Domino [4 + 1]-annulation of α,β-unsaturated δ-amino esters with Rh(II)–carbenoids – a new approach towards multi-functionalized N-aryl pyrroldines†

J. J. Medvedev, O. S. Galkina, A. A. Klinkova, D. S. Giera, L. Hennig, C. Schneider and V. A. Nikolaev*†

Catalytic decomposition of diazomalonates and other diazoesters using Rh(II) and Cu(II)-complexes in the presence of α,β-unsaturated δ-(N-aryl)amino esters gives rise to the formation of multi-functionalized pyrrolidines with yields of up to 82%. The reaction apparently occurs as a domino process involving the initial N-ylide formation followed by intramolecular Michael addition to the conjugated system of amino esters to afford the pyrroldine heterocycle. The whole process can also be classified as a [4 + 1]-annulation of the δ-amino α,β-unsaturated ester with the carbenoid intermediate.

Introduction

The pyrroldine unit is an important heterocyclic element occurring in the structure of different natural and unnatural compounds that display a wide range of biological activities.1,2 In pharmaceutical chemistry pyrroldine is a structural element for many medicines.3-Hence, the development of new methodologies towards the synthesis of functionalized pyrrolidines remains a highly valuable and actual research area for synthetic organic chemists.

Numerous methods are described in the literature for the creation of the pyrroldine structure,6 however to the best of our knowledge only a few catalytic reactions of diazo compounds have been used so far for this purpose.7-9 These primarily involve intramolecular carbenoid N–H insertion reactions of γ-amino diazocarbonyl compounds,7 ring enlargement of N-substituted azetidine derivatives during Cu(n)-catalyzed decomposition of diazocarbonyl compounds,8 and others.9

Closely related to our investigations in this field is the research on the Rh-catalyzed three-component domino reaction of diazocarbonyl compounds with anilines and β,γ-unsaturated α-keto esters to produce pyrrolidines as a mixture of four diastereomers in moderate to good yields (Scheme 1).9b

Herein we present the results of the formal [4 + 1]-cycloaddition of carbenoids, generated by transition metal-catalyzed decomposition of diazomalonates and other diazoesters, with a variety of N-aryl substituted α,β-unsaturated δ-amino esters, which gives rise to multi-functionalized pyrrolidines. The products are obtained in one step with typically good yields as a mixture of two diastereomers.

Results

To elucidate the scope and limitations of the processes studied, a wide range of α,β-unsaturated δ-amino esters 1a–h were employed in the study, which varied by the nature of p-substituents on the N-aryl group (1a, 1b) and at the atom C-5 of the alkyl chain (1c–1h). With regard to diazo compounds typical representatives of the diazoesters were employed as precursors to carbenoids, namely diazomalonates 2a,b, their cyclic analogue diazo Meldrum’s acid 2c, and diazoacetates 2d and 2e (Fig. 1).

Rh(n)-Complexes are currently believed to be among the most suitable catalysts for the reactions of diazo compounds with different substrates.10 At the same time, it has been recently shown that Cu(n), Ru(n), and other transition metal complexes in many cases are no less efficient and selective catalysts for similar processes.11-13 Accordingly, not only typical Rh(n)-catalysts were used for generation of metal–carbenes,
but complexes of copper(II), iron(III), and ruthenium(II) were tested as well (Fig. 1).

Reactions of diazomalonates 2a,b. Preliminary experiments were carried out using amino ester 1a and diazomalonate 2a in methylene chloride at room temperature with dirhodium tetraacetate which is known as the standard catalyst for decomposition reactions of diazo compounds. Based on universally known results of these reactions one might expect that in the presence of ester 1a with a secondary N–H group, the principal direction of diazomalonate 2a reaction should be insertion of the intermediate Rh(II)–carbenoid into the N–H-bond of the amino group.

After work-up and chromatographic separation of the reaction mixture two main products were isolated in 56% combined yield (60% based on the recovered starting material) which by their composition were in fact consistent with the assumed insertion adduct. However, the detailed structural investigation revealed that none of them were the expected N–H-insertion product. In fact, these were pyrrolidine 3a (as a mixture of two diastereomers) and the C–H-insertion product 4a of carbenoid into the p–C–H-bond of the N–phenyl group (Table 1, entry 1).

In order to increase the conversion of amino ester 1a and thus to enhance the yield of the principal reaction product 3a, the proportion of diazomalonate 2a was enhanced at first by 2 times and then by 4 times (entries 2 and 3). But instead of increasing the yield of pyrrolidine 3a this resulted in the appearance of a new reaction product – a 1:2-adduct of the starting amino ester 1a with di(alkoxycarbonyl)carbene, which had the structure of pyrrolidine 5a (35% and 47% yield, respectively). Simultaneously, in the first case the yield of pyrrolidine 3a decreased by almost two times (entry 2), while in the case of the 1:4 ratio of reagents the formation of pyrrolidine 3a was not detected at all (entry 3).

To prevent attack of the Rh(II)–carbenoid on the p–C–H-bond of the N–phenyl group of amino ester 1 and hence to avoid formation of the side products of the types 4 and 5, the ensuing experiments were carried out with p-MeO-phenyl (PMP) amino esters 1b–h. As one would expect, on decomposition of diazomalonates 2a,b with Rh2(OAc)4 in the presence of the new amino ester 1b, the yield of pyrrolidines 3a and 3a′ increased considerably (up to 70%), while the parallel processes of C–H-insertion were completely suppressed (entries 4 and 5).

Thus it was established that the yields of pyrrolidines 3a,b in catalytic reactions of diazomalonates 2a,b in the presence of aminoesters 1 catalyzed by Rh2(OAc)4 did not exceed 70%. In an effort to elucidate the efficiency of other catalysts in these reactions, several alternative transition metal complexes were also tested for this purpose, namely Rh2(Oct)4 and a series of copper complexes, Fe(acac)3 and [RuCl2(μ-cymene)]2 (Table 2). The reactions were carried out in dichloromethane, benzene or trifluoromethylbenzene at 25 °C (CH2Cl2), 80 °C (C6H6) or 103–104 °C (CF3C6H5), using amino esters 1b,c and dimethyl diazomalonate 2a as the reagents in the ratio of 1:2 to 1:3.
The most efficient catalyst in this series of experiments was found to be Rh$_2$(Oct)$_4$ (Table 2). Its application under otherwise identical reaction conditions allowed us to increase the yield of the target pyrrolidines 3b and 3c up to 82% (entry 4), that is 10–15% more than that with dirhodium tetraacetate (entries 1 and 3).

When copper catalysts were used, the highest yields were obtained with copper(II) 1,1,1,5,5,5-hexafluoroacetylacetonate and copper(II) triflate in benzene at 80 °C (Table 2, entries 8 and 9). Decomposition of diazomalonate 2a with Cu(II) acetate does not occur effectively at 25 °C and only by increasing the amount of the catalyst to 10 mol% and heating the reaction mixture to reflux for many hours we succeeded in the preparation of pyrrolidine 3b in low yield (entries 5 and 6).

Copper(II) acetylacetonate, Fe(acac)$_3$, and [RuCl$_2$(p-cymene)$_2$] were all found to be inefficient catalysts for the process studied (entries 7, 10, 11).

In these processes pyrrolidines 3a–c were formed as a mixture of cis- and trans-stereoisomers in different ratios (Table 2). The separation of these mixtures was a challenging task but, nevertheless, in the majority of cases a quantity of both diastereomers of pyrrolidines 3 (trans and cis) was iso-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Ratio 1/2</th>
<th>Yield$^a$ [%]</th>
<th>Combined yield [%]</th>
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<tr>
<td>1</td>
<td>1a; 2a</td>
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<tr>
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<td>1/2</td>
<td>3a: 26</td>
<td>—</td>
</tr>
<tr>
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<tr>
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<td>1b; 2a</td>
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<td>—</td>
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<tr>
<td>5</td>
<td>1b; 2b</td>
<td>1/2</td>
<td>3b’: 70</td>
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</table>

$^a$Rh$_2$(OAc)$_4$ (0.5–1.0 mol%), DCM, r.t., 12.5–16 h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine, no. R, R’</th>
<th>Catalyst (mol%)</th>
<th>Combined yield $^{trans + cis-3}$ [%]</th>
<th>d.r.; $^{trans/cis}$</th>
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<tr>
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<td>1b; H, OMe</td>
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<td>1.75 : 1</td>
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<tr>
<td>2</td>
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<td>Rh$_2$(Oct)$_4$ (2)</td>
<td>3b: 68$^a$</td>
<td>1.6 : 1</td>
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<td>3</td>
<td>1c; Et, OMe</td>
<td>Rh$_2$(OAc)$_4$ (4)</td>
<td>3c: 72$^a$</td>
<td>1.5 : 1</td>
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<td>4</td>
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<td>Rh$_2$(Oct)$_4$ (2)</td>
<td>3c: 82$^a$</td>
<td>1.7 : 1</td>
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<td>3b: 21$^a$</td>
<td>NR$^{bc}$</td>
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<td>6</td>
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<td>3b: 51$^c$</td>
<td>1 : 1</td>
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<td>3b: 49$^c$</td>
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<td>NR$^{abc}$</td>
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<tr>
<td>11</td>
<td>1b; H, OMe</td>
<td>[RuCl$_2$(p-cymene)$_2$] (2)</td>
<td>NR$^{abc}$</td>
<td>—</td>
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</table>

$^a$DCM, r.t., 1.5–10 h. $^b$No reaction. $^c$C$_6$H$_{14}$, 80 °C, 3–7.5 h. $^d$PhCF$_3$, 103.5 °C, 5 h.

The most efficient catalyst in this series of experiments was found to be Rh$_2$(Oct)$_4$ (Table 2). Its application under otherwise identical reaction conditions allowed us to increase the yield of the target pyrrolidines 3b and 3c up to 82% (entry 4), that is 10–15% more than that with dirhodium tetraacetate (entries 1 and 3).

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In these processes pyrrolidines 3a–c were formed as a mixture of cis- and trans-stereoisomers in different ratios (Table 2). The separation of these mixtures was a challenging task but, nevertheless, in the majority of cases a quantity of both diastereomers of pyrrolidines 3 (trans and cis) was iso-
lated in their pure state using a combination of flash chromatography and preparative TLC. The structure of the isolated compounds 3a–c, 4a, and 5a was unambiguously established using spectroscopy methods (1H, 13C NMR, IR, and UV), and their composition was confirmed by HRMS. The relative configuration of the cis-isomer 3e was established based on nOe experiments (Fig. 2), and the structure and configuration of the trans-pyrrolidine 3b was confirmed by X-ray crystal structure analysis (Fig. 3). The configurational assignment of the other pyrrolidines 3 was made by comparison and analogy of the related spectroscopy data of cis- or trans-diastereomers of pyrrolidine 3b (see ESI† p. S2 and S3).

Summing up the results of this part of research one can conclude that the best conditions found for the preparation of pyrrolidines 3a–c from amino esters 1a–c and diazomalonates 2a,b are application of Rh2(Oct)4 and carrying out the catalytic reaction at room temperature in CH2Cl2.

In order to estimate further the scope and limitations of the process studied, a series of experiments with other amino esters 1d–h was performed under the suitable conditions found for 1a–c (Table 3). The reaction time was varied depending on the disappearance of amino esters 1 in the reaction mixture, which was monitored using TLC and 1H NMR spectroscopy.

It was established that amino esters 1d–g carrying 5-Ar’ or 5-Naph groups with different substituents at p-, o- or m-positions of the aryl ring furnished pyrrolidines 3d–g in good yields (62–79%) as well (entries 3–6). A moderately lower yield of pyrrolidine 3h (42%) was only obtained with the 5-(styryl)-substituted amino ester 1b (entry 7). The origin of this might be the competitive cyclopropanation of the electron-rich styryl double bond. In all experiments the trans-stereoisomer of pyrrolidines 3 was produced as the major stereoisomer.

Reactions of diazo Meldrum’s acid 2c (the cyclic analogue of diazomalonates 2a,b) with amino ester 1b were carried out using Rh2(OAc)4 and Rh2(Oct)4 in boiling benzene due to the high thermo-catalytic stability of this diazoo compound. As the main products in these reactions spirocyclic pyrrolidine 3i and indoline-2-one 6 were obtained (Scheme 2).

The yields of pyrrolidine 3i and indolineone 6 were rather low, however, and could not be significantly improved, neither by an increase of the amount of the diazo compound nor by changing the catalyst from Rh2(OAc)4 to Rh2(Oct)4. A two-fold increase of the diazo compound/amino ester ratio (4:1) reduced the yield of pyrrolidine 3i (from 35 to 13%) and slowed down the rate of the process. Replacement of Rh2(OAc)4 with Rh2(Oct)4 notably accelerated the decomposition process but did not increase the yield of pyrrolidine 3i (34%), while the yield of indolineone 6 marked enhanced on changing the catalyst (from 14 to 31%). The structure of compounds 3i and 6 was assigned using a set of spectroscopy methods including two-dimensional NMR-techniques such as 1H–1H-COSY and HMBC (see ESI† p. S2 and S3).

Catalytic decomposition of methyl diazoacetae 2d, contrary to diazomalonates 2a,b and diazoisopropylidene malonic acid 2c, occurred at room temperature very fast. Accordingly, reactions of diazoacetate 2d,e with amino ester 1b were carried out at 0, –15 and –25 °C by slow addition of the diazo compound to a solution of the amino ester-substrate 1b and the catalyst in CH2Cl2.

It was found that with diazoester 2e at 0 °C and using 4 mol% of Rh(II)-catalyst, pyrrolidine 7 was formed in 53% yield as a homogenous 2,3-cis-2,5-trans-stereoisomer (Table 4). At the same time, in the experiments at 0–25 °C with diazoester 2d the N-H-insertion product 8d (29–38%) was isolated.
along with a mixture of methyl maleate–fumarate (6–19%) and amino ester 1b was recovered.

**Discussion**

This study has revealed that the catalytic decomposition of diazoesters 2a–e in the presence of α,β-unsaturated δ-amino esters 1a–h gives rise in one stage to the formation of pyrrolidines 3 and 7 in moderate to good yields. The following mechanistic rationale can be put forth to account for the outcome of the reaction by analogy with literature data (Scheme 3).

The interaction of a catalyst with the carbon atom of the diazo group generates metal–carbene A followed by nitrogen elimination.10,16 The highly electrophilic carbenoid A subsequently attacks the electron-rich amino group and furnishes the intermediate complex B which further breaks down with the formation of the metal-free ylide C and regeneration of the catalyst.17 The ylide C formed easily undergoes intramolecular conjugate addition to the pendant enoate giving rise to pyrrolidines 3 and 7 upon ring-closure followed by 1,4-H-migration within zwitterion D.18

Hence in the course of the catalytic process studied, two sites within the δ-unsaturated amino ester 1 structure were involved, namely the N–H- and C==C-bonds. However, other functional groups may react as well as was observed with 1a and 1h. For example, even at about an equimolar ratio of diazomalonate 2a and amine 1a (1:1.1), the product 4a of metal–carbene A insertion into the p-CH-bond of the phenyl group of amino ester 1a was formed along with pyrrolidine 3a (Scheme 4). It is quite evident10c,19 that the insertion product 4a was produced due to competitive attack of the Rh(II)-carbene-
noid A onto the electron-rich p-CH-bond of the aromatic ring (Scheme 4, right pathway).

Based on the ratio of reaction products 3a/4a formed (9 : 1; Table 1, entry 1) one can conclude that with the ratio of reactants 1.1 : 1 the interaction of carbenoid A with the N–H group (Scheme 4, left pathway) occurs at about 9 times faster than insertion into the p-C–H-bond of the phenyl group (right pathway). At the same time, in the presence of a large excess of diazomalonate 2a (up to 4 : 1; entry 3) the initially formed pyrrolidine 3a and p-CH(CO2Me)2-substituted amino ester 4a both further react with one more equivalent of diazomalonate 2a/carbenoid A producing pyrrolidine 5a as the sole final reaction product (Scheme 4).

Essentially, in all experiments using rhodium catalysts, pyrrolidines 3a–i were formed as a mixture of trans- and cis-isomers in the ratio 1.5–2.4 : 1, while on usage of Cu-complexes this ratio was ~1 : 1, except for Cu(OTf)2, where it was 1.9 : 1. The reason for the notable diastereoselectivity of the processes studied when employing achiral rhodium complexes and copper(II) triflate still remains unclear.

Similar to the formation of 4a a competitive process apparently takes place in the course of catalytic decomposition of diazo Meldrum’s acid 2c in the presence of amino ester 1b (Scheme 5) which results in the isolation of indole 6 along with pyrrolidine 3i.

It is suggested that during this process electrophilic attack of the carbenoid A onto the o-CH-bond of the aromatic (PMP) ring initially takes place to furnish the C–H-insertion product E. On heating the latter eliminates CO2 and acetone20 giving rise to β-amino ketene F followed by intramolecular acylation of the N–H-group to produce indole 6. Similar acylations are well preceded in the chemistry of ketenes.21

In contrast to reactions of diazomalonates 2a,b and diazo Meldrum’s acid 2c, on catalytic decomposition of diazaocetic ester 2d in the presence of amine 1b the formation of tertiary amine 8d was observed as well, which formally arises from insertion of carbenoid A into the N–H-bond of amino ester 1b. The key intermediate of this reaction most likely is also a metal-free N-ylide of type C (Scheme 3),17 which can undergo either 1,2-proton migration to produce N–CH2CO2Me-substituted amine 8d, or can experience intramolecular cyclization into pyrrolidine 7. Apparently, N-ylide C carrying only one ester group is less stabilized than other ylides, derived from β-dicarbonyl compounds, and is more rapidly converted into tertiary amine 8d.

The considered catalytic reactions of diazomalonates and other diazoesters 2 in the presence of unsaturated amino esters 1 with production of pyrrolidines 3 can be classified as a [4 + 1]-annulation process. Metal–carbenes A formed during the decomposition process interact with the α,β-unsaturated δ-NH-system of ester 1 which may be schematically illustrated through transition state G although it apparently proceeds as a domino process (Scheme 6).

Until the present time similar catalytic processes with diazo compounds, which formally take place via transition state G, have essentially not been studied. There is in fact only one report on [4 + 1]-cycloaddition of carbenoids which was demonstrated by the example of catalytic decomposition of
diazocarbonyl compounds in the presence of homopropargylic alcohols to produce the corresponding tetrahydrofurans.\cite{22} In this respect, further investigations of catalytic reactions of diazocarbonyl compounds of different types with α,β-unsaturated δ-N-substituted amino esters are undeniably of great importance and interest.

Conclusions

In conclusion, we have described herein for the first time a catalytic reaction of diazomalonates and other diazoesters with α,β-unsaturated δ-(N-aryl)amino esters. In the case of diazomalonates they provide a good way for the synthesis of multi-substituted functionalized N-aryl pyrrolidines. Among eight transition metal-complexes tested on Rh(II)-, Cu(II)-, Fe(III)- and Ru(II)-basis, the most efficient catalyst was found to be Rh2(OAc)4. Generally, N-aryl pyrrolidines are formed as a mixture of two diastereomers with the trans-isomer being the major one. There was only one case, employing ethyl diazoacetate, when the 2,3-trans-isomer was obtained exclusively. The main side process amounting up to 6–31% yield in these catalytic reactions was an insertion of the electrophilic metal carbene into the electron-rich p- or o-C-H-bond of the N-aryl group.

Experimental section

General methods

All reactions were carried out under an argon atmosphere in the solvents dried and purified before use by common methods. Monitoring of the reaction course was accomplished by thin-layer chromatography (TLC) on precoated silica gel SIL G/UV254 plates [Marchery, Nagel & Co.] Flash chromatography was performed using Merck silica gel 60 230–400 mesh. 1H and 13C NMR spectra were recorded in CDCl3 solutions using Varian Gemini 200 and 2000 (200 MHz), Varian Gemini 300B (300 MHz) and Bruker Avance DRX 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm, and coupling constants are given in Hz. All signals in NMR spectra were normalized relative to signals of CDCl3 (δ = 7.26 ppm in 1H NMR and δ = 77.0 in 13C NMR spectra). A single crystal of the trans-isomer of pyrrolidine 3b was selected from the analytical sample; the supplementary crystallographic data for 3b (CCDC 1039286) are provided in the ESI.† IR spectra were obtained with a FT IR spectrometer (Genesis ATIMattson/Unicam). UV spectra were recorded on a UV spectrometer (DU-650 Beckmann). Melting points are uncorrected. All the ESI/HR mass spectra were recorded on a Brucker APEX II FT-ICR. Amino esters 1a–h and diazo compounds 2a–e were prepared using previously described protocols.\cite{10,23,24}

General procedure for Rh2(OAc)4-catalyzed reactions of diazomalonate 2a with aminoester 1a. Preparation of pyrrolidines 3a, 5a and insertion product 4a

Dimethyl diazomalonate 2a was added in one portion or dropwise to a solution of amino ester 1a and Rh2(OAc)4 in CH2Cl2. The reaction mixture was stirred overnight, the solvent was removed in vacuo, and then the residue was separated by silica gel flash chromatography to afford a mixture of starting amine 1a, a mixture of trans- and cis-isomers of pyrrolidine 3a, as well as insertion products 4a, 5a in separate experiments. The mixture of isomers 3a was further subjected to preparative TLC to give pure trans- and cis-diastereomers of 3a. (The detailed description of these experiments is given in ESI,† p. S4–S7).

(3S*,5R*)-Dimethyl 3-(2-ethoxy-2-oxoethyl)-1,5-diphenylpyrrolidine-2,2-dicarboxylate (trans-3a). Colorless solid; m.p. 124–125 °C; 1H NMR (300 MHz, CDCl3) δ 7.39–7.49 (m, 2H), 7.18–7.38 (m, 3H), 7.12–7.05 (m, 2H), 6.71 (d, J = 7.3, 1.0 Hz, 1H), 6.36–6.48 (m, 2H), 5.05 (d, J = 9.0 Hz, 1H), 4.04–4.14 (m, 2H), 3.88 (2, 3H), 3.73 (s, 3H), 3.22 (dddd, J = 12.4, 10.4, 6.5, 3.9 Hz, 1H), 3.03 (dd, J = 16.1, 4.0 Hz, 1H), 2.55 (dd, J = 12.2, 9.2 Hz, 1H), 2.16–2.25 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H); 13C NMR (50 MHz, CDCl3) δ 171.1, 168.9, 169.9, 145.1, 143.4, 129.4, 128.7, 127.0, 125.8, 114.0, 75.6, 65.5, 60.7, 56.6, 53.0, 52.7, 43.1, 38.9, 34.9, 14.1; HRMS (ESI) calcd for C24H27NO6 [M + H]+ 426.1915, found 426.1917, 426.1915.

(3S*,5R*)-Dimethyl 3-(2-ethoxy-2-oxoethyl)-1,5-diphenylpyrrolidine-2,2-dicarboxylate (cis-3a). Colorless oil; 1H NMR (400 MHz, CDCl3) δ 7.37–7.43 (m, 2H), 7.13–7.33 (m, 3H), 6.98–7.04 (m, 2H), 6.64–6.70 (m, 1H), 6.50–6.59 (m, 2H), 5.04 (dd, J = 9.8, 6.0 Hz, 1H), 4.02–4.22 (m, 2H), 3.93 (s, 3H), 3.53 (s, 3H), 3.27–3.43 (m, 1H), 2.53–2.75 (m, 2H), 2.42 (dd, J = 16.8, 9.1 Hz, 1H), 1.82 (t, d, J = 12.3, 9.9 Hz, 1H), 1.24 (t, J = 7.1 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 171.4, 170.0, 169.7, 144.4, 142.5, 128.6, 128.2, 127.0, 126.3, 118.9, 116.6, 77.9, 64.4, 60.7, 52.6, 52.6, 44.8, 41.7, 35.4, 14.2; HRMS (ESI) calcd for C24H25NO6 [M + H]+ 426.1907, found 426.1915.

(E)-Dimethyl 2-((3-ethoxy-5-oxo-1-phenylpent-3-en-1-yl)-amino)phenyl)malonate (4a). Colorless oil; 1H NMR
(200 MHz, CDCl$_3$) $\delta$ 7.19–7.38 (m, 5H), 7.03–7.16 (m, 2H), 6.88 (dt, $J = 14.7$, 7.2 Hz, 1H), 6.42–6.56 (m, 2H), 5.92 (dt, $J = 15.6$, 1.5 Hz, 1H), 4.47 (s, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 4.11 (broad, 1H), 3.71 (s, 6H), 2.45–2.87 (m, 2H), 1.28 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 169.0; 165.9, 146.8, 144.2, 142.4, 130.0, 128.8, 127.5, 126.2, 124.4, 113.4, 60.4, 56.9, 56.7, 52.7, 41.2, 14.2; HRMS (ESI) caleld for C$_{24}$H$_{27}$NO$_6$ [M + Na]$^+$ 448.1736, found 448.1735.

**Dimethyl 1-(4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)phenyl)-3-(2-ethoxy-2-oxoethyl)-5-phenylpyrrolidine-2,2-dicarboxylate (trans-5a).** Colorless solid; m.p. 143–144 °C; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.19–7.46 (m, 5H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.38 (d, $J = 8.8$ Hz, 2H), 5.02 (d, $J = 8.9$ Hz, 1H), 3.98–4.19 (m, 2H), 3.74 (s, 3H), 3.88 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 3.10–3.37 (m, 1H), 3.01 (dd, $J = 16.1$, 4.0 Hz, 1H), 2.53 (td, $J = 12.2$, 9.0 Hz, 1H), 2.05–2.32 (m, 2H), 1.21 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 171.1, 167.9, 168.9, 145.1, 143.4, 129.4, 128.7, 127.0, 125.8, 121.4, 114.0, 76.0, 65.5, 60.7, 56.6, 53.0, 52.7, 52.6, 43.1, 38.9, 34.9, 14.1; HRMS (ESI) caleld for C$_{25}$H$_{29}$NO$_7$ [M + Na]$^+$ 506.2155, found 506.2152.

**General procedure for Rh(n)-catalyzed decomposition of diazomalonates 2a and 2b in the presence of aminosterases 1b–h. Preparation of pyrrolidines 3b–h.**

A solution of diazomalonate 2a or 2b in DCM was added in one portion to a solution of amino ester 1b–h in DCM with the Rh(n)-catalyst and the reaction mixture was stirred at room temperature until the disappearance of the starting amino ester 1. Then, DCM was removed in vacuo and the residue was purified by silica gel flash chromatography to afford pyrrolidines 3b–h as the mixtures of trans- and cis-isomers which were thereafter subjected to preparative TLC to give pure trans- and cis-diaestereoisomers. (The detailed description of these experiments is given in ESI, p. S4–S7).

(3R*,5R*)-Dimethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxophenyl)-3-phenylpyrrolidine-2,2-dicarboxylate (trans-3b). Colorless solid; m.p. 153–155 °C; IR (KBr) $\nu$$_{max}$ 3052, 2989, 2946, 2927, 2879, 2827, 1735, 1602, 1514, 1454, 1437, 1420, 1380, 1351, 1297 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 (d, $J = 7.3$ Hz, 2H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.22 (t, $J = 7.3$, 1H), 6.66 (d, $J = 9.2$ Hz, 2H), 6.39 (d, $J = 9.2$ Hz, 2H), 4.98 (d, $J = 9.0$ Hz, 1H), 3.71 (s, 3H), 3.87 (s, 3H), 3.11–3.27 (m, 1H), 3.66 (s, 3H), 3.00 (dd, $J = 16.2$, 4.0 Hz, 1H), 2.54 (td, $J = 12.1$, 9.3 Hz, 1H), 2.10–2.28 (m, 2H), 1.20 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.2, 170.1, 169.7, 151.9, 144.0, 139.2, 128.6, 125.9, 115.1, 114.1, 76.4, 65.5, 60.6, 55.4, 52.9, 52.5, 43.1, 39.0, 35.0, 14.0; HRMS (ESI) caleld for C$_{25}$H$_{27}$NO$_7$ [M + Na]$^+$ 478.1834, found 478.1834.

(3S*,5R*)-Dimethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxophenyl)-3-phenylpyrrolidine-2,2-dicarboxylate (cis-3b). Colorless oil; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.09–7.49 (m, 7H), 6.34–6.81 (m, 2H), 4.96 (dd, $J = 9.9$, 5.6 Hz, 1H), 4.08–4.18 (m, 2H), 3.92 (s, 3H), 3.65 (s, 3H), 3.43–3.52 (m, 4H), 2.27–2.78 (m, 3H), 1.76 (td, $J = 12.1$, 10.0 Hz, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); HRMS (ESI) caleld for C$_{25}$H$_{27}$NO$_7$ [M + Na]$^+$ 484.2335, found 484.2335.
(3R*,5R*)-Dimethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxynaphthalen-2-yl)pyrrolidine-2,2-dicarboxylate (trans-3d).

Bright yellow oil; IR (film) \( \nu_{\text{max}} \) 3047, 2981, 2925, 2907, 2835, 1735, 1514, 1462, 1435, 1382, 1295, 1250, 1218, 1194, 1177, 1062, 1032 cm\(^{-1}\); \( 1^H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.56–7.65 (m, 1H), 7.02–7.21 (m, 3H), 6.66 (d, \( J = 9.2 \) Hz, 2H), 6.29 (d, \( J = 9.2 \) Hz, 2H), 5.05 (d, \( J = 9.2 \) Hz, 1H), 4.04–4.12 (m, 2H), 3.90 (s, 3H), 3.74 (s, 3H), 3.67 (s, 3H), 3.40–3.48 (m, 1H); HRMS (ESI) calcld for \( C_{26}H_{23}NO_7 \) [M + Na\(^+\)] 528.1998, found 528.1998.

(3S*,3R*)-Dimethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxynaphthalen-2-yl)pyrrolidine-2,2-dicarboxylate (cis-3d).

Bright yellow oil; IR (film) \( \nu_{\text{max}} \) 3048, 2925, 2926, 2871, 1734, 1509, 1489, 1458, 1436, 1384, 1246, 1217, 1105, 1058, 1032 cm\(^{-1}\); \( 1^H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.54–7.62 (m, 1H), 7.04–7.10 (m, 3H), 6.61 (d, \( J = 9.2 \) Hz, 2H), 6.52 (d, \( J = 9.2 \) Hz, 2H), 5.14 (dd, \( J = 9.8, 5.9 \) Hz, 1H), 4.21 (dd, \( J = 16.2, 10.5 \) Hz, 1H), 2.40 (s, 3H), 3.82 (s, 3H), 3.40–3.53 (m, 4H), 2.57–2.70 (m, 2H), 1.36–1.47 (m, 4H), 1.65 (dd, \( J = 12.1, 9.8 \) Hz, 1H), 1.24 (t, \( J = 7.1 \) Hz, 3H); HRMS (ESI) calcld for \( C_{26}H_{23}NO_7 \) [M + Na\(^+\)] 528.1998, found 528.1998.

(3S*,5R*)-Dimethyl 5-(3-chlorophenyl)-3-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)pyrrolidine-2,2-dicarboxylate (cis-3g).

Bright yellow oil; IR (film) \( \nu_{\text{max}} \) 3041, 2981, 2925, 2907, 2835, 1768, 1747, 1732, 1597, 1574, 1521, 1470, 1464, 1455, 1382, 1339, 1295, 1021 cm\(^{-1}\); \( 1^H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.47–7.53 (m, 1H), 7.15–7.37 (m, 3H), 6.69 (d, \( J = 9.2 \) Hz, 2H), 6.36 (d, \( J = 9.2 \) Hz, 2H), 4.94 (d, \( J = 9.1 \) Hz, 1H), 3.98–4.19 (m, 2H), 3.88 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.11–3.27 (m, 1H), 3.00 (dd, \( J = 16.3, 4.0 \) Hz, 1H), 2.49 (d, \( J = 12.2, 9.3 \) Hz, 1H), 2.15–2.24 (m, 2H), 1.82 (t, \( J = 7.1 \) Hz, 3H); \( 13^C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 171.2, 170.0, 169.5, 152.2, 146.4, 138.9, 134.6, 130.1, 127.3, 126.2, 124.2, 115.1, 114.3, 76.3, 65.2, 60.8, 55.3, 50.6, 52.6, 43.1, 38.9, 34.9, 14.1; HRMS (ESI) calcld for \( C_{26}H_{24}ClNO_6 \) [M + Na\(^+\)] 512.1452, 512.1452, found 512.1451, 514.1424.

(3R*,5R*)-Dimethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)pyrrolidine-2,2-dicarboxylate (trans-3h).

Bright yellow oil; IR (film) \( \nu_{\text{max}} \) 3047, 2981, 2925, 2928, 2925, 2906, 2834, 1736, 1514, 1463, 1448, 1434, 1380, 1350, 1296, 1250, 1214, 1193, 1179, 1096, 1081, 1073, 1055, 1033 cm\(^{-1}\); \( 1^H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.73–7.47 (m, 5H), 6.62–6.80 (m, 3H), 6.45–6.59 (m, 2H), 2.62–2.63 (m, 1H), 4.59 (dd, \( J = 8.6, 4.7 \) Hz, 3H).
Diazomalonate 2a using Cu(II), Fe(III) and Ru(II)-complexes in the presence of amino ester 1b. General procedure for preparation of pyrrolidines 3b

The description of these experiments is given in ESI,† p. S4–S7.

Attempts to carry out catalytic decomposition of diazomalonate 2a using Cu(n), Fe(m) and Ru(n)-complexes in the presence of amino ester 1b

The description of these experiments is given in ESI,† p. S4–S7.

Rh(n)-catalyzed decomposition of diazo Meldrum's acid 2c in the presence of amino ester 1b. General procedure for preparation of pyrrolidines 3i and indoline 6

A solution of amino ester 1b and diazo Meldrum's acid 2c with the Rh(n)-catalyst in anhydrous benzene was refluxed until the disappearance of the starting amino ester. Then the solvent was removed in vacuo and the residue was purified by silica gel flash chromatography to afford pyrrolidines 3i as a mixture of trans- and cis-isomers, which were further separated using preparative thin-layer chromatography, and indoline-2-one 6. The detailed description of these experiments is given in ESI,† p. S4–S7.

(3S*,5R*)-Diethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-5-phenylpyrrolidine-2,2-dicarboxylate (cis-3i). Bright yellow oil; IR (film) νmax 2926, 2853, 1733, 1663, 1604, 1511, 1454, 1355, 1289, 1246, 1179, 1094, 1033 cm⁻¹; ²⁹C NMR (300 MHz, CDCl₃) δ 7.40–7.50 (m, 5H), 7.14–7.34 (m, 3H), 6.62 (d, J = 9.1 Hz, 2H), 6.26 (d, J = 9.1 Hz, 2H), 5.00 (dd, J = 10.0, 5.8 Hz, 1H), 3.99–4.22 (m, 2H), 3.65 (s, 3H), 3.03–3.14 (m, 1H), 2.61–2.68 (m, 4H), 2.54 (dd, J = 16.5, 5.5 Hz, 1H), 2.20–2.31 (m, 1H), 1.95 (s, 3H), 1.83–1.92 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 208.4, 207.0, 171.3, 152.8, 142.0, 138.3, 128.8, 127.3, 126.7, 117.3, 114.5, 86.1, 65.2, 61.1, 55.5, 43.5, 41.9, 34.9, 32.0, 27.8, 14.3; HRMS (ESI) calced for C₂₂H₂₃NO₄ [M + K⁺] 506.1581, found 506.1578.

(E)-Ethyl 5-(5-methoxy-oxoindolin-1-yl)-5-phenylpent-2-enoate 6. Bright yellow oil; IR (film) νmax 2934; 1710; 1655; 1599; 1490; 1486; 1390; 1367; 1311; 1289; 1277; 1189; 1095; 1035 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27–7.41 (m, 5H), 6.78–6.97 (m, 2H), 6.60 (dd, J = 9.8, 6.1 Hz, 1H), 6.49 (d, J = 8.6 Hz, 1H), 5.82 (dt, J = 15.6, 1.4 Hz, 1H), 5.69 (dd, J = 9.8, 6.1 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.56 (s, 2H), 3.08–3.37 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.0, 165.9, 155.6, 143.9, 137.9, 136.4, 128.8, 127.8, 127.0, 125.9, 124.3, 111.9, 111.9, 110.4, 60.3, 55.7, 53.4, 36.0, 33.1, 14.2; HRMS (ESI) calced for C₂₂H₂₃NO₄ [M + Na⁺] 388.1525, found 388.1518.

Rh(n)-catalyzed reactions of diazoacetates 2d and 2e with amino ester 1b. General procedure

Diazooacetate 2d or 2e was added to a solution of amine 1b at the relevant temperature (0 °C, −10 °C, −25 °C) in DCM with Rh₂(OAc)₄. The reaction mixture was stirred for an appropriate period of time keeping the temperature of the reaction mixture constant. Then the solvent was removed in vacuo and the residue was purified by silica gel flash chromatography to afford starting amine 1b, a mixture of dimethyl fumarate and maleate 9, N–H insertion product 8, and pyrrolidone 7 (in the case of reaction with diazo acetate 2e). The detailed description of these experiments is given in ESI,† p. S4–S7.

Ethyl ((E)-5-[(2-methoxy-2-oxoethyl)(4-methoxyphenyl)-amino]-5-phenylpent-2-enoate (8d). Bright yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 7.22–7.38 (m, 7H), 6.75–6.98 (m, 3H), 5.81 (dt, J = 15.7, 1.5 Hz, 1H), 4.91 (dd, J = 8.0, 6.4 Hz, 1H), 3.97–4.22 (m, 2H), 3.76 (s, 3H), 3.69 (dd, J = 7.2 Hz, 2H), 3.60 (s, 3H), 2.59–2.97 (m, 2H), 1.24 (t, J = 7.13 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.8, 166.2, 153.8, 145.6, 142.2, 139.5, 128.6, 128.0, 127.7, 123.3, 118.9, 114.6, 62.9, 60.2, 55.6, 51.7, 50.7, 35.4, 14.2; HRMS (ESI) calced for C₂₃H₂₄NO₅ [M + Na⁺] 420.1787, found 420.1792.

(2R*,3R*,5R*)-ethyl 3-(2-ethoxy-2-oxoethyl)-1-(4-methoxyphenyl)-5-phenylpyrrolidine-2-carboxylate (7). Colorless oil; IR (film) νmax 2981, 1736, 1620, 1513, 1450, 1363, 1242, 1178, 1028 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.22–7.33 (m, 5H), 6.70 (d, J = 9.0 Hz, 2H), 6.38 (d, J = 9.0 Hz, 2H), 4.98 (d, J = 9.0 Hz, 1H), 4.78 (d, J = 7.5 Hz, 1H), 4.14–4.23 (m, 4H), 3.68 (s, 3H), 3.09–3.22 (m, 1H), 2.52 (ddd, J = 9.5, 12.0, 12.0 Hz, 1H), 2.43 (dd, J = 8.5, 17.0 Hz, 1H), 2.34 (dd, J = 7.0, 17.0 Hz, 1H), 2.08 (qd, J = 15.7, 7.1 Hz, 1H), 1.85 (dd, J = 9.1, 6.1 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H). View Article Online
1.98 (dd, J = 6.5, 12.0 Hz, 1H), 1.24–1.29 (m, 6H); 13C NMR (101 MHz, CDCl3) δ 172.8, 171.5, 151.4, 144.4, 139.9, 128.6, 126.8, 125.8, 114.7, 113.5, 64.9, 62.7, 60.8, 60.6, 55.6, 39.4, 35.4, 34.8, 14.3, 14.2; MS [ESI] calcd for C24H29NO5 [M + H]+ 412, found 412; HRMS [ESI] calcd for C24H29NO5 [M + Na]+ 434.1943, found 434.1946.

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References


