz, 2H), 1.51 – 1.43 (m, 2H), 1.32 (dd, J = 15.2, 7.6 Hz, 2H), 1.27 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.59, 167.34, 134.55, 129.05 , 128.20, 77.48 , 77.16 , 76.84 , 69.62 , 58.86 , 39.54 , 31.48 , 21.75 , 21.51 , 20.09 , 13.79. IR (KBr) 3297, 3087, 2974, 2956, 2868, 1741, 1645, 1558, 1455, 1368, 1281, 1235, 1172, 1103, 984, 797, 702, 614 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{16}H_{24}NO_3$ m/z $[M + H]^+$: 278.1756; found: 278.1760.

Isopropyl 3-oxo-2-phenyl-3-(propylamino)propanoate (3d). Prepared according to the general procedure A. Compound **3d** was isolated as a white solid in 82% yield (216 mg). Melting point: 108°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.34 (ddd, J = 7.5, 4.8, 1.8 Hz, 2H), 7.31 – 7.27 (m, 1H), 6.92 (s, 1H), 5.04 (hept, J = 6.3 Hz, 1H), 4.46 (s, 1H), 3.20 (dd, J = 13.4, 6.5 Hz, 2H), 1.49 (dt, J = 14.6, 7.3 Hz, 2H), 1.26 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.52, 167.38, 134.50, 129.01, 128.18, 77.48, 77.16, 76.84, 69.58, 58.81, 41.42, 22.66, 21.72, 21.48, 11.34. IR (KBr) 3332, 3017, 2963, 2910, 2841, 1768, 1693, 1541, 1449, 1369, 1303, 1284, 1244, 1201, 1158, 1011, 985, 818, 740, 717, 622, 600, 534 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{15}H_{22}NO_3$, m/z $[M + H]^+$: 264.1600; found: 264.1594.

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Isopropyl 3-(methylamino)-3-oxo-2-phenylpropanoate (3e). Prepared according to the general procedure A. Compound **3e** was isolated as a white solid in 58% yield (137 mg). Melting point: 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.30 (m, 2H), 7.30 – 7.27 (m, 1H), 6.95 (s, 1H), 5.09 – 4.97 (m, 1H), 4.46 (s, 1H), 2.77 (dd, J = 4.8, 1.4 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.35, 168.11, 134.34, 128.97, 128.19, 77.48 , 77.16, 76.84, 69.55, 58.62, 26.52, 21.67, 21.44. IR (KBr) 3448, 3338, 1738, 1648, 1543, 1454, 1410, 1308, 1410, 1279, 1182, 1106, 974, 718, 576 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{12}H_{16}NO_3$, m/z $[M + H]^+$: 236.1287; found: 236.1287.

Isopropyl 3-(dipropylamino)-3-oxo-2-phenylpropanoate (3f). Prepared according to the general procedure A. Compound **3f** was isolated as a white solid in 77% yield (235 mg). Melting point: 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 1.8 Hz, 1H), 7.29 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 7.23 – 7.17 (m, 1H), 5.03 – 4.91 (m, 1H), 4.69 (s, 1H), 3.32 – 3.15 (m, 2H), 3.13 – 3.01 (m, 2H), 1.57 – 1.35 (m, 4H), 1.16 (dd, J = 6.2, 2.8 Hz, 6H), 0.77 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.53, 167.57, 133.93, 129.35, 128.54, 127.83, 77.48, 77.16, 76.84, 69.13, 56.35, 47.82, 22.14, 21.75, 21.53, 20.61, 11.22. IR (KBr) 3299, 3070, 2985, 2926, 1734, 1654, 1591, 1553, 1474, 1370, 1342, 1314, 1239, 1186, 1038, 1008, 835, 811, 747, 697, 641, 504 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{28}NO_3$, m/z $[M + H]^+$: 306.2069; found: 306.2077.

Isopropyl 3-(cyclohexylamino)-3-oxo-2-phenylpropanoate (3g). Prepared according to the general procedure A. Compound **3g** was isolated as a white solid in 82% yield (252 mg). Melting point: 84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.34 (s, 2H), 7.32 (s, 1H), 6.84 (s, 1H), 5.05 (dd, J = 12.6, 6.1 Hz, 1H), 4.44 (s, 1H), 3.78 (d, J = 9.3 Hz, 1H), 1.86 (t, J = 13.9 Hz, 2H), 1.74 (d, J = 14.1 Hz, 2H), 1.64 (s, 4H), 1.38 – 1.31 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.58, 166.37, 153.56, 134.63, 133.55, 128.78, 128.19, 77.47, 77.16, 76.84, 69.56, 58.84, 48.27, 32.72, 25.13, 21.75. IR (KBr) 3420, 2933, 2854, 1741, 1645, 1540, 1452, 1373, 1165, 1110, 1031, 894, 579 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{26}NO_3$, m/z $[M + H]^+$: 304.1913; found: 304.1905.

Isopropyl 3-(dicyclohexylamino)-3-oxo-2-phenylpropanoate (3h). Prepared according to the general procedure A. Compound **3h** was isolated as a white solid in 85% yield (328 mg). Melting

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point: 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2H), 7.32 (s, 2H), 7.31 – 7.26 (m, 1H), 5.04 (hept, J = 6.3 Hz, 1H), 4.73 (s, 1H), 3.40 (dd, J = 15.8, 7.4 Hz, 1H), 2.80 (s, 1H), 2.52 (s, 2H), 1.83 – 1.76 (m, 2H), 1.74 (s, 2H), 1.53 (dd, J = 19.0, 10.7 Hz, 4H), 1.47 – 1.30 (m, 2H), 1.23 (d, J = 6.3 Hz, 6H), 1.20 (d, J = 9.8 Hz, 4H), 1.13 – 0.92 (m, 2H), 0.92 – 0.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.78, 166.96, 134.57, 129.34, 128.58, 127.72, 77.48, 77.16, 76.84, 69.09, 58.68, 56.55, 29.80, 29.26, 26.65, 26.13, 25.85, 25.30, 21.83. IR (KBr) 3462, 2978, 2928, 2854, 1741, 1635, 1450, 1361, 1307, 1176, 1110, 992, 896, 714, 567 (cm^{-1}). HRMS (ESI-MS) $C_{24}H_{36}NO_3$, m/z $[M + H]^+$: calcd for 386.2695; found: 386.2704.

Isopropyl 3-oxo-3-(phenethylamino)-2-phenylpropanoate (3i). Prepared according to the general procedure A. Compound **3i** was isolated as a white solid in 87% yield **(**283 mg). Melting point: 83°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.30 – 7.26 (m, 2H), 7.25 – 7.20 (m, 1H), 7.13 – 7.10 (m, 2H), 6.83 (dd, J = 6.7, 2.2 Hz, 1H), 5.05 (hept, J = 6.3 Hz, 1H), 4.46 (s, 1H), 3.56 – 3.50 (m, 2H), 2.80 (t, J = 6.9 Hz, 2H), 1.28 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.31 (s), 167.44 (s), 138.80 (s), 134.26 (s), 129.09 (s), 128.88 (s), 128.68 (s), 128.25 (d, J = 3.3 *Hz*), 126.56, 77.48, 77.16, 76.84, 69.64, 58.94, 41.03, 35.51, 21.76, 21.53. IR (KBr) 3307, 3080, 3030, 2871, 1730, 1653, 1521, 1461, 1356, 1279, 1226, 1108, 1087, 1008, 904, 806, 741, 697, 536, 538, 497 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{20}H_{24}NO_3$, m/z $[M + H]^+$: 326.1756; found: 326.1768.

Isopropyl 3-((3,4-dimethoxyphenethyl)amino)-3-oxo-2-phenylpropanoate (3j). Prepared according to the general procedure A. Compound **3j** was isolated as a white solid in 84% yield (324 mg). Melting point: 78.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 4H), 6.88 (s, 1H), 6.76 – 6.72 (m, 1H), 6.67 – 6.61 (m, 2H), 5.01 (hept, J = 6.3 Hz, 1H), 4.43 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.48 (ddd, J = 12.5, 7.0, 2.3 Hz, 2H), 2.73 (t, J = 7.0 Hz, 2H), 1.24 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.27, 167.38, 149.03, 147.68, 134.25, 131.26, 128.96, 128.15, 120.70, 111.97, 111.41, 77.48, 77.16, 76.84, 69.56, 58.80, 55.89, 41.03, 35.00, 21.66, 21.43. IR (KBr) 3313, 3056, 2984, 2936, 2838, 1733, 1652, 1523, 1455, 1235, 1190, 1147, 1102, 1027, 850, 808, 708 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{22}H_{28}NO_5$, m/z $[M + H]^+$: 386.1967; found: 386.1972.

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Isopropyl 3-((4-fluorobenzyl)amino)-3-oxo-2-phenylpropanoate (3k). Prepared according to the general procedure A. Compound **3k** was isolated as a white solid in 85% yield (330 mg). Melting point: 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 6.9 Hz, 2H), 7.41 (d, J = 6.4 Hz, 1H), 7.39 (s, 2H), 7.35 (d, J = 6.5 Hz, 2H), 7.33 – 7.27 (m, 2H), 5.19 – 5.05 (m, 1H), 4.61 (s, 1H), 4.49 (d, J = 5.5 Hz, 2H), 1.33 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.09, 167.47, 137.97, 134.20, 129.49, 129.10, 129.10, 128.00, 127.52, 127.43, 77.48, 77.16, 76.84, 69.59, 58.70, 43.55, 23.19, 20.52. IR (KBr) 3314, 3060, 2982, 2940, 1740, 1650, 1608, 1532, 1453, 1356, 1211, 1228, 1179, 1102, 1020, 973, 829, 750, 704, 581, 487 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{19}H_{21}FNO_3$, m/z $[M + H]^+$: 330.1505; found: 330.1500.

Isopropyl 3-(benzylamino)-3-oxo-2-phenylpropanoate (3l). Prepared according to the general procedure A. Compound **3l** was isolated as a white solid in 92% yield (285 mg). Melting point: 107.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dt, J = 3.9, 2.2 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.33 (dd, J = 3.2, 1.7 Hz, 1H), 7.31 (dd, J = 4.2, 1.2 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.22 (dd, J = 5.2, 2.9 Hz, 2H), 5.06 (hept, J = 6.3 Hz, 1H), 4.54 (s, 1H), 4.46 (d, J = 5.8 Hz, 2H), 1.27 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.42, 138.06, 134.36, 129.17, 128.80, 128.33, 127.62, 77.48, 77.16, 76.84, 69.80, 58.91, 43.77, 21.80, 21.54. IR (KBr) 3348, 3033, 2980, 2938, 1732, 1656, 1521, 1455, 1355, 1309, 1278, 1230, 1178, 1102, 1017, 973, 807, 742, 702, 605, 505, 422 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{19}H_{22}NO_3$, m/z $[M + H]^+$: 312.1600; found: 312.1602.

Isopropyl 3-((4-methoxybenzyl)amino)-3-oxo-2-phenylpropanoate (3m). Prepared according to the general procedure A. Compound **3m** was isolated as a white solid in 82% yield (280 mg). Melting point: 79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 1H), 7.39 (dq, J = 3.3, 2.2 Hz, 2H), 7.37 (dd, J = 3.4, 1.1 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.36 – 7.32 (m, 2H), 7.34 – 7.29 (m, 1H), 5.06 (dq, J = 12.5, 6.3 Hz, 1H), 4.60 (s, 1H), 3.75 (s, 3H), 1.26 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.87, 167.68, 132.92, 129.86, 129.35, 128.70, 128.30, 128.07, 77.21, 76.84, 76.84, 69.62, 58.13, 52.83, 21.63. IR (KBr) 3348, 3033, 2980, 2938, 1732, 1656, 1521, 1455, 1355, 1309, 1278, 1230, 1178, 1102, 1017, 973, 807, 742, 702, 605, 505, 422 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{19}H_{22}NO_3$, m/z $[M + H]^+$: 312.1600; found: 312.1602.

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Isopropyl 3-((4-methylbenzyl)amino)-3-oxo-2-phenylpropanoate (3n). Prepared according to the general procedure A. Compound **3n** was isolated as a white solid in 88% yield (287 mg). Melting point: 79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dt, J = 4.0, 2.2 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.50 – 7.45 (m, 2H), 7.48 – 7.44 (m, 1H), 7.46 – 7.40 (m, 1H), 7.34 – 7.27 (m, 1H), 5.21 (hept, J = 6.3 Hz, 1H), 4.70 (s, 1H), 4.54 (d, J = 5.7 Hz, 2H), 2.47 (s, 3H), 1.43 (d, J = 6.3 Hz, 3H), 1.33 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.01 – 170.10, 170.00, 168.68, 187.01 – 135.06, 152.30, 187.01, 129.32, 187.01, 128.96, 187.01, 128.46, 141.22, 187.01, 127.82, 219.37, 127.34, 113.96, 77.48, 77.16, 76.84, 69.48, 58.67, 43.28, 21.59, 21.38, 21.02. IR (KBr) 3351, 3024, 2994, 2905, 1741, 1662, 1533, 1441, 1325, 1313, 1262, 1209, 1182, 1102, 1007, 981, 800, 736, 698, 627, 514, 438 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{20}H_{24}NO_4$, m/z $[M + H]^+$: 342.1705; found: 342.1711.

Ethyl 3-(methylamino)-3-oxo-2-phenylpropanoate (6a). Prepared according to the general procedure A. Compound **6a** was isolated as a white solid in 59% yield (131 mg). Melting point: 75°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dt, J = 8.3, 2.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.14 – 7.10 (m, 1H), 6.84 – 6.74 (m, 1H), 4.51 (s, 1H), 4.17 (ddd, J = 7.4, 5.1, 4.7 Hz, 2H), 2.78 (dd, J = 4.8, 0.7 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.73, 168.00, 134.19, 128.99, 128.28, 127.78, 114.02, 77.48, 77.16, 76.84, 61.84, 58.50, 26.54, 13.98. IR (KBr) 3453, 3324, 1758, 1653, 1555, 1474, 1410, 1399, 1321, 1283, 1179, 1096, 981, 743, 601, 581 cm^{-1}. HRMS (ESI-MS) calcd for $C_{12}H_{16}NO_3$, m/z $[M + H]^+$: 222.1130; found: 222.1125.

Ethyl 2-(4-bromophenyl)-3-(butylamino)-3-oxopropanoate (6b). Prepared according to the general procedure A. Compound **6b** was isolated as a white solid in 88% yield (302 mg). Melting point: 72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 7.30 – 7.21 (m, 2H), 6.95 (s, 1H), 4.43 (s, 1H), 4.26 – 4.11 (m, 2H), 3.23 (dd, J = 13.4, 6.6 Hz, 2H), 1.49 – 1.41 (m, 2H), 1.34 – 1.26 (m, 2H), 1.23 (dd, J = 7.4, 6.9 Hz, 3H), 0.89 (d, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.59, 166.67, 133.38, 132.12, 130.06, 122.46, 77.47, 77.16, 76.84, 62.11, 57.85, 39.62, 31.36, 20.06, 14.02, 13.74. IR (KBr) 3242, 3081, 2995, 2953, 2879, 1744, 1650, 1559, 1441, 1378, 1275, 1221, 1173, 1052, 982, 748, 690, 602, 596 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{15}H_{21}BrNO_3$, m/z $[M + H]^+$: 342.0705; found: 342.0699.

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Ethyl 3-(butylamino)-3-oxo-2-phenylpropanoate (6c). Prepared according to the general procedure A. Compound **6c** was isolated as a white solid in 86% yield **(**227 mg). Melting point: 82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.30 (d, J = 2.3 Hz, 1H), 7.28 – 7.22 (m, 2H), 6.89 (s, 1H), 4.45 (s, 1H), 4.20 – 4.06 (m, 2H), 3.18 (td, J = 7.1, 5.8 Hz, 2H), 1.40 (dt, J = 12.4, 7.2 Hz, 2H), 1.25 (dd, J = 15.2, 7.6 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.83, 167.23, 134.32, 128.96, 128.22,77.48, 77.16, 76.85, 61.80, 58.56, 39.48, 31.36, 19.99, 13.97, 13.69. IR (KBr) 3237, 3074, 2981, 2961, 2884, 1753, 1662, 1571, 1461, 1382, 1267, 1241, 1192, 1092, 971, 771, 695, 596 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{15}H_{22}NO_3$, m/z $[M + H]^+$: 264.1600; found: 264.1599.

Ethyl 2-(4-bromophenyl)-3-(isopropylamino)-3-oxopropanoate (6d). Prepared according to the general procedure A. Compound **6d** was isolated as a white solid in 71% yield (233 mg). Melting point: 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.76 (s, 1H), 4.40 (s, 1H), 4.24 – 4.13 (m, 2H), 4.04 (dd, J = 13.7, 6.9 Hz, 1H), 1.25 (d, J = 7.1 Hz, 3H), 1.13 (t, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.56, 165.80, 133.39, 132.10, 130.05, 122.42, 77.48, 77.00, 62.09, 57.81, 41.86, 22.51, 14.02. IR (KBr) 3272, 3088, 2972, 2929, 2873, 1737, 1644, 1555, 1514, 1460, 1365, 1275, 1234, 1172, 1031, 757, 681, 507 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{14}H_{19}BrNO_3$, m/z $[M + H]^+$: 328.0548; found: 328.0551.

Ethyl 3-(isopropylamino)-3-oxo-2-(*p*-tolyl)propanoate (6e). Prepared according to the general procedure A. Compound **6e** was isolated as a white solid in 68% yield (179 mg).` Melting point: 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 7.7 Hz, 2H), 6.70 (s, 1H), 4.45 (s, 1H), 4.25 – 4.14 (m, 2H), 4.12 – 4.02 (m, 1H), 2.34 (s, 3H), 1.26 (td, J = 7.1, 1.2 Hz, 3H), 1.14 (dd, J = 10.4, 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.33, 139.58, 128.63, 128.03, 127.19, 60.74, 51.92, 33.46, 29.87, 22.59, 14.26, 14.02. IR (KBr) 3373, 3041, 2974, 2917, 1744, 1695, 1544, 1463, 1430, 1372, 1309, 1230, 1180, 1077, 1025, 847, 740, 699, 606, 563, 502 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{14}H_{19}BrNO_3$, m/z $[M + H]^+$: 328.0548; found: 328.0535.

Ethyl 3-(benzylamino)-2-(4-bromophenyl)-3-oxopropanoate (6f). Prepared according to the general procedure A. Compound **6f** was isolated as a white solid in 94% yield (356 mg). Melting point: 84°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 7.39 – 7.34 (m, 1H), 7.33 (d, J = 4.8 Hz, 2H), 7.31 (d, J = 2.1 Hz, 2H), 7.27 (d, J = 4.4 Hz, 2H), 5.24 – 5.14 (m, 2H), 4.62 (s,

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1H), 4.26 – 4.12 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.05, 131.27, 130.54, 128.02, 127.70, 76.85, 76.54, 76.22, 67.09, 61.60, 56.80, 13.44. IR (KBr) 3329, 3030, 2962, 2923, 2871, 1627, 1570, 1452, 1365, 1260, 1090, 1021, 866, 802, 751, 697, 589, 483 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{19}BrNO_3$, m/z $[M + H]^+$: 376.0548; found: 376.0546.

Methyl 3-(benzylamino)-3-oxo-2-phenylpropanoate (6g). Prepared according to the general procedure A. Compound **6g** was isolated as a white solid in 90% yield (255 mg). Melting point: 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.39 (s, 1H), 7.37 (d, J = 1.9 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.26 – 7.22 (m, 2H), 7.19 – 7.10 (m, 2H), 6.86 – 6.82 (m, 1H), 4.62 (s, 1H), 4.49 (d, J = 5.8 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.22, 167.28, 133.96, 129.21, 128.78, 128.46, 127.87, 127.60, 114.05, 77.4, 77.16, 76.84, 58.45, 52.94, 43.76. IR (KBr) 3315, 3049, 3001, 2957, 2824, 1720, 1663, 1504, 1442, 1256, 1187, 1112, 1100, 1077, 987, 845, 804, 757 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{17}H_{18}NO_3$, m/z $[M + H]^+$: 284.1287; found: 284.1290.

Ethyl 3-(benzylamino)-3-oxo-2-phenylpropanoate (6h). Prepared according to the general procedure A. Compound **6h** was isolated as a white solid in 91 % yield (271 mg). Melting point: 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.47 – 7.43 (m, 2H), 7.42 – 7.38 (m, 2H), 7.38 – 7.36 (m, 1H), 7.34 (dd, *J* = 5.8, 1.5 Hz, 2H), 7.32 – 7.29 (m, 1H), 7.25 (d, *J* = 6.5 Hz, 2H), 4.61 (s, 1H), 4.49 (d, *J* = 5.8 Hz, 2H), 4.24 (qd, *J* = 10.8, 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.81, 167.39, 137.97, 134.17, 129.17, 128.77, 128.39, 127.59, 77.48, 77.16, 76.84, 62.03, 58.66, 43.75, 14.06. IR (KBr) 3386, 3030, 2983, 2937, 1723, 1672, 1527, 1453, 1428, 1366, 1310, 1227, 1178, 1078, 1021, 925, 808, 740, 699, 606, 563, 502, 473 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{20}NO_3$, m/z $[M + H]^+$: 298.1443; found: 298.1438.

Ethyl 3-(benzylamino)-2-(2,4-dichlorophenyl)-3-oxopropanoate (6i). Prepared according to the general procedure A. Compound **6i** was isolated as a white solid in 88% yield (324 mg). Melting point: 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.50 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 2.2 Hz, 1H), 7.33 (ddd, *J* = 7.3, 4.5, 1.6 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.25 (s, 1H), 6.86 (s, 1H), 4.97 (s, 1H), 4.48 (qd, *J* = 14.9, 5.8 Hz, 2H), 4.22 (qd, *J* = 7.1, 0.8 Hz, 2H), 1.58 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 131.52, 130.87, 129.66, 128.89, 127.93, 127.66, 77.48,

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77.16, 76.84, 62.44, 54.70, 44.09, 14.09. IR (KBr) 3031, 2975, 2918, 2864, 1633, 1581, 1448, 1379, 1271, 1088, 1017, 859, 817, 756, 700, 588, 472 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{18}Cl_2NO_3$, m/z $[M + H]^+$: 366.0664; found: 366.0667.

Ethyl 3-(benzylamino)-2-(4-fluorophenyl)-3-oxopropanoate (6j). Prepared according to the general procedure A. Compound **6j** was isolated as a white solid in 88% yield (278 mg). Melting point: 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 6.9 Hz, 2H), 7.40 (d, J = 7.3 Hz, 2H), 7.35 (d, J = 6.5 Hz, 2H), 7.32 (d, J = 6.3 Hz, 1H), 7.27 (d, J = 7.1 Hz, 2H), 5.18 – 5.05 (m, 1H), 4.61 (s, 1H), 4.49 (d, J = 5.5 Hz, 2H), 1.33 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.09, 167.47, 137.97, 134.20, 129.49, 129.10, 129.10, 128.00, 127.43, 77.48, 77.16, 76.84, 69.59, 58.70, 43.55, 21.38. IR (KBr) 3389, 3031, 2981, 2936, 1730, 1658, 1518, 1454, 1428, 1365, 1310, 1280, 1231, 1180, 1106, 1079, 1013, 976, 914, 809, 743, 700, 606, 561, 505, 479, 421 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{19}FNO_3$, m/z $[M + H]^+$: 316.1349; found: 316.1345.

Ethyl 3-((4-methylbenzyl)amino)-3-oxo-2-phenylpropanoate (6k). Prepared according to the general procedure A. Compound **6k** was isolated as a white solid in 89 % yield (277 mg). Melting point: 94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.31 – 7.27 (m, 2H), 7.16 (d, J = 4.5 Hz, 1H), 7.12 (s, 1H), 7.12 (s, 2H), 4.48 (s, 1H), 4.40 (dd, J = 5.7, 2.6 Hz, 2H), 4.19 (dddd, J = 17.9, 10.8, 7.1, 3.7 Hz, 2H), 2.33 (s, 3H), 1.25 (dd, J = 9.5, 4.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.50, 166.67, 133.20, 132.25, 130.13, 129.52, 127.75, 77.48, 77.16, 76.84, 62.26, 57.89, 43.66, 21.23, 14.07. IR (KBr)3348, 3033, 2980, 2938, 1732, 1656, 1521, 1455, 1355, 1309, 1578, 1230, 1178, 1102, 1017,973, 807, 742, 702, 605, 505, 422 cm-1. HRMS (ESI-MS) calcd for $C_{19}H_{22}NO_3$, m/z $[M + H]^+$: 312.1600; found: 312.1613.

Methyl 3-((4-methylbenzyl)amino)-3-oxo-2-phenylpropanoate (6l). Prepared according to the general procedure A. Compound **6l** was isolated as a white solid in 81 % yield (241 mg). Melting point: 92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.55 (m, 4H), 7.53 (dd, J = 8.0, 5.1 Hz, 4H), 7.49 – 7.47 (m, 2H), 7.34 – 7.30 (m, 4H), 7.28 (s, 4H), 7.01 – 6.93 (m, 1H), 4.74 (s, 2H), 4.55 (d, J = 5.7 Hz, 4H), 3.89 (s, 6H), 2.48 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.14, 167.17, 137.20, 134.84, 133.99, 129.40, 129.14, 128.43, 127.62, 114.05, 77.48, 77.16, 76.84, 58.46, 52.86, 43.52,

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21.17. IR (KBr) 3300, 3023, 2991, 2945, 2837, 1731, 1641, 1510, 1439, 1251, 1178, 1137, 1114, 1077, 968, 839, 822, 743 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{20}NO_3$, m/z $[M + H]^+$: 298.1443; found: 298.1447.

Ethyl 3-((4-methylbenzyl)amino)-3-oxo-2-(*p*-tolyl)propanoate (6m). Prepared according to the general procedure A. Compound **6m** was isolated as a white solid in 89% yield (290 mg). Melting point: 83°C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.31 (s, 2H), 7.30 (d, J = 2.9 Hz, 2H), 7.19 (s, 1H), 4.67 (s, 1H), 4.55 (dd, J = 5.7, 1.9 Hz, 2H), 4.34 (dd, J = 15.7, 7.2 Hz, 2H), 2.48 (s, 3H), 2.47 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.95, 167.52, 138.24, 137.22, 134.98, 131.17, 129.88, 129.51, 128.27, 127.98, 127.66, 77.48, 77.16, 76.84, 61.94, 58.39, 43.53, 21.21, 14.09. IR (KBr) 3386, 3030, 2983, 2937, 1723, 1672, 1527, 1453, 1428, 1366, 1310, 1227, 1178, 1078, 1021, 740, 699, 606, 563, 502 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{20}H_{24}NO_3$, m/z $[M + H]^+$: 326.1756; found: 326.1748.

Ethyl 2-(4-bromophenyl)-3-((4-methylbenzyl)amino)-3-oxopropanoate (6n). Prepared according to the general procedure A. Compound **3b** was isolated as a white solid in 83% yield (325 mg). Melting point: 112 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.43 (m, 2H), 7.30 – 7.26 (m, 2H), 7.18 – 7.12 (m, 2H), 7.12 (s, 2H), 4.48 (s, 1H), 4.40 (dd, J = 5.7, 2.6 Hz, 2H), 4.19 (dd, J = 10.7, 7.1 Hz, 2H), 2.33 (s, 3H), 1.23 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.50, 166.67, 133.20, 132.25, 130.13, 129.52, 127.75, 77.48, 77.16, 76.84, 62.26, 57.89, 43.66, 21.23, 14.07. IR (KBr) 3456, 3283, 3064, 2978, 2924, 1739, 1646, 1544, 1488, 1448, 1366, 1327, 1268, 1232, 1178, 1073, 1019, 890, 805, 737, 600, 502 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{19}H_{21}BrNO_3$, m/z $[M + H]^+$: 390.0705; found: 390.0683.

Ethyl 3-((4-fluorobenzyl)amino)-3-oxo-2-phenylpropanoate (6o). Prepared according to the general procedure A. Compound **3b** was isolated as a white solid in 81% yield (256 mg). Melting point: 66 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 4.2, 2.1 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.35 (dd, J = 4.8, 2.4 Hz, 2H), 7.18 (dd, J = 8.7, 5.4 Hz, 3H), 6.98 (t, J = 8.7 Hz, 2H), 4.56 (s, 1H), 4.42 (d, J = 5.8 Hz, 2H), 4.27 – 4.13 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.94, 167.43, 134.15, 129.55, 129.16, 128.50, 128.30, 115.75, 115.54, 77.48, 77.16, 76.84, 62.12, 58.61, 43.05, 14.08. IR (KBr) 3303, 3065, 2982, 2937, 1740, 1652, 1610, 1536, 1510, 1438,

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1364, 1311, 1228, 1184, 1095, 1022, 827, 751, 701, 585, 491 (cm^{-1}). HRMS (ESI-MS) calcd for $C_{18}H_{19}FNO_3$, m/z $[M + H]^+$: 316.1349; found: 316.1358.

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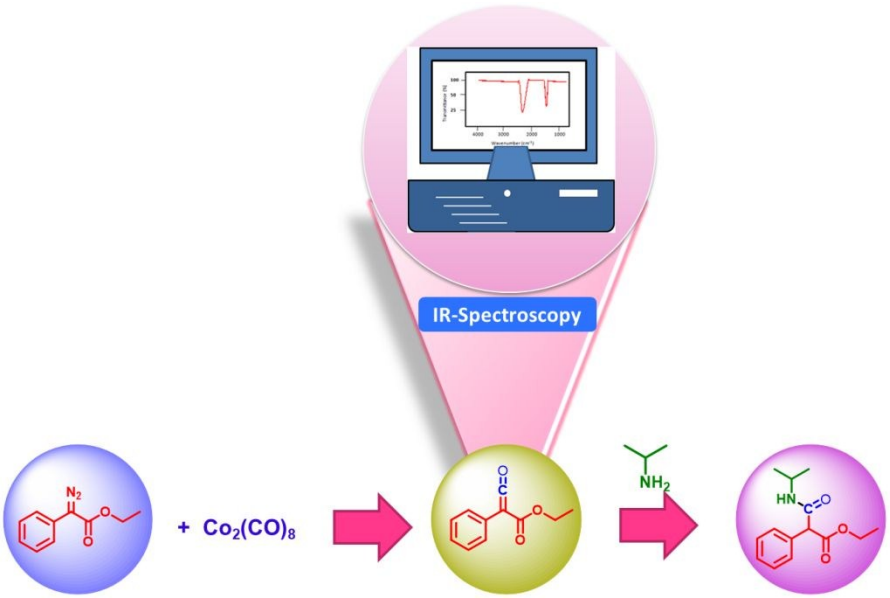

An effective methodology to detect the highly reactive ketene intermediate which is formed insitu during the course of organic transformation.