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# New reaction of enamines with aryldiazoacetates catalyzed by transition metal complexes

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**Abstract**—The reaction of aryldiazoacetates with enamines catalyzed by copper and rhodium complexes provided γ-keto esters in good yields. A full investigation of the effects of solvents, catalysts, enamines and aryldiazoacetates on the reaction was carried out. Careful analysis of the crude reaction mixture revealed a substituted enamine as the primary product, which was hydrolyzed over silica gel to give a γ-keto ester as the final product. A reaction mechanism involving nucleophilic addition of an enamine to a metal carbene and subsequent hydrogen transfer was proposed. Chiral dirhodium and copper catalysts were examined and found to provide γ-keto esters with no enantioselectivity. The result could be rationalized based on the proposed reaction mechanism. Attempts to trap the enamine intermediate with several electrophilic reagents were not successful.


## 1. Introduction

Transition metal catalyzed reactions of diazo compounds have been widely used in organic synthesis in the past two decades.[1] The reactions of diazo compounds with electron-rich olefins usually provide cyclopropanes in good yields. However, in the reaction of diazo compounds with some polarizable olefins such as enol ethers, dihydrofurans and enamines, the formation of other abnormal products has been reported. Wenkert et al. reported the cyclopropanation of enol ether with diazoacetates catalyzed by copper salts provided oxycyclopropanes,[2] but Alonso found that the reaction of enol ethers with diazomalonates afforded 'apparent' vinyl insertion product.[3] The reaction of enamines with ethyl diazoacetate (EDA) in the presence of cuprous chloride or silver oxide unexpectedly gave α-diazo-β-amino-ester in good yield.[4] The reaction was probably proceeded via a nucleophilic addition of EDA to iminium cation formed by isomerization of enamine under the reaction conditions. The addition of EDA to enamine catalyzed by *N*-α-(4-chlorophenyl)isobutyl-(salicylaldimino)copper complex was reported to give aminocyclopropane product in low yield,[5] however, the addition of diazomethane to enamine catalyzed by cuprous chloride could provide aminocyclopropane derivatives in good yields.[6] The reaction of semicyclic enaminocarbonyl compounds with EDA provided enamino esters probably via the rearrangement of the 2-acyl-3-aminocyclopropane-1-carboxylate intermediates.[7] On the other hand, the reaction of semicyclic enaminocarbonyl compounds with vinyldiazoacetates was found to afford betaines as major products.[8] In the absence of transition metal catalysts, the addition of EDA to enamines could provide either dihydropyrazoles or azo coupling products depending on the structure of the enamine.[9] In our preliminary study of the catalyzed reaction of enamines with aryldiazoacetates, we have found the reaction could provide γ-keto esters in excellent yields.[10] In this paper, we report the full investigation of this new reaction.

## 2. Results and discussion

The reaction of methyl phenyldiazoacetate (**1a**) with *N*-(1-styryl)morpholine (**2a**) was studied in the presence of 1 mol% $Rh_2(OAc)_4$. Disappearance of **1a** was observed in less than 1 h. Purification of reaction mixture via column chromatography over silica gel provided a white solid in good yield, which was unambiguously confirmed as methyl 4-oxo-2,4-diphenylbutanoate (**3a**) by combination of $^1H$, $^{13}C$ NMR and mass spectral analyses (Scheme 1).[11] None of the expected aminocyclopropane product was found after careful examination of the reaction mixture. This unusual result promoted us to study the new reaction in detail.

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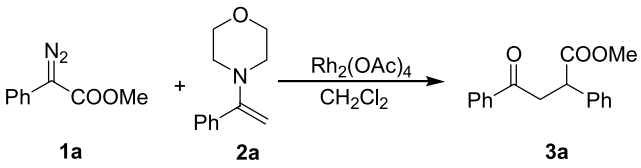



**Scheme 1.**

## 2.1. Catalysts

The reaction of methyl phenyldiazoacetate (**1a**) with *N*-(1-styryl)morpholine (**2a**) did not occur in the absence of a catalyst. In addition to $Rh_2(OAc)_4$, a variety of dirhodium and copper catalysts were also examined in this transformation and the results were summarized in Table 1. Most of tested dirhodium and copper catalysts showed very good catalytic activity. $Cu(hfacac)_2$ was preferred due to its excellent chemical yield and relative low price. It was noticeable that in previous studies copper catalysts were found to be less effective than $Rh_2(OAc)_4$ for the reaction involving aryldiazoacetates.[12] The ratio of enamine to diazo compound also played an important role for the yield of the reaction. The use of excess enamine efficiently increases the yield probably due to partly decomposition of enamine under reaction conditions (entry 6 vs entry 3).

**Table 1**. Reaction of **1a** with **2a** catalyzed by copper and dirhodium complexes[a]

| Entry | Catalyst (mol%) | **2a**:**1a** (mol/mol) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Rh_2(OAc)_4$ (1 mol%) | 1:1 | 0.5 | 63 |
| 2 | $Cu(hfacac)_2$ (1 mol%)[c] | 1:1 | 0.5 | 58 |
| 3 | $Cu(hfacac)_2$ (3 mol%) | 1:1 | 0.5 | 63 |
| 4 | $Cu(OTf)_2$ (3 mol%)[d] | 1:1 | 1 | 59 |
| 5 | CuI (3 mol%) | 1:1 | 10 | 50 |
| 6 | $Cu(hfacac)_2$ (3 mol%) | 1.5:1 | 0.5 | 80 |
| 7 | $CuPF_6$ (3 mol%) | 1.5:1 | 0.5 | 78 |
| 8 | $Cu(acac)_2$ (3 mol%) | 1.5:1 | 6 | 78 |
| 9 | **4** (1 mol%) | 1.5:1 | 3.5 | 84 |
| 10 | **5**/$Cu(hfacac)_2$ (1.1/1 mol%) | 1.5:1 | 1 | 60 |
| 11 | **5**/$Cu(OTf)_2$ (1.1/1 mol%) | 1.5:1 | 4 | 46 |
| 12 | **5**/$CuPF_6$ (1.1/1 mol%) | 1.5:1 | 1 | 60 |
| 13 | **6**/$Cu(hfacac)_2$ (1.1/1 mol%) | 1.5:1 | 9.5 | 0 |

[a] The reactions were carried out with 1 mmol **1a** in refluxing dichloromethane.
[b] Isolated yields after column chromatography.
[c] $Cu(hfacac)_2$=bis-hexafluoroacetoacetonato copper (II).
[d] $Cu(OTf)_2$=copper (II) bis-trifluoromethanesulfonate

Chiral dirhodium and copper catalysts were also examined in the reaction to achieve enantioselectivity (Scheme 2). Davies' catalyst **4** provided **3a** in excellent yield (entry 9). Readily available chiral diimine ligand **5** combined with $Cu(hfacac)_2$, $Cu(OTf)_2$ or $CuPF_6$ could also give **3a** in good yield (entries 10–12). However, in these reactions the product **3a** was found to be racemic after determination by chiral HPLC. On the other hand, the complex of chiral salen **6** and copper salt did not show any catalytic activity (entry 13).

## 2.2. Solvent choice

The reaction of **1a** with **2a** was carried out in a variety of solvents using $Cu(hfacac)_2$ as the catalyst and the results were summarized in Table 2. It is amazing that all tested solvents provided good yields of **3a**, despite in the hexane $Cu(hfacac)_2$ and $Rh_2(OAc)_4$ were almost insoluble. The extremely high reactivity of enamines toward the carbenoid may overturn the possible solvent effects.

**Table 2**. Solvent effect in the reaction of **1a** with **2a**[a]

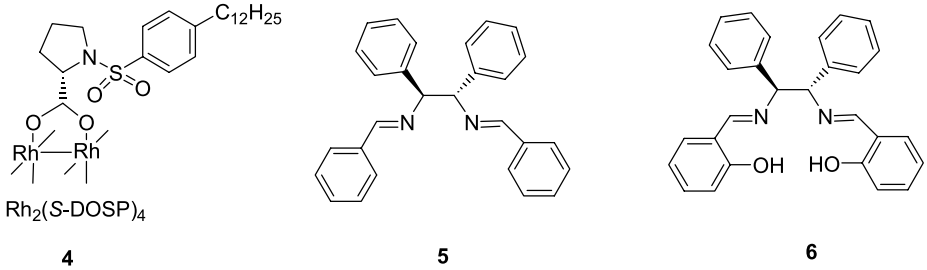
| Solvent | Yield (%)[b] |
|---|---|
| $CH_2Cl_2$ | 80 |
| Hexane | 72 |
| Hexane[c] | 75 |
| Benzene | 78 |
| Toluene | 78 |
| THF | 77 |
| $ClCH_2CH_2Cl$ | 77 |

[a] The reactions were carried out with 1 mmol **1a**, 1.5 mmol **2a** and 0.03 mmol $Cu(hfacac)_2$ under refluxing.
[b] Isolated yields after column chromatography.
[c] 1 mol% $Rh_2(OAc)_4$ was used as catalyst.

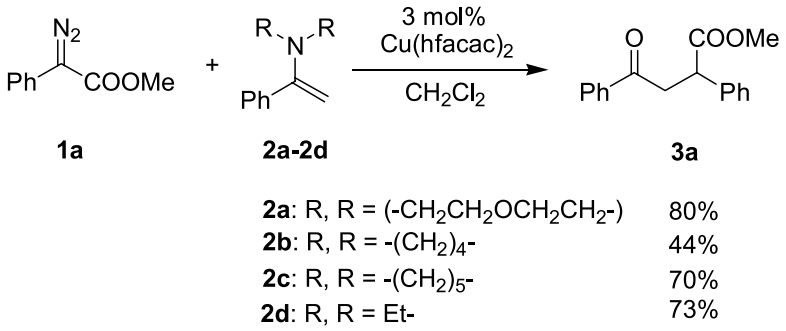
## 2.3. The effect of enamines

Enamines **2a**–**2d** were prepared from acetophenone and several secondary amines and examined in the reaction with methyl phenyldiazoacetate **1a** (Scheme 3). Both cyclic and acyclic secondary amines could be used for this transformation and provided variable yields of **3a**. Enamine **2a** derived from morpholine afforded best yield of **3a**.

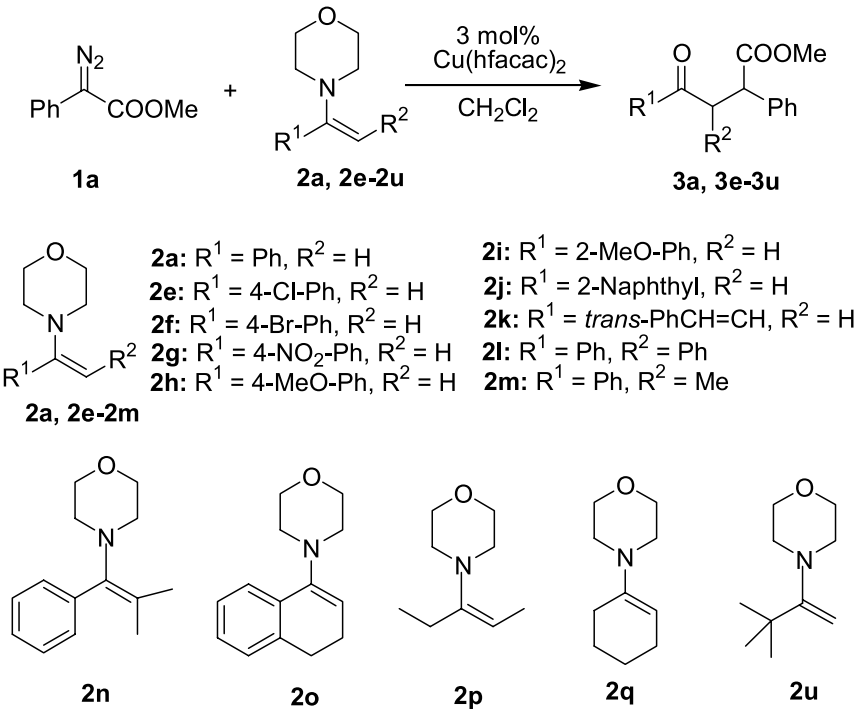
Enamines **2e**–**2u** derived from morpholine and different ketones were also examined in the reaction with **1a** (Scheme 4). The experiment results were summarized in Table 3. Enamines **2a**, **2e**–**2h** derived from unhindered aryl methyl ketone provided good yields of γ-keto esters. However, low yields were observed with enamines **2i** and **2j**, presumably due to their intense steric hindrance. β-Phenyl or methyl substituted enamines **2l** or **2m** also gave good yield of γ-keto esters as a mixture of two diastereomers. β,β-Disubstituted enamine **2n** and sterically demanding enamine **2o** did not afford substantial amount of




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

**Table 3**. Reaction of enamines **2a**, **2e**–**2u** with **1a**[a]

| Entry | Enamine | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | **2a** | 0.5 | 80 |
| 2 | **2e** | 1 | 67 |
| 3 | **2f** | 0.5 | 60 |
| 4 | **2g** | 1 | 54 |
| 5 | **2h** | 1 | 79 |
| 6 | **2i** | | 33 |
| 7 | **2j** | 1 | 50 |
| 8 | **2k** | 3 | 0 |
| 9 | **2l** | 3.5 | 78[c] |
| 10 | **2m** | 1 | 79[d] |
| 11 | **2n** | 0.5 | 0 |
| 12 | **2o** | 1 | 0 |
| 13 | **2p** | 0.5 | 0 |
| 14 | **2q** | 1 | 0 |
| 15 | **2u** | 1 | 0 |

[a] The reactions were carried out with 1 mmol **1a**, 1.5 mmol enamine and 0.03 mmol $Cu(hfacac)_2$ in refluxing $CH_2Cl_2$.
[b] Isolated yields after column chromatography.
[c] The product was obtained as a mixture of two diastereomer (2:1).
[d] The product was obtained as a mixture of two diastereomer (1.5:1).

γ-keto esters. It is unexpected that the dialkyl ketone derived enamines **2p**–**2u** could not react with methyl phenyldiazoacetate, although these enamines were found to be good nucleophilic reagents in previous studies. No reliable explanation can be proposed at the present time.

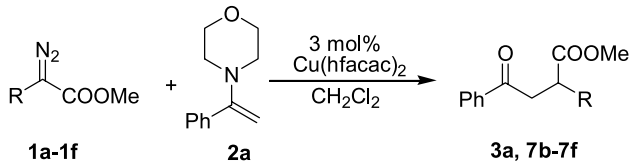
### 2.4. The effect of diazo compounds

Several methyl aryldiazoacetates **1a**–**1f** were prepared and tested in the reaction with enamine **2a**. The results were summarized in Table 4. All aryl- and heteroaryl-diazoacetates examined in the reaction gave good yields of γ-keto esters. In another study, we also found the reaction of enamines with ethyl diazoacetate (EDA) provided corresponding γ-keto esters in excellent yields.[13]

### 2.5. Asymmetric synthesis of γ-keto esters

To the best of our knowledge, no efficient synthesis of chiral 2-aryl γ-keto esters had been reported. Our present studies

**Table 4**. The reactions of methyl aryldiazoacetates **1a–1f** with enamine **2a**[a]




| R | Time (h) | Yield (%)[b] |
|---|---|---|
| Ph (**1a**) | 0.5 | 80 |
| 4-$BrC_6H_4$ (**1b**) | 1.5 | 85 |
| β-Naphthyl (**1c**) | 1 | 83 |
| α-Naphthyl (**1d**) | 1 | 76 |
| 2-Thiophyl (**1e**) | 1 | 55 |
| 3-Indolyl (**1f**) | 1 | 60 |

[a] The reactions were carried out with 1 mmol **1a–1f**, 1.5 mmol **2a** and 0.03 mmol $Cu(hfacac)_2$ in refluxing $CH_2Cl_2$.
[b] Isolated yields after column chromatography.

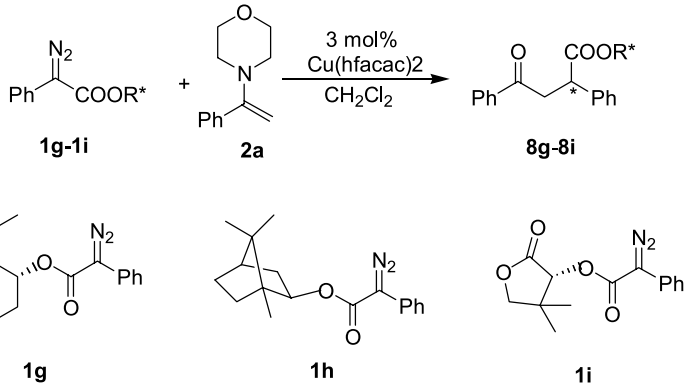
provided two possible pathways for the asymmetric synthesis of γ-keto esters. Davies catalyst **4** and chiral diimine-copper catalysts were studied, but the resulting γ-keto esters were found to be racemic (vide anti). Alternatively, phenyldiazoacetates derived from several commercially available chiral alcohols were prepared and studied in the reaction (Scheme 5). The structure of chiral alcohols showed profound effect on the results of the reactions. **1g** and **1h** did not react with enamine **2a** using $Cu(hfacac)_2$ or $Rh_2(OAc)_4$ as the catalyst, but **1i** could react with **2a** to give γ-keto ester **8i** in good yield using $Cu(hfacac)_2$ as the catalyst. The low reactivity of **1g** and **1h** may be resulted from larger steric hindrance than **1i**.

Other two copper salts and $Rh_2(OAc)_4$ were also examined as the catalyst in the reaction of **1i** with **2a** and the results were summarized in Table 5. The catalysts showed significant effects on the chemical yields of the reactions. The product **8i** obtained from the copper catalysts showed the same diastereoisomer ratio about 2:1 via the $^1H$ NMR analysis. It is very interesting that $Rh_2(OAc)_4$ was inefficient for the reaction of **1i** with **2a**.

In recent years, proline catalyzed asymmetric aldol reactions received much attention.[14] The formation of chiral enamine intermediate from proline and ketones was thought to be the key step in this methodology. We studied the possible formation of the enamine intermediate in situ from acetophenone and proline, which could undergo a consequent reaction with diazo compound to provide chiral γ-keto esters. Unfortunately, the reaction failed to give γ-keto ester **3a** (Scheme 6).

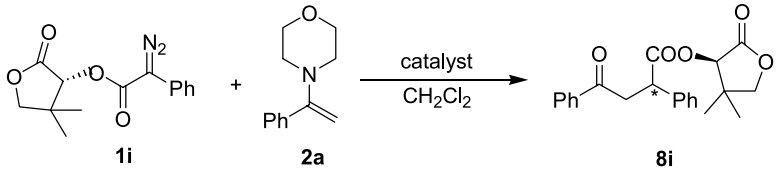
## 2.6. Reaction mechanism

In the reaction of enamine **2a** with methyl phenyldiazoacetate **1a** catalyzed by $Rh_2(OAc)_4$, analysis of the crude reaction mixture with $^1H$ NMR revealed only very weak



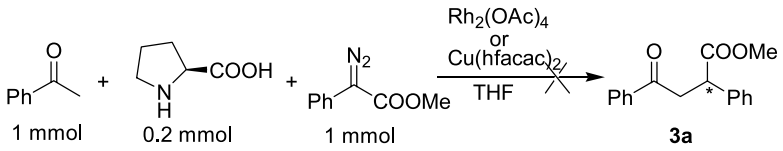

**Scheme 5.**

**Table 5**. The reaction of **1i** with **2a**[a]



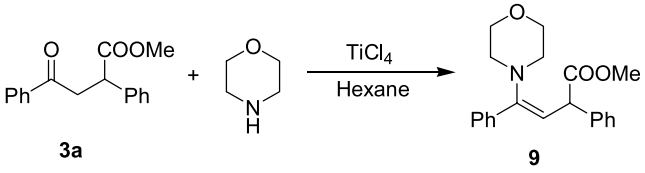

| Catalyst (mol%) | Time (h) | Yield (%)[b] | Diastereomer ratio[c] |
|---|---|---|---|
| $Cu(hfacac)_2$ (3 mol%) | 0.5 | 70 | 2:1 |
| $CuPF_6$ (3 mol%) | 2.5 | 40 | 2:1 |
| $Cu(CF_3SO_3)_2$(3 mol%) | 6 | 30 | 2:1 |
| $Rh_2(OAc)_4$(1 mol%) | 8 | N.R.[d] | N.A.[e] |

[a] The reactions were carried out with 1 mmol **1i** and 1.5 mmol **2a** in refluxing $CH_2Cl_2$.
[b] Isolated yields after column chromatography.
[c] Determined by the $^1H$ NMR of crude product.
[d] No reaction.
[e] Not applicable.




**Scheme 6.**

signals assigned for γ-keto ester **3a**. Instead another compound was found to be the major component, which provided the following $^1$H NMR spectrum: 7.36–7.19 (comp, 10H), 5.08 (d, $J$=10.4 Hz, 1H), 4.18 (d, $J$=10.4 Hz, 1H), 3.87–3.78 (comp, 2H), 3.71–3.65 (comp, 2H), 3.63 (s, 3H), 3.10–2.96 (comp, 2H), 2.83–2.74 (comp, 2H). Its IR spectrum revealed two strong absorption bands at 1731.38 and 1615 cm$^{-1}$, indicating existence of a carbonyl group and a double bond. According to these data this compound was assigned as the enamine **9**. Further attempt to purify and characterize **9** was unsuccessful due to its unstable property. A control test was carried out to verify the structure of **9**. Treatment of **3a** with morpholine in the presence of $TiCl_4$ gave a crude product, which provided identical $^1$H NMR and IR spectra with **9** obtained above (Scheme 7).



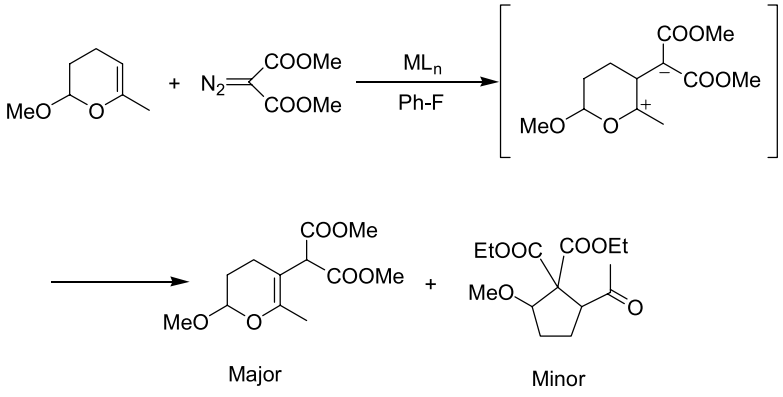

**Scheme 7.**

Transition metal catalyzed reactions of olefins with diazo compounds usually provide cyclopropanes in good yield. The early proposed reaction mechanism of involving metallocyclobutane has been discarded.[15] Instead a concert reaction mechanism was suggested, in which no considerable charge buildup was occurred in the transition state.[16] However, in the reaction of some polarizable olefins with diazo compounds, formation of abnormal products was observed. Alonso et al. found a vinyl C–H insertion in the reaction of vinyl ether with diazomalonates and suggested an addition–elimination mechanism through highly polarized zwitterionic intermediates (Scheme 8).[3] Doyle suggested a similar explanation, in which a competitive hydrogen transfer step was proposed.[1a] Davies suggested the involvement of zwitterionic intermediates in rhodium-catalyzed reaction of vinyldiazoacetates with electron-rich dienes.[17] Mass also proposed an addition-proton transfer mechanism to rationalize the formation of 'apparent' enaminic C–H insertion products in the reaction of enaminocarbonyl compounds with vinyldiazoacetates.[8]

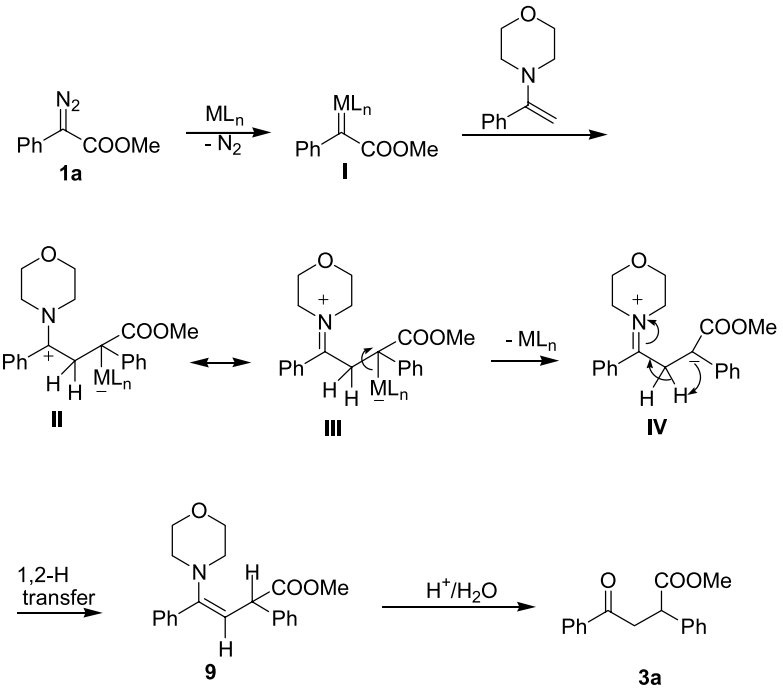
Based on these suggestions and our present experiment results, a possible mechanism for the reaction of enamine **2a** with methyl phenyldiazoacetate **1a** was proposed (Scheme 9). Nucleophilic addition of **2a** to the highly electron-deficient metal carbene (**I**) produced a zwitterionic intermediate (**II**). The developed positive charge at the carbon could be stabilized efficiently by nitrogen atom through resonance structure (**III**). The observed results, which chiral dirhodium and copper catalysts did not provide any enantioselectivity, supported the occurrence of an intermediate **IV** without association of chiral catalysts. The **IV** underwent a proton transfer with complete preference over the competitive cyclopropanation process to provide enamine **9**, which was hydrolyzed over silica gel to give γ-keto ester **3a** as the final product.

## 2.7. Trapping the enamine intermediate 9

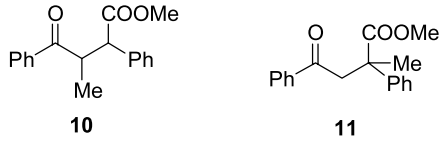
The enamine intermediate **9** may be trapped by electrophilic reagents. For this purpose, the reaction of enamine **2a** with methyl phenyldiazoacetate **1a** was carried out in the presence of excess methyl iodide (3 equiv). The reaction still gave γ-keto ester **3a** in good yield. No alkylation product **10** (from enamine intermediate **9**) or **11** (from intermediate **IV**) was observed (Scheme 10). Other electrophilic reagents such as allyl bromide and benzaldehyde were also examined and no addition product from enamine **9** could be determined.




**Scheme 8.**




**Scheme 9.**




**Scheme 10.**

## 3. Conclusions

In conclusion, we have found an unusual reaction of aryldiazoacetates with enamines leading to γ-keto esters. A reaction mechanism involving nucleophilic addition of enamines to metal carbenes and subsequent hydrogen transfer was proposed. Enamines derived from aryl alkyl ketone underwent this transformation to provide γ-keto esters in good yield, however, enamines derived from dialkyl ketones and α,α-disubstituted aryl alkyl ketones were not applicable for this reaction. On the other hand, the reaction tolerated many aryl and heteroaryl diazoacetates. Enantioselectivity of the reaction could not be achieved with chiral dirhodium and copper catalysts. The result could be rationalized based on the proposed reaction mechanism. Further studies are under the way to expand the reaction to other types of diazo compounds.

## 4. Experimental

### 4.1. General

All reactions were carried out in oven-dried glassware using standard Schlenk technique under argon atmosphere. Hexane, THF, benzene and toluene were distilled from sodium–benzophenone. Dichloromethane and 1,2-dichloroethane were distilled over $CaH_2$. Other solvents were used as their commercial anhydrous grade. The Flash column chromatography was carried out on Merck Silica gel (230–400 mesh). $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer as solutions in $d_3$-chloroform. Chemical shifts in $^1H$ NMR spectra are reported in parts per million (ppm, $\delta$) downfield from the internal standard $Me_4Si$ (TMS). Chemical shifts in $^{13}C$ NMR spectra are reported relative to the central line of the chloroform signal ($\delta = 77.00$ ppm). Infrared spectra were recorded on a Nicolet FT-IR500 spectrometer using KBr pellets and absorption is reported in wave-numbers ($cm^{-1}$). High-resolution mass spectra were obtained with a GCT-TOF instrument. Elemental analyses were performed on a Carlo–Erba EA1110 CNNO-S analyzer. Unless otherwise stated, all chemicals were purchased from Aldrich or Acros chemical company and used thus, without further purification. *p*-Acetamidobenzenesulfonyl azide (ABSA),[18] aryldiazoacetates[19] and enamines[20] were prepared according to known procedures.

**4.1.1. Representative procedure for the preparation of methyl aryldiazoacetates.** To a solution of methyl phenylacetate (600 mg, 4 mmol) and ABSA (4-acetamidobenzenesulfonyl azide) (1.06 g, 4.4 mmol) in anhydrous acetonitrile (8 mL) under an ice-bath, was added DBU (0.64 mL, 4.4 mmol) over 15 min. The resulting solution was stirred under an ice-bath for 2 h. The solution was passed through a short silica gel plug and eluted with dichloromethane until all red color had been collected. The filtrate was concentrated under reduced pressure at 20 °C and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 15/1) to afford methyl phenyldiazoacetate (**1a**) as red oil (539 mg, 76.6%). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.50–7.20 (comp, 5H), 3.86 (s, 3H).

**4.1.2. Representative procedure for the preparation of phenyldiazoacetates derived from chiral alcohols.** To a solution of (*R*)-pantolactonyl phenylacetate (0.78 g, 3.14 mmol) and ABSA (0.98 g, 4.08 mmol) in acetonitrile (30 mL), was added dropwise DBU (0.47 mL, 3.14 mmol) at 0 °C. The solution was stirred at room temperature for 15 h and quenched with saturated solution of $NH_4Cl$ (30 mL). The aqueous layer was extracted with ether (30 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was evaporated in vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=4/1) to afford **1i** as brown oil (0.64 g, 75%). IR ($CHCl_3$) ($\nu_{max}$): 2100 (m), 1745 (s), 1705 (s) $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.51–7.19 (m, 5H), 5.55 (s, 1H), 4.09 (s, 2H), 1.28 (s, 3H), 1.15 (s, 3H).

**4.1.3. Representative procedure for the preparation of enamines.** To a solution of acetophenone (5 mL, 43 mmol) and morpholine (22.4 mL, 257 mmol) in anhydrous hexane (100 mL), was added $TiCl_4$ (2.6 mL, 23 mmol) over 10 min. The reaction mixture was stirred at room temperature for 24 h and filtered. The filtrate was evaporated under vacuum to give colorless oil, which was distilled under reduced pressure (0.03 mmHg, 85–90 °C) to give *N*-(1-styryl)morpholine (**2a**) as a pale yellow liquid. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.56–7.26 (comp, 5H), 4.33 (s, 1H), 4.20 (s, 1H), 3.77 (s, 4H), 2.85 (s, 4H).

**4.1.4. Representative procedure for the reaction of aryldiazoacetates with enamines.** To a round-bottomed flask equipped with a stirrer and an addition funnel under argon atmosphere, was charged *N*-(styryl)morpholine (**2a**) (0.284 g, 1.5 mmol), $Cu(hfacac)_2$ (14.3 mg, 0.03 mmol) and dichloromethane (3 mL). The reaction solution was heated in an oil-bath and kept refluxing. The addition funnel was charged with a solution of methyl phenyldiazoacetate (**1a**) (0.176 g, 1 mmol) in dichloromethane (3 mL), which was added dropwise to the reaction solution over 30 min. The reaction mixture was refluxed for additional 30 min. After the solvent was evaporated under vacuum, the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate=10/1) over silica gel to give methyl 4-oxo-2,4-diphenylbutanoate (**3a**) as a white powder (0.214 g, 80%). IR (KBr): 3449 (w), 3062 (w), 2991 (w), 2951 (w), 1733 (s), 1685 (s), 1446 (m), 1336 (s), 1226 (m), 1202 (m), 1161 (s) $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.98 (d, $J$=7.2 Hz, 2H), 7.57 (t, $J$=7.2, 6.8 Hz, 1H), 7.48–7.45 (comp, 2H), 7.32–7.27 (comp, 5H), 4.30 (dd, $J$=4.4, 10.4 Hz, 1H), 3.96 (dd, $J$=10.4, 19.2 Hz, 1H), 3.70 (s, 3H), 3.28 (dd, $J$=4.4, 19.2 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 198.0, 174.2, 138.7, 136.7, 133.7, 129.3, 129.0, 128.4, 128.2, 127.9, 52.7, 46.7, 43.2. HRMS ($EI^+$) calcd for $C_{17}H_{16}O_3$ ($M^+$): 268.1099; found: 268.1112. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 75.99; H, 6.11.

**4.1.5. Methyl-4-oxo-4-(4-chlorophenyl)-2-phenylbutanoate (3e).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.91 (d, $J$=8.4 Hz, 2H), 7.42 (d, $J$=8.4 Hz, 2H), 7.34–7.25 (comp, 5H), 4.28 (dd, $J$=2.8, 10.4 Hz, 1H), 3.92 (dd, $J$=10.4, 17.6 Hz, 1H), 3.69 (s, 3H), 3.22 (dd, $J$=3.2, 17.6 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 196.2, 174.2, 140.2, 138.6, 135.1, 129.9, 129.4, 129.39, 128.2, 128.1, 52.9, 46.7, 43.2. HRMS ($EI^+$) calcd for $C_{17}H_{15}O_3Cl(35)$ ($M^+$): 302.0710; found: 302.0698.

**4.1.6. Methyl-4-oxo-4-(4-bromophenyl)-2-phenylbutanoate (3f).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.82 (d, $J$=8.8 Hz, 2H), 7.59 (d, $J$=8.8 Hz, 2H), 7.34–7.25 (comp, 5H), 4.28 (dd, $J$=4.0, 10.0 Hz, 1H), 3.91 (dd, $J$=11.2, 18.4 Hz, 1H), 3.69 (s, 3H), 3.21 (dd, $J$=4.0, 18.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 197.1, 174.2, 138.5, 135.4, 132.3, 130.0, 129.4, 128.9, 128.2, 128.1, 52.8, 46.7, 43.1. HRMS ($EI^+$) calcd for $C_{17}H_{15}O_3Br(79)$ ($M^+$): 346.0205; found: 346.0197.

**4.1.7. Methyl-4-oxo-4-(4-nitrophenyl)-2-phenyl-butanoate (3g).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.31 (d, $J$=8.8 Hz, 2H), 8.13 (d, $J$=8.8 Hz, 2H), 7.38–7.26 (comp, 5H), 4.32 (dd, $J$=3.6, 10.4 Hz, 1H), 3.99 (dd, $J$=11.8, 18.0 Hz, 1H), 3.70 (s, 3H), 3.29 (dd, $J$=4.0, 18.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 196.7, 174.0, 150.8, 141.1, 138.2, 129.6, 129.5, 128.2, 128.1, 124.3, 52.9, 46.7, 43.7. HRMS ($EI^+$) calcd for $C_{17}H_{15}NO_5$($M^+$): 313.0950; found: 313.0965.

**4.1.8. Methyl 4-oxo-4-(4-methoxyl-phenyl)-2-phenylbutanoate (3h).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.95 (d, $J$=8.8 Hz, 2H), 7.35–7.26 (comp, 5H), 6.92 (d, $J$=8.8 Hz, 2H), 4.29 (dd, $J$=4.4, 10.4 Hz, 1H), 3.91 (dd, $J$=10.4, 17.6 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.23 (dd, $J$=4.4, 17.6 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 199.6, 174.4, 164.0, 138.9, 130.8, 129.8, 129.3, 128.2, 127.9, 114.1, 55.9, 52.8, 46.8, 42.9. HRMS ($EI^+$) calcd for $C_{18}H_{18}O_4$ ($M^+$): 298.1205; found: 298.1204. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.45; H, 6.09; found: C, 72.69; H, 6.24.

**4.1.9. Methyl 4-oxo-4-(2-methoxyl-phenyl)-2-phenylbutanoate (3i).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.77 (d, $J$=8.0 Hz, 1H), 7.47 (t, $J$=8.0, 7.6 Hz, 1H), 7.35–7.26 (comp, 5H), 7.01–6.94 (comp, 2H), 4.26 (dd, $J$=4.0, 10.8 Hz, 1H), 3.93 (dd, $J$=10.8, 19.6 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 3.36 (dd, $J$=4.0, 19.6 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 199.7, 174.6, 159.4, 139.0, 134.4, 131.0, 129.2, 128.3, 127.8, 127.5, 121.0, 111.9, 55.9, 52.7, 48.4, 47.2. HRMS ($EI^+$) calcd for $C_{18}H_{18}O_4$ ($M^+$): 298.1205; found: 298.1218.

**4.1.10. Methyl-4-oxo-4-(2-naphthyl)-2-phenyl-butanoate (3j).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.49 (s, 1H), 8.03 (s, 1H), 7.93–7.86 (comp, 3H), 7.57 (d, $J$=5.2 Hz, 2H), 7.39–7.24 (comp, 5H), 4.37 (dd, $J$=4.0, 8.0 Hz, 1H), 4.10 (dd, $J$=8.0, 18.0 Hz, 1H), 3.72 (s, 3H), 3.42 (dd, $J$=18.0, 4.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 198.0, 174.4, 138.8, 136.1, 134.1, 132.8, 130.3, 130.0, 129.4, 129.0, 128.9, 128.0, 127.2, 124.1, 52.8, 46.9, 43.3. HRMS ($EI^+$) calcd for $C_{21}H_{18}O_3$ ($M^+$): 318.1256; found: 318.1251.

**4.1.11. Methyl 4-oxo-2,3,4-triphenylbutanoate (3l).** *Major isomer*: $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.99 (d, $J$=7.2 Hz, 2H), 7.53–7.22 (comp, 10H), 7.20–6.96 (comp, 3H), 5.18 (d, $J$=11.6 Hz, 1H), 4.43 (d, $J$=10.4 Hz, 1H), 3.65 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 200.9, 174.7, 129.7, 129.65, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1,

128.7, 128.5, 128.1, 128.0, 58.6, 56.0, 53.1. HRMS ($EI^+$) calcd for $C_{23}H_{20}O_3$ ($M^+$): 344.1412; found: 344.1416.

*Minor isomer*: $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.86 (d, $J$=7.2 Hz, 2H), 7.53–7.22 (comp, 10H), 7.20–6.96 (comp, 3H), 5.49 (d, $J$=11.6 Hz, 1H), 4.66 (d, $J$=11.6 Hz, 1H), 3.39 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 198.0, 172.9, 131.3, 130.7, 130.0, 129.9, 129.63, 129.6, 129.4, 129.23, 129.2, 128.5, 128.4, 128.3, 56.9, 55.9, 52.6. HRMS ($EI^+$) calcd for $C_{23}H_{20}O_3$ ($M^+$): 344.1412; found: 344.1416.

**4.1.12. Methyl 4-oxo-3-methyl-2,4-diphenylbutanoate (3m).** *Major isomer*: $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.82 (d, $J$=7.6 Hz, 2H), 7.50–7.23 (comp, 6H), 7.19 (t, $J$=7.2, 10.8 Hz, 2H), 4.20–4.07 (comp, 2H), 3.70 (s, 3H), 1.27 (d, $J$=6.0 Hz, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 202.1, 172.9, 137.4, 136.5, 133.4, 129.0, 128.8, 128.6, 128.5, 127.7, 55.2, 52.5, 44.4, 16.4. HRMS ($EI^+$) calcd for $C_{18}H_{18}O_3$($M^+$): 282.1256; found: 282.1250.

*Minor isomer*: $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.06 (d, $J$=7.2 Hz, 2H), 7.60–7.23 (comp, 6H), 7.12 (t, $J$=6.8, 14.0 Hz, 2H), 4.41–4.34 (comp, 2H), 3.54 (s, 3H), 0.90 (d, $J$=6.0 Hz, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 204.0, 174.4, 137.3, 136.1, 133.5, 129.2, 128.9, 128.6, 128.5, 128.0, 55.2, 52.5, 44.6, 14.5. HRMS ($EI^+$) calcd for $C_{18}H_{18}O_3$ ($M^+$): 282.1256; found: 282.1250.

**4.1.13. Methyl 4-oxo-4-phenyl-2-(4-bromophenyl)-butanoate (7b).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.97 (d, $J$=7.2 Hz, 2H), 7.58 (t, $J$=7.2 Hz, 1H), 7.48–7.44 (comp, 4H), 7.26–7.23 (comp, 2H), 4.26 (dd, $J$=4.0, 9.6 Hz, 1H), 3.92 (dd, $J$=9.6, 18.0 Hz, 1H), 3.70 (s, 3H), 3.28 (dd, $J$=4.0, 18.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 197.7, 173.9, 137.7, 136.6, 133.9, 132.4, 130.0, 129.1, 128.5, 122.0, 53.0, 46.2, 42.9. HRMS ($EI^+$) calcd for $C_{17}H_{15}O_3Br(81)$ ($M^+$): 348.0184; found: 348.0216. HRMS ($EI^+$) calcd for $C_{17}H_{15}O_3Br(79)$ ($M^+$): 346.0205; found: 346.0226. Anal. Calcd for $C_{17}H_{15}O_3Br$: C, 58.96; H, 4.37. Found: C, 58.88; H, 4.51.

**4.1.14. Methyl 4-oxo-4-phenyl-2-(2-naphthyl)-butanoate (7c).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.99 (d, $J$=7.6 Hz, 2H), 7.84–7.81 (comp, 4H), 7.56 (t, $J$=6.8, 4.0 Hz, 1H), 7.45–7.24 (comp, 5H), 4.47 (dd, $J$=4.4, 10.0 Hz, 1H), 4.06 (dd, $J$=10.0, 18.0 Hz, 1H), 3.70 (s, 3H), 3.36 (dd, $J$=4.4, 18.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 198.0, 174.3, 136.7, 136.1, 133.87, 133.84, 133.1, 129.1, 129.0, 128.5, 128.2, 128.1, 127.1, 126.8, 126.5, 126.2, 52.9, 46.8, 43.2. HRMS ($EI^+$) calcd for $C_{21}H_{18}O_3$ ($M^+$): 318.1256; found: 318.1275.

**4.1.15. Methyl 4-oxo-4-phenyl-2-(1-naphthyl)-butanoate (7d).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.14 (d, $J$=8.8 Hz, 1H), 7.97 (d, $J$=7.6 Hz, 2H), 7.87 (d, $J$=8.0 Hz, 1H), 7.79 (d, $J$=7.6 Hz, 1H), 7.56–7.39 (comp, 7H), 5.19 (dd, $J$=4.0, 10.0 Hz, 1H), 4.10 (dd, $J$=10.0, 17.6 Hz, 1H), 3.69 (s, 3H), 3.31 (dd, $J$=4.0, 17.6 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 198.2, 174.7, 136.6, 135.1, 134.5, 133.8, 131.4, 129.5, 129.0, 128.59, 128.54, 127.1, 126.3, 125.9, 125.4, 123.3, 52.9, 42.9, 42.2. HRMS ($EI^+$) calcd for $C_{21}H_{18}O_3$ ($M^+$): 318.1256; found: 318.1242.

**4.1.16. Methyl 4-oxo-4-phenyl-2-(2-thiophenyl)-butanoate (7e).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.99 (d, $J$=7.6 Hz, 2H), 7.58 (t, $J$=8.0 Hz, 1H), 7.49–7.45 (comp, 2H), 7.23 (s, 1H), 7.01 (s, 1H), 6.98 (s, 1H), 4.59 (dd, $J$=5.2, 10.4 Hz, 1H), 3.97 (dd, $J$=10.4, 18.0 Hz, 1H), 3.74 (s, 3H), 3.42 (d, $J$=18.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 197.6, 173.4, 140.6, 136.5, 133.9, 129.1, 128.5, 127.4, 126.0, 125.2, 53.1, 43.6, 41.9. HRMS ($EI^+$) calcd for $C_{15}H_{14}O_3S$ ($M^+$): 274.0664; found: 274.0692.

**4.1.17. Methyl-4-oxo-4-phenyl-2-(1-*tert*-butyloxycarbonyl-indol-3-yl)-butanoate (7f).** $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 8.15 (d, $J$=6.8 Hz, 1H), 8.0 (d, $J$=8.0 Hz, 2H), 7.70 (d, $J$=7.6 Hz, 1H), 7.58–7.55 (comp, 2H), 7.47–7.44 (comp, 2H), 7.35 (d, $J$=7.2 Hz, 1H), 7.27 (d, $J$=7.2 Hz, 1H), 4.57 (dd, $J$=4.0, 10.0 Hz, 1H), 4.08 (dd, $J$=10.0 Hz, 18.4 Hz, 1H), 3.71 (s, 3H), 3.37 (dd, $J$=4.0, 18.4 Hz, 1H), 1.67 (s, 9H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 198.1, 174.0, 149.9, 136.7, 133.8, 129.5, 129.1, 128.5, 125.2, 123.9, 123.2, 119.8, 118.0, 115.8, 84.4, 52.9, 41.6, 37.9, 28.6. HRMS ($EI^+$) calcd for $C_{24}H_{25}NO_5$ ($M^+$): 407.1733; found: 407.1740.

**4.1.18. (*R*)-Pantolactonyl 4-oxo-2,4-diphenylbutanoate (8i).** *Major isomer*: $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.98 (d, $J$=7.6 Hz, 2H), 7.60 (d, $J$=7.6 Hz, 1H), 7.47–7.41 (comp, 4H), 7.37–7.34 (comp, 2H), 7.28 (d, $J$=12 Hz, 1H), 5.38 (s, 1H), 4.47 (dd, $J$=5.2, 9.6 Hz, 1H), 3.95 (dd, $J$=9.6, 15.2 Hz, 1H), 3.92 (s, 2H), 3.41 (dd, $J$=5.2, 15.2 Hz, 1H), 1.03 (s, 3H), 0.71 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 197.4, 172.6, 172.5, 138.4, 136.6, 133.8, 129.4, 129.1, 128.5, 128.4, 128.3, 76.5, 75.6, 46.9, 42.6, 40.9, 23.3, 19.7. HRMS (ESI) calcd for $C_{22}H_{22}NaO_5$ ($M+Na^+$): 389.1365; found: 389.1346. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.10; H, 6.06. Found: C, 72.03; H, 6.01.

*Minor isomer*: $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.98 (d, $J$=7.6 Hz, 2H), 7.58 (d, $J$=6.0 Hz, 1H), 7.47–7.41 (comp, 4H), 7.37–7.34 (comp, 2H), 7.27 (d, $J$=6.8 Hz, 1H), 5.35 (s, 1H), 4.38 (dd, $J$=3.6, 10.8 Hz, 1H), 4.07 (dd, $J$=16.0, 10.8 Hz, 1H), 3.94 (s, 2H), 3.37 (dd, $J$=16.0, 3.6 Hz, 1H), 1.26 (s, 3H), 1.24 (s, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 197.8, 172.5, 172.3, 137.5, 136.6, 133.82, 128.4, 128.2, 128.1, 76.4, 75.8, 46.5, 43.4, 40.9, 23.2, 20.2. HRMS (ESI) calcd for $C_{22}H_{22}NaO_5$ ($M+Na^+$): 389.1365; found: 389.1346. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.10; H, 6.06. Found: C, 72.03; H, 6.01.

**4.1.19. Preparation of 4-morpholin-4-yl-2,4-diphenyl-but-3-enoic acid methyl ester (9).** To a solution of methyl 4-oxo-2,4-diphenylbutanoate (**3a**) (0.268 g, 1 mmol) and morpholine (0.522 g, 6 mmol) in 10 mL anhydrous hexane, was added $TiCl_4$ (0.06 mL, 0.55 mmol) over 10 min. The reaction mixture was stirred at room temperature for 24 h and was filtered. The filtrate was evaporated under vacuum to give a light yellow solid. $^1H$ NMR (400 MHz, $CDCl_3$): 7.36–7.19 (comp, 10H), 5.08 (d, $J$=10.4 Hz, 1H), 4.18 (d, $J$=10.4 Hz, 1H), 3.82 (m, 2H), 3.68 (m, 2H), 3.63 (s, 3H), 3.04 (m, 2H), 2.78 (m, 2H). IR (KBr): 2962 (s), 2910 (s), 2717 (m), 2443 (w), 1731 (s), 1615 (s), 1599 (s), 1495 (s) $cm^{-1}$. HRMS (ESI) calcd for $C_{21}H_{24}O_3N$ ($M+H^+$): 338.1756; found: 338.1739.

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