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Lewis acid catalyzed reactions of donor–acceptor cyclopropanes with 1- and 2-pyrazolines: formation of substituted 2-pyrazolines and 1,2-diazabicyclo[3.3.0] octanes

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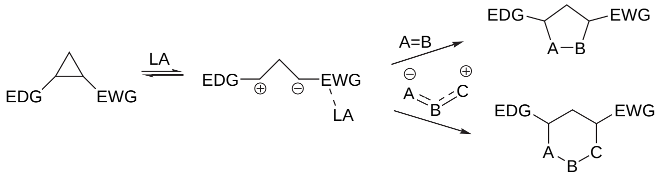
ABSTRACT

The reaction of 2-substituted cyclopropane-1,1-dicarboxylates with 1- and 2-pyrazolines is efficiently catalyzed by scandium or ytterbium triflates to give *N*-substituted 2-pyrazolines or 1,2-diazabicyclo[3.3.0]octanes. The reactions of 2-pyrazolines give diazabicyclooctanes as the major products. In contrast, the reactions starting from 1-pyrazolines predominantly give *N*-substituted 2-pyrazolines, which become the major compounds obtained if an equimolar amount of $GaCl_3$ is used. A possible reaction mechanism is suggested.

1. Introduction

It is known that cyclopropanes with electron-donating and electron-withdrawing substituents at the vicinal position can undergo opening of the three-membered ring[1] upon thermolysis or under catalysis by Lewis acids due to cleavage of the σ-1,2-bond of the cyclopropane ring. The resulting dipolar intermediate can enter formal [2+3]- or [3+3]-cycloaddition with double and triple bonds and with 1,3-dipoles to give five- or six-membered rings, including rings containing heteroatoms (Scheme 1). Reactions of donor–acceptor cyclopropanes with alkenes,[2,3] acetylenes,[4,5] aldehydes,[6–8] isocyanates,[9] imines,[10–12] diazenes,[13,14] nitriles,[15,16] α,β-unsaturated ketones,[17] azomethineimines,[18] and nitrones[19–21] have been reported. Recently,[22] the reaction of hydrazinoethyl 1,1-cyclopropanediesters with aldehydes in the presence of catalytic $Yb(OTf)_3$ was carried out as intramolecular cyclization into 1,2-diazabicyclo[3.3.0]octane derivatives. The products of these reactions are used as convenient synthons to obtain various classes of organic compounds, primarily ones that are of interest as biologically active compounds.[10,16,21,23]

Aryl, and sometimes alkyl or alkoxy groups, are used as electron-donating substituents in cyclopropanes, whereas alkoxycarbonyls are used as electron-withdrawing substituents. Tin(II) triflates[6] and rare-earth triflates[20,23] as well as chloroalanes[2] are the most popular Lewis acids; gallium and indium compounds[14] are less common. Examples of enantioselective [2+3]-cycloaddition of cyclopropanedicarboxylates with nitrones have been reported, where Lewis acids with chiral ligands were used as catalysts.[20]



LA – Lewis acid; EDG – electron-donating group; EWG – electron-withdrawing group

Scheme 1.

Two studies have been published dealing with reactions of donor–acceptor cyclopropanes with compounds incorporating an N=N bond.[13,14] One of them[13] reports the addition of methyl 2,2-dimethoxycyclopropane-1-carboxylate to diazene derivatives under thermolysis conditions, while the other one[14] describes the addition of 2-substituted dimethyl cyclopropane-1,1-dicarboxylates to diazene derivatives catalyzed by gallium trichloride; both reactions result in substituted pyrazolidines.

Reactions of donor–acceptor cyclopropanes with 1- or 2-pyrazolines containing N=N or C=N bonds have not yet been studied. In turn, successful implementation of these reactions might result

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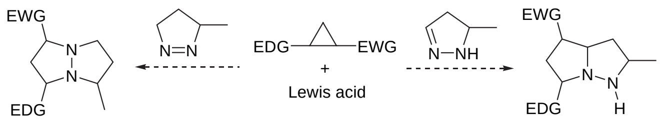
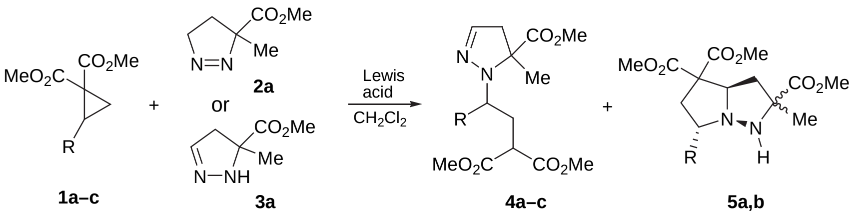
in derivatives of 1,5- or 1,2-diazabicyclo[3.3.0]octanes (Scheme 2) that are of interest as biologically active compounds and as accessible synthons for constructing various nitrogen-containing heterocyclic compounds.



Scheme 2.

2. Results and discussion

In order to optimize the reaction conditions and determine the reaction direction, we chose dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1a**) and isomeric pyrazolines **2a** and **3a** as the starting reagents. Prolonged refluxing in the absence of Lewis acids does not cause compounds **1a** and **2a** to react. However, cyclopropane **1a** reacts with pyrazolines **2a** or **3a** in the presence of scandium, indium, or ytterbium triflates even at room temperature, $Sc(OTf)_3$ being the most efficient of the catalysts used. Complete conversion of cyclopropane **1a** in the presence of $Sc(OTf)_3$ takes 3 days (1 mol % of the catalyst) or 10–12 h (5 mol %). In all cases, *N*-substituted 2-pyrazoline **4a** and fused pyrazolidine **5a** are the main reaction products from cyclopropane **1a** both with 1-pyrazoline **2a** and with 2-pyrazoline **3a** (Scheme 3, Table 1); both products are formed as mixtures of two diastereomers in a about 1:1 ratio.



R = C_6H_5 (**a**); 2-Thienyl (**b**); H (**c**)

Scheme 3.

Stereoisomers **5a** can be easily separated from each other and from isomeric pyrazolines **4a** by means of column chromatography. The fact that only two isomers of **5a** out of four are formed is due to steric factors, which ensure that only the *anti*-8-phenyl-1,2-diazabicyclo[3.3.0]octane fragment with varying orientation of substituents at C(3) is formed. The structures of *anti*- and *syn*-**5a** are confirmed by NOE spectra (Fig. 1). The 2D ^1H NOESY spectrum of *anti*-**5a** features a cross-peak between the signals of H-8 (δ 4.10) and protons of the CH_3-group (δ 1.52) as opposed to *syn*-**5a**, which features a cross-peak between the signals of CH_3 (δ 1.45) and H-5 (δ 4.49).

Table 1
Yields of compounds **4a** and **5a** in Lewis acid catalyzed reactions of cyclopropane **1a** with pyrazolines **2a** and **3a** (reagent ratios: **1a**:**2a**=1.2:1, **1a**:**3a** 1:1; solvent: CH_2Cl_2)

Pyrazoline	Lewis acid	mol %	*T* (°C)	*t*	Isolated yield (%)	
					4a[a]	**5a**[a]
2a	$Sc(OTf)_3$	5	20	12 h	61	29
2a	$Sc(OTf)_3$	1	20	72 h	60	26
3a	$Sc(OTf)_3$	5	20	12 h	31	61
2a	$Yb(OTf)_3$	5	20	72 h	55	27
3a	$Yb(OTf)_3$	5	20	72 h	30	54
2a	$In(OTf)_3$	5	20	72 h	19	10
2a	$GaCl_3$	20	0–5	5 min	18	0
2a	$GaCl_3$	100	20	5 min	59	0
2a	$GaCl_3$	100	0–5	5 min	72	0
2a	$EtAlCl_2$	100	20	5 min	0	0
2a	$EtAlCl_2$	100	−60	20 min	32	0

[a] Compounds **4a** and **5a** are formed as a mixture of diastereomers in about 1:1 ratio.

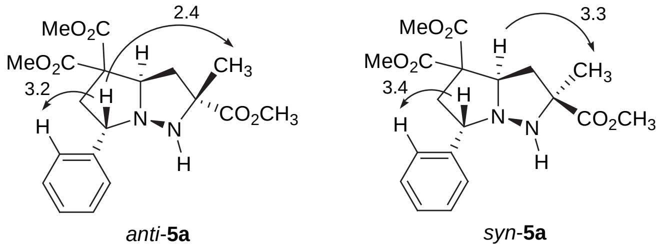


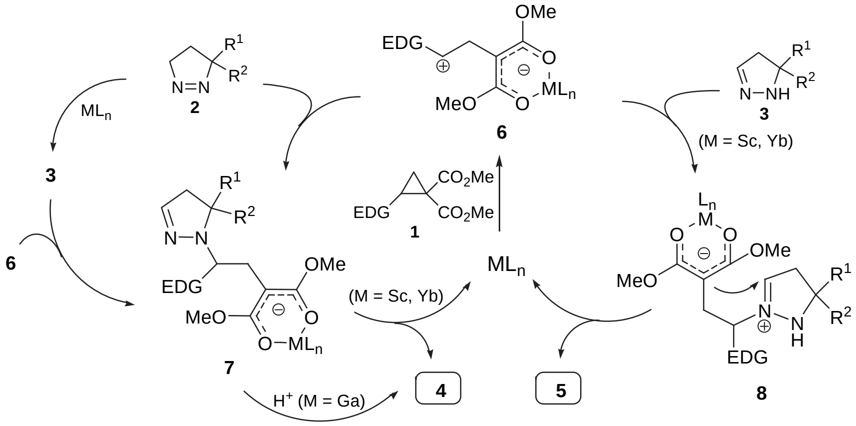
Fig.1. Key cross-peaks in 2D ^1H NOESY spectra of *anti*- and *syn*-**5a**.

As one can see from the structure of compounds **4a** and **5a**, the formation of these structures formally involves the addition of the 1,3-dipolar intermediate, which is formed due to opening of the cyclopropane ring, either to the N–H bond or to the C=N bond in 2-pyrazoline **3a** as a result of preliminary isomerization of 1-pyrazoline **2a**. However, although the same compounds **4a** and **5a** are formed, their ratio depends considerably on the nature of the starting pyrazolines **2a** or **3a**. In fact, the reaction using 1-pyrazoline **2a** produces two times as much pyrazoline **4a** as pyrazolidine **5a**, whereas their ratio is reversed in the case of 2-pyrazoline **3a** (Table 1). Ytterbium triflate acts less readily; however, the selectivities of formation of compounds **4a** and **5a** in the presence of this compound are the same as in the case of $Sc(OTf)_3$.

The use of anhydrous $GaCl_3$ also ensures that the reaction of cyclopropanedicarboxylate **1a** with pyrazoline **2a** will occur, but an equimolar amount of $GaCl_3$ and cooling to 0 °C are required. No 1,5- or 1,2-diazabicyclo[3.3.0]octanes are formed at all in this case; moreover, as concerns 1:1 adducts, only *N*-substituted 2-pyrazoline **4a** (Table 1) is formed as two diastereomers in a 1:1 ratio, just like in the presence of $Sc(OTf)_3$ or $Yb(OTf)_3$ as catalysts. Ethyl dichloroalane at low temperatures acts similarly to $GaCl_3$; however, the yield of pyrazoline **4a** is rather low due to considerable side reactions (Table 1).

Formally, the observed formation of substituted pyrazoline **4a** corresponds to the addition of the 1,3-dipolar intermediate (formed due to the cyclopropane ring opening) to the N–H bond in 2-pyrazoline **3a**. However, in reality, the reaction of cyclopropane **1a** with pre-synthesized 2-pyrazoline **3a** in the presence of $GaCl_3$ is more complicated than in the case of 1-pyrazoline **2a**. In fact, the use of equimolar amounts of **1a**, **3a**, and $GaCl_3$ yields a complex mixture of compounds, in which the content of pyrazoline **4a** does not exceed 20%. Furthermore, we have shown in a special experiment that in the absence of cyclopropane **1a**, noticeable isomerization of **2a** to **3a** in the presence of an equimolar amount of $GaCl_3$ requires a few hours, whereas the reaction of cyclopropane **1a** with pyrazolines is complete within 5 min.

Based on the above results and the literature data[1,6,14] concerning three-membered ring opening in cyclopropane-1,1-dicarboxylates, a likely reaction mechanism can be suggested. The main contribution of Lewis acids probably involves activation of a σ-C–C bond in the cyclopropane ring, which is favored by coordination of the Lewis acid to the ester oxygen atoms. Electron-donating groups (EDG) at C(2) in the cyclopropane stabilize dipolar intermediate **6**, which then reacts with pyrazolines **2a** or **3a** (Scheme 4).



Scheme 4.

In the case of 1-pyrazoline, intermediate **6** attacks the nucleophilic nitrogen atom with simultaneous or subsequent proton elimination from the CH_2 group to give intermediate **7**, which adds a proton to the carbon atom bound to two ester groups, thus regenerating the catalyst (M=Sc, Yb, In) and giving *N*-substituted pyrazolines **4** or their stable complexes in the case of $GaCl_3$; the latter effect makes it necessary to use an equimolar amount of gallium trichloride, so pyrazolines **4** can only be isolated by acidic treatment of the reaction mixture. Cyclopropane **1a** and pyrazoline **3a** in the presence of $GaCl_3$ undergo deeper conversions, as it is in fact observed if compound **3a** is used as the starting substrate.

In the case of Sc, Yb, and In triflates, cyclopropane **1a** reacts with pyrazolines **2a** and **3a** much more slowly than in the presence of $GaCl_3$, and a considerable fraction of 1-pyrazoline undergoes isomerization to 2-pyrazoline under these conditions. As a result, intermediate **7** can be formed both from 1-pyrazolines **2** and from 2-pyrazolines **3**. Although the basic properties of the NH group in pyrazoline **3** are weak, activated cyclopropane **6** can attack it to give intermediate **7**. A similar addition of amines to donor–acceptor cyclopropanes has been described elsewhere.[24] Yet, pyrazoline **3** predominantly reacts with cyclopropane **1** in a different way. Apparently, electrophilic intermediate **6** can attack the imine nitrogen atom to give intermediate **8**, which undergoes cyclization to bicyclic pyrazoline **5** (Scheme 4). At least, this mechanism explains both the formation of a mixture of compounds **4** and **5** if Sc, Yb, or In are used, and the predominant formation of each of them depending on which of the starting pyrazolines **2** or **3** is used in the reaction.

We have then studied the reactions of 2-phenylcyclopropan-1,1-dicarboxylate **1a** with other 1- and 2-pyrazolines and the reactions of pyrazolines **2a** and **3a** with 2-thienyl- (**1b**) and unsubstituted (**1c**) dimethyl cyclopropane-1,1-dicarboxylates.

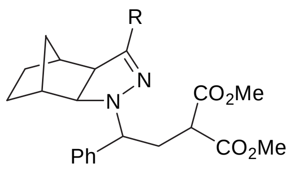
2-Thienylcyclopropanedicarboxylate **1b** reacts with pyrazolines **2a** or **3a** similarly to cyclopropane **1a** to predominantly give substituted pyrazoline **4b** in the presence of $GaCl_3$ or, depending on the pyrazoline nature, either mostly the same compound **4b** or 1,2-diazabicyclo[3.3.0]octane **5b** in the presence of $Sc(OTf)_3$ (Scheme 3, Table 2). Based on ^1H and ^{13}C NMR spectra, both compounds are mixtures of diastereomers formed in a about 1:1 ratio.

Unlike compounds **1a** and **1b**, cyclopropanedicarboxylate **1c** is much less reactive: its reaction with pyrazoline **2a** requires the presence of $GaCl_3$. As expected, substituted pyrazoline **4c** is the only 1:1 product that was isolated (Scheme 3, Table 2).

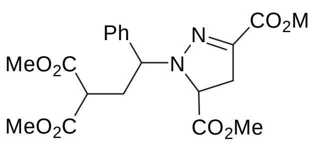
The presence of just one ester group at the cyclopropane ring (even if a vicinal electron-donating substituent is present) can also affect its reactivity to a considerable extent. In fact, the *E*-isomer of methyl 2-ethoxycyclopropanecarboxylate does not react with pyrazoline **2a** even in the presence of $GaCl_3$, whereas the *Z*-isomer undergoes reactions resulting in a complex mixture of various compounds.

Geminal phenyl substituents in pyrazolines **2b** and **3b** considerably shield the nitrogen atom, which is nearest to them and hence the attack of cyclopropane **1a** on the N atom is hindered significantly. In both cases, diazabicyclooctane **5d** is the major product of the reaction of cyclopropane **1a** with pyrazolines **2b** and **3b**; it is formed according to Scheme 4 due to attack of intermediate **6** on the N(2) atom in 2-pyrazoline **3b**. In the case of 1-pyrazoline **2b**, the formation of diazabicyclooctane **5d** is apparently preceded by its isomerization to 2-pyrazoline **3b**, whereas the fraction of substituted pyrazoline **4d** is as low as about 5% due to steric hindrance (Scheme 5, Table 2).

Reactions of cyclopropanedicarboxylate **1a** with polycyclic pyrazolines **2c** and **3c** or with 3,5-disubstituted 2-pyrazoline **3d**, both in the presence of $GaCl_3$ and $Sc(OTf)_3$, give only 'open' structures, namely *N*-substituted 2-pyrazolines **4e**–**g**. The absence of diazabicyclooctanes in the case of 2-pyrazolines **3c**,**d** is apparently due to the presence of an electron-withdrawing substituent at the C=N bond, which makes the formation of an **8** type intermediate impossible; as a result, the selectivity of the formation of *N*-substituted 2-pyrazolines **4** increases significantly.



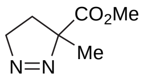
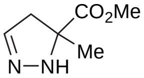
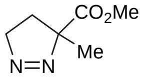
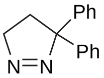
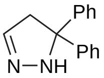
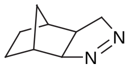
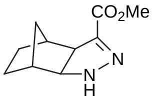
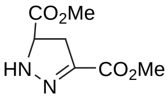
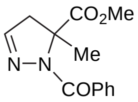
4e,f: R = H (**e**); CO_2Me (**f**)



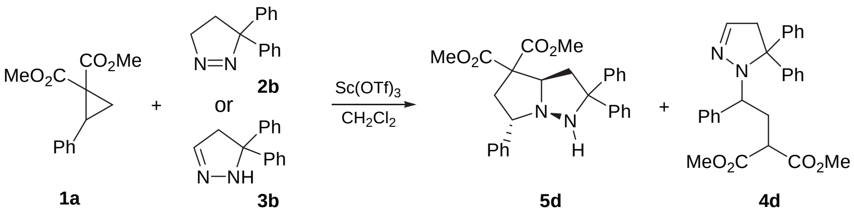
4g

As expected, incorporation of an electron-withdrawing substituent at position 1 of 2-pyrazoline **3e** drastically decreases the reactivity of the C=N bond; however, even in this case the 1,2-diazabicyclo[3.3.0]octane structure can be formed. In fact, it is only in boiling dichloroethane that the reaction of cyclopropane **1a** with benzoylated pyrazoline **3e** in the presence of 10 mol %

Table 2
Reaction of cyclopropane-1,1-dicarboxylates **1a**–**c** with pyrazolines **2** and **3** in the presence of Lewis acids in CH_2Cl_2 as the solvent

Cyclopropane	Pyrazoline		Lewis acid	Molar ratio	Temperature (°C)	Time	Products obtained (ratio of isomers)	Yields (%)	
								4	5
1b		**2a** **2a**	$GaCl_3$ $Sc(OTf)_3$	1.2:1:1 1.2:1:0.05	5 20	15 min 9 h	**4b** (1:1) **4b** (1:1) and **5b** (1:1)	72 66	— 18
1b		**3a**	$Sc(OTf)_3$	1:1:0.05	20	3 h	**4b** (1:1) and **5b** (1:1)	28	57
1c		**2a**	$GaCl_3$	1.2:1:1	20	3 h	**4c**	79	—
1a		**2b**	$Sc(OTf)_3$	1.2:1:0.05	20	160 h	**4d** and **5d**	5	63
1a		**3b**	$Sc(OTf)_3$	1:1:0.05	20	24 h	**5d**	—	82
1a		**2c**	$GaCl_3$	1.2:1:1	10	5 min	**4e** (1.5:1)	60	—
1a		**3c** **3c**	$GaCl_3$ $Sc(OTf)_3$	1.2:1:1 1:1:0.05	10 20	5 min 12 h	**4f** (2:1) **4f** (2:1)	85 95	
1a		**3d**	$Sc(OTf)_3$	1:1:0.05	20	3 h	**4g** (1.8:1)	96	
1a		**3e**	$Sc(OTf)_3$	3:1:0.1	80, $(ClCH_2)_2$	12 h	**5e** (1:1)		22[a]

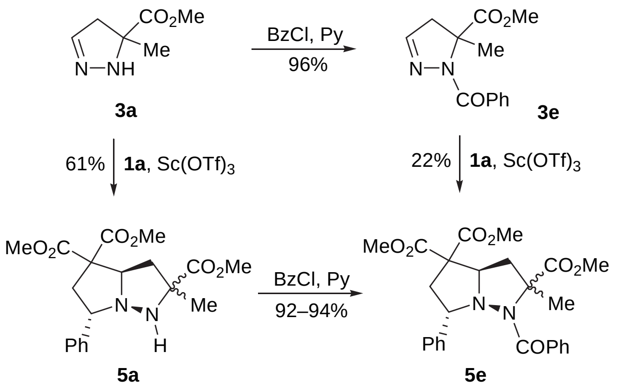
[a] Conversion of **3e** is about 25% under full consumption of cyclopropane **1a**; ratio of diastereomers was estimated from the ^{1}H NMR spectrum.



Scheme 5.

Sc(OTf)$_3$ occurs to a noticeable extent; the conversion of **3e** to diazabicyclooctane **5e** is as low as 25% even after a period of 12 h (Table 2). The same product **5e** is selectively formed as *anti*- or *syn*-stereoisomers upon benzoylation of individual diazabicyclooctanes of *anti*- and *syn*-**5a** with benzoyl chloride in pyridine (Scheme 6).

As one can see from Scheme 4, the reactions of donor–acceptor cyclopropanes **1** with 1-pyrazolines **2** along any of these two directions requires the presence of an α-proton at the N=N bond. It could be expected that a 1-pyrazoline in which the α-protons are substituted and hence its isomerization to a 2-pyrazoline is impossible, would react with a donor–acceptor cyclopropane at the N=N bond. However, unlike aryl-substituted azo compounds and azodicarboxylates,[13,14] we failed to observe a similar reaction of dimethyl 3,5-dimethyl-1-pyrazoline-3,5-dicarboxylate. Even under



Scheme 6.

drastic reaction conditions (Sc(OTf)$_3$, toluene, 110 °C, 24 h), cyclopropane **1a** did not give products of addition of this 1-pyrazoline to the N═N bond.

3. Conclusion

In summary, we report the first study of the reactions of 2-substituted cyclopropane-1,1-dicarboxylates with 1- and 2-pyrazolines of various structures in the presence of Lewis acids (mainly Sc(OTf)$_3$ and GaCl$_3$). We have shown that, depending on the reaction conditions, the Lewis acid used, and the type of substituents in the starting pyrazolines, the reaction mostly occurs along two directions to predominantly give *N*-substituted 2-pyrazolines **4** or 1,2-diazabicyclo[3.3.0]octanes **5**. A Lewis acid present in the system activates the opening of the cyclopropane ring and addition of the electrophilic intermediate formed to the nitrogen atoms of the pyrazoline ring followed by proton migration from the ring CH-fragment to an electronegative C atom or cyclization at the C═N bond of 2-pyrazoline. Furthermore, Sc(OTf)$_3$ and Yb(OTf)$_3$ can be used in 5 mol %. Thus, we have suggested a new method for synthesizing mono- and bicyclic nitrogen-containing heterocycles, including such compounds that are hard to obtain by other methods. These compounds contain various functional groups that can subsequently be modified.

4. Experimental section

4.1. General

All reagents and solvents used were commercial grade chemicals. Cyclopropanes **1a** and **1b** were obtained using the Cory–Chaikovsky reaction;[25–27] cyclopropane **1c** was prepared using a procedure reported previously.[28,29] Pyrazolines **2a**–**c** and **3a**–**d** were synthesized on the dipolar cycloaddition reaction of diazo compounds to alkenes as described early for **2a**,[30,31] **2b**,[32] **2c**,[33] **3a**,[34] **3b**,[35] **3c**,[36] **3d**.[37,38] The following Lewis acids were used in the study: Sc(OTf)$_3$ from Acros Organics, as well as EtAlCl$_2$ (0.8 M solution in hexane), GaCl$_3$, Yb(OTf)$_3$, and In(OTf)$_3$ from Aldrich. TLC analysis was performed on Silufol chromatographic plates (Merck). For preparative chromatography, silica gel 60 (0.040–0.063 mm; Merck) was used. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer (400 and 100.7 MHz, respectively) in CDCl$_3$ containing 0.05% Me$_4$Si as the internal standard. Assignments of ^{1}H and ^{13}C signals were made with the aid of 2D COSY, NOESY, HSQC, and HMBC spectra where necessary. IR spectra were obtained using a Specord M80-2 or Bruker ALPHA-T spectrometers as potassium bromide disks or in CHCl$_3$ solution. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (EI, 70 eV, direct inlet probe). High resolution mass spectra were obtained on a micrOTOF instrument. The elemental compositions were determined on a Perkin–Elmer Series II 2400 CHN Analyzer.

4.2. General procedure for reactions of donor–acceptor cyclopropanes with pyrazolines in the presence of Lewis acids

To a solution of cyclopropane **1** (1.45 mmol) and pyrazoline **2** (1.2 mmol) or cyclopropane **1** (1.2 mmol) and pyrazoline **3** (1.2 mmol) in 5 mL of dichloromethane was added Sc(OTf)$_3$ (0.06 mmol) in one portion or solution of GaCl$_3$ (1.2 mmol) in 1 mL of dichloromethane and reaction mixture was stirred at a temperature and during a time indicated in Tables 1 or 2. After that aqueous solution of HCl (5%) was added at 0 °C until pH 3 was achieved and the reaction mixture was extracted with dichloromethane (3×8 mL). The organic layer was dried over MgSO$_4$ and the solvent was removed in vacuo. The residue was separated by column chromatography on silica gel to afford *N*-substituted 2-pyrazolines **4** and 1,2-diazabicyclo[3.3.0]octanes **5**.

*4.2.1. Dimethyl 2-[2-(4,5-dihydro-5-methoxycarbonyl-5-methyl-1H-pyrazol-1-yl)-2-phenylethyl]malonate (**4a**).*

4.2.1.1. Method A. The residue from reaction of **1a** (338 mg, 1.44 mmol) and **2a** (170 mg, 1.2 mmol) in the presence of GaCl$_3$ (211 mg, 1.2 mmol) was purified by column chromatography (benzene–EtOAc, 8:1) to give **4a** (325 mg, 72%) as a colorless oil (about 1:1 mixture of two diastereomers). IR (CHCl$_3$) 1732 br (C═O), 1587, 1493, 1455, 1437 cm^{-1}; MS (*m*/*z*, %): 376 (4, M$^+$), 345 (5, M$^+$–OCH$_3$); 317 (24, M$^+$–CO$_2$CH$_3$), 285 (5), 235 (74), 231 (25), 203 (24), 175 (44), 171 (50), 143 (36), 115 (100), 104 (32), 83 (45), 77 (15), 59 (13). Anal. Calcd for C$_{19}$H$_{24}$N$_2$O$_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.60; H, 6.49; N, 6.96. The product obtained (12 mg) was additionally separated by Silufol chromatographic plate (20×20 cm) eluting with benzene–EtOAc, 10:1 to afford the pure isomers. *S**,*R**-**4a**: ^{1}H NMR δ 1.43 (s, 3H, CH$_3$), 2.39 (ddd, 1H, H$_a$(1′), ^2J=13.9, ^3J=8.7 and 6.2 Hz), 2.64 (dd, 1H, H$_a$(4″), ^2J=17.3, ^3J=1.8 Hz), 2.76 (ddd, 1H, H$_b$(1′), ^2J=13.9, ^3J=9.6 and 6.1 Hz), 2.92 (s, 3H, OCH$_3$), 3.28 (dd, 1H, H$_b$(4″), ^2J=17.3, ^3J=1.8 Hz), 3.54 (dd, 1H, H(2), ^3J=8.7 and 6.1 Hz), 3.71 and 3.73 (all s, 2×3H, 2OCH$_3$), 4.18 (dd, 1H, H(2′), ^3J=9.6 and 6.2 Hz), 6.55 (br.t, 1H, HC═, ^3J=1.8 Hz), 7.19–7.34 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 21.3 (CH$_3$), 36.4 (H$_2$C(1′)), 46.3 (H$_2$C(4″)), 49.2 (HC(2)), 51.4, 52.4 and 52.5 (3OCH$_3$), 59.0 (HC(2′)), 67.4 (C(5″)), 127.3 (*p*-C), 127.9 and 128.1 (2 *o*-C and 2 *m*-C), 136.4 (HC═), 141.1 (*i*-C), 169.8, 170.2 and 173.8 (3COO). *R**,*R**-**4a**: ^{1}H NMR δ 0.96 (s, 3H, CH$_3$), 2.34 (ddd, 1H, H$_a$(1′), ^2J=14.0, ^3J=9.3 and 5.0 Hz), 2.54 (dd, 1H, H$_a$(4″), ^2J=17.5, ^3J=1.8 Hz), 2.72 (ddd, 1H, H$_b$(1′), ^2J=14.0, ^3J=10.2 and 5.0 Hz), 3.30 (dd, 1H, H$_b$(4″), ^2J=17.5, ^3J=1.8 Hz), 3.73 (dd, 1H, H(2), ^3J=9.3 and 5.0 Hz), 3.69, 3.75 and 3.77 (all s, 3×3H, 3OCH$_3$), 4.34 (dd, 1H, H(2′), ^3J=10.2 and 5.0 Hz), 6.49 (br t, 1H, HC═, ^3J=1.8 Hz), 7.20–7.44 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 21.9 (CH$_3$), 36.5 (H$_2$C(1′)), 46.4 (H$_2$C(4″)), 49.0 (HC(2)), 52.3, 52.4 and 52.5 (3OCH$_3$), 60.1 (HC(2′)), 69.6 (C(5″)), 127.1 (*p*-C), 127.5 and 128.3 (2 *o*-C and 2 *m*-C), 134.8 (HC═), 144.2 (*i*-C), 169.7, 169.9 and 172.4 (3COO).

4.2.1.2. Method B. The residue from reaction of **1a** (337 mg, 1.45 mmol) and **2a** (170 mg, 1.2 mmol) in the presence of Sc(OTf)$_3$ (29 mg, 0.06 mmol) was separated by column chromatography (benzene–EtOAc, 8:1) to give **4a** (275 mg, 61%), which was identical to the sample prepared above and *anti*- and *syn*-**5a** (summary yield 131 mg, 29%), which ^{1}H and ^{13}C NMR spectra are the same as described below.

*4.2.2. Trimethyl 3-methyl-8-phenyl-1,2-diazabicyclo[3.3.0]octane-3,6,6-tricarboxylate (**5a**).* The residue from reaction of **1a** (281 mg, 1.2 mmol) and **3a** (171 mg, 1.2 mmol) in the presence of Sc(OTf)$_3$ (30 mg, 0.06 mmol) was separated by column chromatography (benzene–EtOAc, 10:1 to 1:1) to give **4a** (140 mg, 31%), which was identical to the sample prepared above and *anti*-**5a** (138 mg, 31%) and *syn*-**5a** (135 mg, 30%). *anti*-**5a**: Colorless thick oil; IR (CHCl$_3$) 3320 br (NH), 1735 br (C═O), 1700, 1601, 1494, 1450, 1436 cm^{-1}; ^{1}H NMR δ 1.52 (s, 3H, CH$_3$), 1.96 (dd, 1H, H$_a$(4), ^2J=13.2, ^3J=12.4 Hz), 2.00 (dd, 1H, H$_a$(7), ^2J=13.6, ^3J=10.6 Hz), 2.55 (dd, 1H, H$_b$(4), ^2J=13.2, ^3J=6.0 Hz), 3.09 (dd, 1H, H$_b$(7), ^2J=13.6, ^3J=7.0 Hz), 3.72, 3.76 and 3.78 (all s, 3×3H, 3OCH$_3$), 4.10 (dd, 1H, H(8), ^3J=10.6 and 7.0 Hz), 4.39 (dd, 1H, H(5), ^3J=12.4 and 6.0 Hz), 5.09 (br s, 1H, NH), 7.22 (br t, 1H, *p*-CH, ^3J=7.6 Hz), 7.31 (br dd, 2H, 2 *m*-CH, ^3J=7.5 and 7.6 Hz), 7.39 (br t, 1H, *o*-CH, ^3J=7.5 Hz); ^{13}C NMR δ 27.9 (CH$_3$), 41.0 (C(4)), 41.2 (C(7)), 52.8, 52.9 and 53.1 (3OCH$_3$), 58.9 (C(6)), 67.9 (C(5)), 69.0 (C(3)), 70.0 (C(8)), 127.3 (2 *o*-C), 127.4 (*p*-C), 128.4 (2 *m*-C), 141.0 (*i*-C), 170.3, 171.1 and 176.4 (3COO); MS (*m*/*z*, %): 376 (34, M$^+$), 345 (3, M$^+$–OCH$_3$), 317 (42, M$^+$–CO$_2$CH$_3$), 283 (5), 255 (10), 203 (13), 171 (94), 146 (32), 143 (39), 121 (28), 115 (55), 104 (41), 91 (28), 83

(100), 59 (22). Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.48; H, 6.48; N, 7.38. *syn*-**5a**: Colorless thick oil; ^{1}H NMR δ 1.45 (s, 3H, CH_3), 2.03 (dd, 1H, H_a(7), ^2J=13.7, ^3J=10.4 Hz), 2.05 (dd, 1H, H_a(4), ^2J=12.9, ^3J=6.9 Hz), 2.55 (dd, 1H, H_b(4), ^2J=12.9, ^3J=11.3 Hz), 3.13 (dd, 1H, H_b(7), ^2J=13.7, ^3J=7.4 Hz), 3.73, 3.75 and 3.78 (all s, 3×3H, $3OCH_3$), 4.06 (br s, 1H, NH), 4.18 (dd, 1H, H(8), ^3J=10.4 and 7.4 Hz), 4.49 (dd, 1H, H(5), ^3J=11.3 and 6.9 Hz), 7.22 (br t, 1H, *p*-CH, ^3J=7.3 Hz), 7.30 (br dd, 2H, 2 *m*-CH, ^3J=7.3 and 7.7 Hz), 7.37 (br t, 1H, *o*-CH, ^3J=7.7 Hz); ^{13}C NMR δ 25.1 (CH_3), 40.2 (C(7)), 40.9 (C(4)), 52.6, 52.9 and 53.2 ($3OCH_3$), 59.2 (C(6)), 67.3 (C(8)), 68.3 (C(3)), 69.0 (C(5)), 127.4 (*p*-C), 127.5 (2 *o*-C), 128.5 (2 *m*-C), 141.6 (*i*-C), 170.0, 171.4 and 176.3 (3COO); MS (*m/z*, %): 376 (58, M^+), 345 (5, M^+-OCH_3), 317 (42, $M^+-CO_2CH_3$), 283 (2), 255 (11), 203 (16), 171 (93), 146 (52), 143 (41), 121 (41), 115 (66), 104 (56), 91 (32), 83 (100), 59 (22), 44 (46), 32 (86). Anal. Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.41; H, 6.50; N, 7.33.

*4.2.3. Dimethyl 2-[2-(4,5-dihydro-5-methoxycarbonyl-5-methyl-1H-pyrazol-1-yl)-2-(2-thienyl)ethyl]malonate (**4b**).*

4.2.3.1. Method A. The residue from reaction of **1b** (348 mg, 1.45 mmol) and **2a** (170 mg, 1.2 mmol) in the presence of $GaCl_3$ (210 mg, 1.2 mmol) was purified by column chromatography (benzene–EtOAc, 5:1) giving diastereomers *R**,*R**-**4b** (170 mg, 37%) and *S**,*R**-**4b** (161 mg, 35%). *R**,*R**-**4b**: Colorless thick oil; IR ($CHCl_3$) 1733 br (C=O), 1585, 1510, 1455, 1436 cm^{-1}; ^{1}H NMR δ 1.15 (s, 3H, CH_3), 2.41 (ddd, 1H, $H_a(1')$, ^2J=13.8, ^3J=8.9 and 5.0 Hz), 2.55 (dd, 1H, $H_a(4'')$, ^2J=17.4, ^3J=1.4 Hz), 2.71 (ddd, 1H, $H_b(1')$, ^2J=13.8, ^3J=10.3 and 5.2 Hz), 3.32 (dd, 1H, $H_b(4'')$, ^2J=17.4, ^3J=1.1 Hz), 3.70, 3.77 and 3.78 (all s, 3×3H, $3OCH_3$), 3.75 (dd, 1H, H(2), ^3J=8.9 and 5.2 Hz), 4.80 (dd, 1H, H(2′), ^3J=10.3 and 5.0 Hz), 6.65 (br dd, 1H, HC=, ^3J=1.4 and 1.1 Hz), 6.89 (dd, 1H, H_{thi}(4), ^3J=5.1 and 3.4), 6.97 (dd, 1H, H_{thi}(3), ^3J=3.4, ^4J=0.9), 7.16 (dd, 1H, H_{thi}(5), ^3J=5.1, ^4J=0.9); ^{13}C NMR δ 22.0 (CH_3), 37.7 ($H_2C(1')$), 46.0 ($H_2C(4'')$), 49.1 (HC(2)), 51.6, 52.5 and 52.6 ($3OCH_3$), 55.1 (HC(2′)), 67.4 (C(5″)), 125.3 (C_{thi}(5)), 125.6 (C_{thi}(4)), 126.1 (C_{thi}(3)), 138.6 (HC=), 143.3 (C_{thi}(2)), 169.7, 169.8 and 172.1 (3COO); MS (*m/z*, %): 382 (3, M^+), 351 (5, M^+-OCH_3), 323 (17, $M^+-CO_2CH_3$), 241 (98), 237 (41), 209 (26), 181 (97), 177 (73), 121 (100), 110 (49), 83 (76). *S**,*R**-**4b**: Colorless thick oil; NMR δ 1.48 (s, 3H, CH_3), 2.44 (ddd, 1H, $H_a(1')$, ^2J=13.9, ^3J=8.6 and 6.0 Hz), 2.65 (dd, 1H, $H_a(4'')$, ^2J=17.3, ^3J=1.4 Hz), 2.71 (ddd, 1H, $H_b(1')$, ^2J=13.9, ^3J=9.5 and 6.1 Hz), 3.10 (s, 1H, OCH_3), 3.27 (dd, 1H, $H_b(4'')$, ^2J=17.3, ^3J=1.7 Hz), 3.59 (dd, 1H, H(2), ^3J=8.6 and 6.1 Hz), 3.72 and 3.75 (all s, 2×3H, $2OCH_3$), 4.57 (dd, 1H, H(2′), ^3J=9.5 and 6.0 Hz), 6.67 (br dd, 1H, HC=, ^3J=1.7 and 1.4 Hz), 6.83 (dd, 1H, H_{thi}(3), ^3J=3.4, ^4J=1.2), 6.87 (dd, 1H, H_{thi}(4), ^3J=5.1 and 3.4), 7.17 (dd, 1H, H_{thi}(5), ^3J=5.1, ^4J=1.2); ^{13}C NMR δ 20.9 (CH_3), 37.9 ($H_2C(1')$), 46.2 ($H_2C(4'')$), 48.9 (HC(2)), 52.4, 52.5 and 52.6 ($3OCH_3$), 56.1 (HC(2′)), 70.1 (C(5″)), 124.8 (C_{thi}(5)), 125.2 (C_{thi}(3)), 126.0 (C_{thi}(4)), 137.2 (HC=), 146.2 (C_{thi}(2)), 169.8, 170.1 and 173.6 (3COO); MS (*m/z*, %): 382 (2, M^+), 351 (3, M^+-OCH_3), 323 (8, $M^+-CO_2CH_3$), 241 (41), 237 (17), 209 (12), 181 (41), 177 (34), 121 (51), 110 (23), 83 (38), 44 (65), 32 (100). Anal. Calcd for $C_{17}H_{22}N_2SO_6$: C, 53.39; H, 5.80; N, 7.33. Found: C, 53.01; H, 5.91; N, 7.02.

4.2.3.2. Method B. The residue from reaction of **1b** (347 mg, 1.44 mmol) and **2a** (171 mg, 1.2 mmol) in the presence of $Sc(OTf)_3$ (29 mg, 0.06 mmol) was separated by column chromatography (benzene–EtOAc, 10:1 to 1:1) to give *R**,*R**-**4b** (153 mg, 33%) and *S**,*R**-**4b** (0.150 mg, 33%), which were identical to the samples prepared above, and *anti*-**5b** (42 mg, 9%) and *syn*-**5b** (40 mg, 9%), which properties are the same as described below.

*4.2.4. Trimethyl 3-methyl-8(2-thienyl)-1,2-diazabicyclo[3.3.0]octane-3,6,6-tricarboxylate (**5b**).* The residue from reaction of **1b** (288 mg, 1.2 mmol) and **3a** (172 mg, 1.2 mmol) in the presence of Sc $(OTf)_3$ (30 mg, 0.06 mmol) was separated by column chromatography (benzene–EtOAc, 10:1 to 1:1) to give *R**,*R**-**4b** (67 mg, 15%) and *S**,*R**-**4b** (59 mg, 13%), which were identical to the samples prepared above, and *anti*-**5b** (133 mg, 29%) and *syn*-**5b** (129 mg, 28%). *anti*-**5b**: Colorless thick oil; IR ($CHCl_3$) 3360 br (NH), 1732 br (C=O), 1700, 1684, 1651, 1520, 1456, 1436 cm^{-1}; ^{1}H NMR δ 1.52 (s, 3H, CH_3), 1.88 (dd, 1H, H_a(4), ^2J=12.7, ^3J=12.4 Hz), 2.15 (dd, 1H, H_a(7), ^2J=13.6, ^3J=10.3 Hz), 2.55 (dd, 1H, H_b(4), ^2J=12.7, ^3J=6.2 Hz), 3.12 (dd, 1H, H_b(7), ^2J=13.6, ^3J=6.9 Hz), 3.72, 3.77 and 3.78 (all s, 3×3H, $3OCH_3$), 4.35 (dd, 1H, H(8), ^3J=10.3 and 6.9 Hz), 4.39 (dd, 1H, H(5), ^3J=12.4 and 6.2 Hz), 5.18 (br s, 1H, NH), 6.93 (dd, 1H, H_{thi}(4), ^3J=5.0 and 3.4), 6.95 (dd, 1H, H_{thi}(3), ^3J=3.4, ^4J=1.4), 7.19 (dd, 1H, H_{thi}(5), ^3J=5.0, ^4J=1.4); ^{13}C NMR δ 27.7 (CH_3), 40.8 (C(4)), 41.0 (C(7)), 52.9, 53.0 and 53.2 ($3OCH_3$), 59.1 (C(6)), 66.2 (C(8)), 67.8 (C(5)), 69.0 (C(3)), 124.2 (C_{thi}(3)), 124.5 (C_{thi}(5)), 126.7 (C_{thi}(4)), 146.2 (C_{thi}(2)), 170.1, 170.8 and 176.2 (3COO); MS (*m/z*, %): 382 (18, M^+), 351 (1, M^+-OCH_3), 323 (14, $M^+-CO_2CH_3$), 261 (2), 240 (11), 208 (28), 177 (47), 149 (19), 121 (33), 97 (30), 83 (100), 59 (19). Anal. Calcd for $C_{17}H_{22}N_2SO_6$: C, 53.39; H, 5.80; N, 7.33. Found: C, 53.28; H, 5.58; N, 7.17. *syn* -**5b**: Colorless thick oil; IR ($CHCl_3$) 3370 br (NH), 1732 br (C=O), 1699, 1682, 1650, 1520, 1455, 1435 cm^{-1}; ^{1}H NMR δ 1.47 (s, 3H, CH_3), 2.03 (dd, 1H, H_a(4), ^2J=12.8, ^3J=7.0 Hz), 2.17 (dd, 1H, H_a(7), ^2J=13.7, ^3J=9.9 Hz), 2.49 (dd, 1H, H_b(4), ^2J=12.8, ^3J=11.2 Hz), 3.16 (dd, 1H, H_b(7), ^2J=13.7, ^3J=7.4 Hz), 3.73, 3.75 and 3.78 (all s, 3×3H, $3OCH_3$), 4.02 (br s, 1H, NH), 4.49 (m, 2H, H(5) and H(8)), 6.92 (dd, 1H, H_{thi}(4), ^3J=4.9 and 3.5), 6.94 (dd, 1H, H_{thi}(3), ^3J=3.5, ^4J=1.4), 7.18 (dd, 1H, H_{thi}(5), ^3J=4.9, ^4J=1.4); ^{13}C NMR δ 25.0 (CH_3), 40.2 (C(7)), 40.9 (C(4)), 52.7, 53.0 and 53.2 ($3OCH_3$), 59.3 (C (6)), 63.5 (C(8)), 68.3 (C(3)), 68.9 (C(5)), 124.6 (C_{thi}(5)), 124.7 (C_{thi}(3)), 126.7 (C_{thi}(4)), 146.3 (C_{thi}(2)), 169.9, 171.0 and 176.2 (3COO); MS (*m/z*, %): 382 (21, M^+), 351 (1, M^+-OCH_3), 323 (9, $M^+-CO_2CH_3$), 261 (3), 240 (11), 208 (45), 177 (41), 149 (20), 121 (38), 97 (32), 83 (100), 59 (20). HRMS calcd for $C_{17}H_{22}N_2SO_6$: M+H, 383.1271; M+Na, 405.1091. Found: *m/z* 383.1269, 405.1089.

*4.2.5. Dimethyl 2-[2-(4,5-dihydro-5-methoxycarbonyl-5-methyl-1H-pyrazol-1-yl)ethyl]malonate (**4c**).* The residue from reaction of **1c** (228 mg, 1.44 mmol) and **2a** (170 mg, 1.2 mmol) in the presence of $GaCl_3$ (209 mg, 1.2 mmol) was purified by column chromatography (benzene–EtOAc, 5:1) to give **4c** (285 mg, 79%) as a colorless thick oil; ^{1}H NMR δ 1.31 (s, 3H, CH_3), 2.32 (m, 2H, $H_2C(1')$), 2.61 (dd, 1H, $H_a(4'')$, ^2J=17.0, ^3J=1.8 Hz), 3.04 (m, 2H, $H_2C(2')$), 3.23 (dd, 1H, $H_b(4'')$, ^2J=17.0, ^3J=1.7 Hz), 3.72, 3.73 and 3.74 (all s, 3×3H, $3OCH_3$), 3.76 (dd, 1H, H(2), ^3J=7.8 and 7.0 Hz), 6.64 (br dd, 1H, HC=, ^3J=1.8 and 1.7 Hz); ^{13}C NMR δ 18.8 (CH_3), 28.2 ($H_2C(1')$), 46.1 ($H_2C(4'')$), 46.2 (HC(2′)), 48.8 (HC(2)), 52.2 (OCH_3), 52.4 ($2OCH_3$), 69.9 (C(5″)), 139.3 (HC=), 170.0 (2COO), 173.3 (COO); MS (*m/z*, %): 300 (2) [M^+], 269 (3, M^+-OCH_3), 241 (28, $M^+-CO_2CH_3$), 237 (9), 209 (23), 177 (100), 159 (11), 127 (11), 95 (14), 59 (13). Anal. Calcd for $C_{13}H_{20}N_2O_6$: C, 51.99; H, 6.71; N, 9.33. Found: C, 51.75; H, 6.98; N, 9.09.

*4.2.6. Dimethyl 3,3,8-triphenyl-1,2-diazabicyclo[3.3.0]octane-6,6-dicarboxylate (**5d**).*

4.2.6.1. Method A. The residue from reaction of **1a** (280 mg, 1.2 mmol) and **3b** (267 mg, 1.2 mmol) in the presence of $Sc(OTf)_3$ (30 mg, 0.06 mmol) was purified by column chromatography (benzene–EtOAc, 2:1) to give **5d** (450 mg, 82%) as a colorless thick oil; IR ($CHCl_3$) 3370 br (NH), 1736 br (C=O), 1686, 1600, 1492, 1448 cm^{-1}; ^{1}H NMR δ 2.27 (ddd, 1H, $H_a(1')$, ^2J=13.9, ^3J=9.6 and 4.9 Hz), 2.63 (ddd, 1H, $H_b(1')$, ^2J=13.9, ^3J=10.3 and 5.2 Hz), 2.93 (dd, 1H, H(2), ^3J=9.6 and 5.2 Hz), 3.40 (dd, 1H, $H_a(4'')$, ^2J=18.0, ^3J=1.8 Hz), 3.47 (dd, 1H, $H_b(4'')$, ^2J=18.0, ^3J=1.7 Hz), 3.53 and 3.62 (both s, 2×3H, $2OCH_3$), 4.02 (dd, 1H, H(2), ^3J=10.3 and 4.9 Hz), 4.50 (br s, 1H, NH), 6.68 (dd, 1H, HC=, ^3J=1.8 and 1.7 Hz), 6.87–7.50 (m, 15H, $3C_6H_5$); ^{13}C NMR δ 40.9 (C(7)), 44.0 (C(4)), 53.0 and 53.2 ($2OCH_3$), 59.6 (C(6)), 67.4 (C(8)), 70.8 (C(5)), 74.8 (C(3)), 126.2, 127.1, 127.7, 128.0, 128.4 and

128.8 (3 *o*-C and 3 *m*-C), 126.5, 127.2 and 127.3 (3 *p*-C), 142.3, 147.3 and 149.8 (3 *i*-C), 170.3 and 171.5 (2COO); MS (*m*/*z*, %): 456 (31, M^{+}), 425 (2, M^{+}−OCH$_3$), 379 (5, M^{+}−C$_6$H$_5$), 320 (4, M^{+}−CO$_2$CH$_3$−C$_6$H$_5$), 296 (35), 276 (15), 217 (85), 180 (99), 115 (78), 104 (100), 91 (60), 77 (82), 59 (49). Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.14. Found: C, 73.47; H, 6.09; N, 6.20.

4.2.6.2. Method B. The residue from reaction of **1a** (336 mg, 1.44 mmol) and **2b** (266 mg, 1.2 mmol) in the presence of Sc(OTf)$_3$ (29 mg, 0.06 mmol) was separated by column chromatography (benzene−EtOAc, 2:1) to give **5d** (345 mg, 63%), which was identical to the sample prepared above, and a small amount of *dimethyl 2-[2-(4,5-dihydro-5,5-diphenyl-1H-pyrazol-1-yl)-2-phenylethyl]malonate* **4d** (27 mg, 5%) as a colorless thick oil. **4d**: ^{1}H NMR δ 2.00 (dd, 1H, H$_a$(7), ^{2}J=13.9, ^{3}J=10.3 Hz), 2.41 (dd, 1H, H$_a$(4), ^{2}J=13.3, ^{3}J=12.0 Hz), 3.05 (dd, 1H, H$_b$(7), ^{2}J=13.9, ^{3}J=7.4 Hz), 3.18 (dd, 1H, H$_b$(4), ^{2}J=13.3, ^{3}J=6.7 Hz), 3.75 and 3.79 (both s, 2×3H, 2OCH$_3$), 4.03 (dd, 1H, H(2), ^{3}J=10.3 and 7.4 Hz), 4.50 (br s, 1H, NH), 4.73 (dd, 1H, H(5), ^{3}J=12.0 and 6.7 Hz), 7.13−7.47 (m, 15H, 3C$_6$H$_5$); ^{13}C NMR δ 35.5 (H$_2$C(1′)), 49.1 (H$_2$C(4″)), 49.2 (HC(2)), 52.4 and 52.5 (2OCH$_3$), 60.5 (HC(2′)), 75.7 (C(5″)), 126.6, 127.1 and 127.2 (3 *p*-C), 127.7, 127.8, 127.85, 127.9, 128.5 and 128.55 (3 *o*-C and 3 *m*-C), 135.6 (HC=), 141.1, 144.7 and 145.9 (3 *i*-C), 169.6 and 172.4 (2COO). HRMS calcd for $C_{28}H_{28}N_2O_4$: M+H, 457.2122; M+Na, 479.1941. Found: *m*/*z* 457.2116, 479.1936.

*4.2.7. Dimethyl 2-[2-(3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-en-3-yl)-2-phenylethyl]malonate (**4e**).* The residue from reaction of **1a** (337 mg, 1.45 mmol) and **2c** (163 mg, 1.2 mmol) in the presence of GaCl$_3$ (208 mg, 1.2 mmol) was purified by column chromatography (benzene−EtOAc, 5:1) to give diastereomeric *R**,*S**-**4e** (160 mg, 36%) and *R**,*R**-**4e** (106 mg, 24%). *R**,*S**-**4e**: Colorless oil; IR (CHCl$_3$) 1748 and 1731 (C=O), 1577, 1493, 1454, 1437 cm^{-1}; ^{1}H NMR δ 0.98−1.50 (m, 6H, H$_2$C(8″), H$_2$C(9″) and H$_2$C(10″)), 2.17 and 2.24 (both m, 2×1H, H(1″) and H(7″)), 2.39 (ddd, 1H, H$_a$(1′), ^{2}J=13.9, ^{3}J=9.9 and 5.5 Hz), 2.68 (br d, 1H, H(6″), ^{3}J=9.8), 2.79 (ddd, 1H, H$_b$(1′), ^{2}J=13.9, ^{3}J=10.5 and 5.3 Hz), 3.06 (br d, 1H, H(2″), ^{3}J=9.8), 3.72 and 3.75 (both s, 2×3H, 2OCH$_3$), 3.83 (dd, 1H, H(2), ^{3}J=9.9 and 5.3 Hz), 3.99 (dd, 1H, H(2′), ^{3}J=10.5 and 5.5 Hz), 6.38 (br s, 1H, H(5″)), 7.21−7.33 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 24.4 and 28.6 (C(8″) and C(9″)), 33.8 (C(10″)), 33.9 (C(1′)), 40.7 and 41.9 (C(1″) and C(7″)), 49.2 (HC(2)), 52.3 and 52.5 (2OCH$_3$), 57.0 (C(6″)), 63.1 (HC(2′)), 67.6 (C(2″)), 127.4 (*p*-C), 128.2 and 128.3 (2 *o*-C and 2 *m*-C), 140.3 (*i*-C), 142.4 (C(5″)), 170.0 and 170.2 (2COO); MS (*m*/*z*, %): 370 (4, M^{+}), 339 (3, M^{+}−OCH$_3$), 293 (2, M^{+}−C$_6$H$_5$), 225 (100), 175 (5), 171 (8), 143 (6), 115 (37), 91 (8). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.63; H, 7.18; N, 7.27. *R**,*R**-**4e** Colorless oil; ^{1}H NMR δ 0.91−1.46 (m, 6H, H$_2$C(8″), H$_2$C(9″) and H$_2$C(10″)), 2.01 and 2.22 (both m, 2×1H, H(1″) and H(7″)), 2.47 (ddd, 1H, H$_a$(1′), ^{2}J=14.2, ^{3}J=8.0 and 6.7 Hz), 2.72 (ddd, 1H, H$_b$(1′), ^{2}J=14.2, ^{3}J=8.7 and 6.5 Hz), 2.75 (br d, 1H, H(6″), ^{3}J=9.5), 3.05 (br d, 1H, H(2″), ^{3}J=9.5), 3.62 (dd, 1H, H(2), ^{3}J=8.0 and 6.5 Hz), 3.69 and 3.74 (both s, 2×3H, 2OCH$_3$), 4.24 (dd, 1H, H(2′), ^{3}J=8.7 and 6.7 Hz), 6.40 (br s, 1H, H(5″)), 7.25−7.36 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 24.9 and 28.6 (C(8″) and C(9″)), 32.7 (C(1′)), 33.6 (C(10″)), 40.3 and 43.2 (C(1″)) and (C(7″)), 49.2 (HC(2)), 52.55 and 52.6 (2OCH$_3$), 57.7 (C(6″)), 64.8 (HC(2′)), 67.1 (C(2″)), 127.6 (*p*-C), 128.3 and 128.5 (2 *o*-C and 2 *m*-C), 139.6 (*i*-C), 143.2 (C(5″)), 169.9 and 170.2 (2COO); MS (*m*/*z*, %): 370 (3, M^{+}), 339 (2, M^{+}−OCH$_3$), 225 (100), 175 (4), 171 (6), 143 (4), 115 (28), 91 (8), 77 (6).

*4.2.8. Dimethyl 2-[2-(5-metoxycarbonyl-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-en-3-yl)-2-phenylethyl]malonate (**4f**).* The residue from reaction of **1a** (281 mg, 1.2 mmol) and **3c** (233 mg, 1.2 mmol) in the presence of Sc(OTf)$_3$ (30 mg, 0.06 mmol) was purified by column chromatography (benzene−EtOAc, 9:1) to give diastereomeric *R**,*R**-**4f** (324 mg, 63%) and *R**,*S**-**4f** (164 mg, 32%). *R**,*R**-**4f**: Colorless thick oil; ^{1}H NMR δ 0.97−1.50 (m, 6H, H$_2$C(8″), H$_2$C(9″) and H$_2$C(10″)), 2.28 and 2.55 (both m, 2×1H, H(1″) and H(7″)), 2.49 (ddd, 1H, H$_a$(1′), ^{2}J=14.4, ^{3}J=9.5 and 5.7 Hz), 2.84 (ddd, 1H, H$_b$(1′), ^{2}J=14.4, ^{3}J=10.0 and 5.7 Hz), 3.03 (br d, 1H, H(6″), ^{3}J=10.5), 3.45 (br d, 1H, H(2″), ^{3}J=10.5), 3.61 (dd, 1H, H(2), ^{3}J=9.5 and 5.7 Hz), 3.72, 3.74 and 3.81 (all s, 3×3H, 3OCH$_3$), 4.28 (dd, 1H, H(2′), ^{3}J=10.0 and 5.7 Hz), 7.19−7.35 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 24.2 and 28.6 (C(8″) and C(9″)), 33.7 (C(1′)), 33.8 (C(10″)), 41.3 and 42.0 (C(1″) and C(7″)), 49.1 (HC(2)), 51.7, 52.5 and 52.6 (3OCH$_3$), 53.9 (C(6″)), 62.3 (HC(2′)), 71.3 (C(2″)), 127.6 and 128.7 (2 *o*-C and 2 *m*-C), 128.0 (*p*-C), 139.3 (C(5″)), 139.7 (*i*-C), 163.7, 169.6 and 169.7 (3COO); MS (*m*/*z*, %): 428 (3, M^{+}), 397 (4, M^{+}−OCH$_3$), 369 (3, M^{+}−CO$_2$CH$_3$), 296 (5), 283 (84), 235 (8), 175 (9), 143 (9), 115 (44), 91 (10), 44 (32), 32 (100). Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.05; H, 6.38; N, 6.37. *R**,*S**-**4f**: Colorless thick oil; IR (CHCl$_3$) 1748, 1732 and 1696 (C=O), 1542, 1523, 1438 cm^{-1}; ^{1}H NMR δ 0.97−1.49 (m, 6H, H$_2$C(8″), H$_2$C(9″) and H$_2$C(10″)), 2.16 and 2.50 (both m, 2×1H, H(1″) and H(7″)), 2.55 (ddd, 1H, H$_a$(1′), ^{2}J=14.4, ^{3}J=8.5 and 6.3 Hz), 2.72 (ddd, 1H, H$_b$(1′), ^{2}J=14.4, ^{3}J=9.5 and 6.0 Hz), 3.10 (br d, 1H, H(6″), ^{3}J=10.4), 3.50 (dd, 1H, H(2), ^{3}J=8.5, 6.0, 9.5 Hz), 3.55 (br d, 1H, H(2″), ^{3}J=10.4), 3.72, 3.74 and 3.81 (all s, 3×3H, 3OCH$_3$), 4.57 (dd, 1H, H(2′), ^{3}J=9.5 and 6.3 Hz), 7.26−7.37 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 24.5 and 28.0 (C(8″) and C(9″)), 33.1 (C(1′)), 33.4 (C(10″)), 40.6 and 43.4 (C(1″) and C(7″)), 48.9 (HC(2)), 51.6, 52.6 and 52.65 (3OCH$_3$), 54.2 (C(6″)), 63.4 (HC(2′)), 71.5 (C(2″)), 127.5 and 128.6 (2 *o*-C and 2 *m*-C), 127.9 (*p*-C), 138.8 (C(5″)), 139.5 (*i*-C), 163.4, 169.4 and 169.6 (3COO); MS (*m*/*z*, %): 428 (3, M^{+}), 397 (3, M^{+}−OCH$_3$), 369 (4, M^{+}−CO$_2$CH$_3$), 296 (7), 283 (80), 235 (9), 175 (9), 143 (10), 115 (42), 91 (10), 44 (38), 32 (100). Anal. Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.09; H, 6.55; N, 6.29.

*4.2.9. Dimethyl 2-[2-phenyl-2-(3,3-bismetoxycarbonyl-4,5-dihydro-1H-pyrazol-1-yl)ethyl]malonate (**4g**).* The residue from reaction of **1a** (280 mg, 1.2 mmol) and **3d** (224 mg, 1.2 mmol) in the presence of Sc(OTf)$_3$ (30 mg, 0.06 mmol) was purified by column chromatography (benzene−EtOAc, 10:1 to 5:1) to give diastereomeric *R**,*R**-**4g** (313 mg, 62%) and *R**,*S**-**4g** (171 mg, 34%). *R**,*R**-**4g**: Colorless crystals; mp 90−91 °C; IR (KBr) 1740, 1728 and 1708 (C=O), 1572, 1540, 1520, 1496, 1436 cm^{-1}; ^{1}H NMR δ 2.54 (ddd, 1H, H$_a$(1′), ^{2}J=14.1, ^{3}J=9.5 and 5.6 Hz), 2.96 (ddd, 1H, H$_b$(1′), ^{2}J=14.1, ^{3}J=10.0 and 5.4 Hz), 3.06 (dd, 1H, H$_a$(4″), ^{2}J=17.4, ^{3}J=13.1 Hz), 3.14 (dd, 1H, H$_b$(4″), ^{2}J=17.4, ^{3}J=12.8 Hz), 3.71 (dd, 1H, H(2), ^{3}J=9.5 and 5.4 Hz), 3.72, 3.74, 3.80 and 3.82 (all s, 4×3H, 4OCH$_3$), 3.92 (dd, 1H, H(5″), ^{3}J=13.1 and 12.8 Hz), 4.45 (dd, 1H, H(2′), ^{3}J=10.0 and 5.6 Hz), 7.22−7.35 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 33.6 (H$_2$C(1′)), 35.3 (H$_2$C(4″)), 48.8 (HC(2)), 52.0, 52.4, 52.5 and 52.6 (4OCH$_3$), 63.2 (HC(2′)), 64.7 (C(5″)), 128.2 and 128.7 (2 *o*-C and 2 *m*-C), 128.3 (*p*-C), 137.6 and 139.0 (*i*-C and C(3″)), 162.4, 169.5, 169.6 and 170.3 (4COO); MS (*m*/*z*, %): 420 (2, M^{+}), 389 (4, M^{+}−OCH$_3$), 361 (13, M^{+}−CO$_2$CH$_3$), 319 (8), 288 (10), 275 (28), 235 (32), 203 (11), 175 (32), 171 (35), 143 (22), 115 (100), 59 (20). Anal. Calcd for $C_{20}H_{24}N_2O_8$: C, 57.14; H, 5.75; N, 6.66. Found: C, 56.87; H, 5.68; N, 6.60. *R**,*S**-**4g**: Colorless thick oil; ^{1}H NMR δ 2.49 (ddd, 1H, H$_a$(1′), ^{2}J=14.3, ^{3}J=8.2 and 6.6 Hz), 2.71 (ddd, 1H, H$_b$(1′), ^{2}J=14.3, ^{3}J=9.2 and 6.3 Hz), 3.11 (dd, 1H, H$_a$(4″), ^{2}J=17.4, ^{3}J=11.3 Hz), 3.18 (dd, 1H, H$_b$(4″), ^{2}J=17.4, ^{3}J=12.5 Hz), 3.50, 3.71, 3.73, and 3.82 (all s, 4×3H, 4OCH$_3$), 3.56 (dd, 1H, H(2), ^{3}J=8.2 and 6.3 Hz), 4.08 (dd, 1H, H(5″), ^{3}J=12.5 and 11.3 Hz), 4.64 (dd, 1H, H(2′), ^{3}J=9.2 and 6.6 Hz), 7.25−7.37 (m, 5H, C$_6$H$_5$); ^{13}C NMR δ 32.5 (H$_2$C(1′)), 36.7 (H$_2$C(4″)), 48.9 (HC(2)), 52.1, 52.4, 52.6 and 52.65 (4OCH$_3$), 64.5 (HC(2′)), 64.6 (C(5″)), 128.1 and 128.6 (2 *o*-C and 2 *m*-C), 128.3 (*p*-C), 137.7 and 138.3 (*i*-C and C(3″)), 162.3, 169.5, 169.6 and 171.1 (4COO); MS (*m*/*z*, %): 420 (3, M^{+}), 389 (4, M^{+}−OCH$_3$), 361 (15, M^{+}−CO$_2$CH$_3$), 319 (9), 288 (9), 275 (26), 235 (34), 203 (10), 175 (33), 171 (35), 143 (24), 115 (100), 59 (22). Anal. Calcd for $C_{20}H_{24}N_2O_8$: C, 57.14; H, 5.75; N, 6.66. Found: C, 56.84; H, 5.69; N, 6.41.

*4.2.10. Methyl 1-benzoyl-4,5-dihydro-5-methoxycarbonyl-5-methyl-1H-pyrazol (**3e**).* Benzoyl chloride (0.70 g, 5 mmol) was added to a solution of pyrazoline **3a** (0.50 g, 3.5 mmol) in anhydrous pyridine

(10 mL) and the mixture was stirred at 100 °C for 5 h. Then a reaction mixture together with a residue formed was transferred into hydrochloric acid (50 mL, 10%) at 0–10 °C and the aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic layer was washed with 10% aq $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the substituted pyrazoline **3e** (0.83 g, 96%) was obtained as pale yellow crystals; mp 96–97 °C; IR ($CHCl_3$) 1746 br (C=O), 1644, 1605, 1578, 1449, 1412 cm^{-1}; ^1H NMR δ 1.78 (s, 3H, CH_3), 2.85 and 3.23 (both dd, 2×1H, $H_2C(4)$, ^2J=18.2, ^3J=1.7 Hz), 3.78 (s, 3H, OCH_3), 6.86 (t, 1H, H(3), ^3J=1.7 Hz), 7.40 (m, 1H, 2 *m*-CH), 7.46 (m, 1H, *p*-CH), 7.82 (m, 2H, *o*-CH); ^{13}C NMR δ 21.8 (CH_3), 47.5 (C(4), 52.9 (OCH_3)), 65.1 (C(5)), 127.7 (2 *o*-C), 129.6 (2 *m*-C), 131.0 (*p*-C), 134.2 (*i*-C), 144.3 (C(3)), 172.0 (COO); MS (*m*/*z*, %): 246 (7, M^+), 215 (1, M^+-OCH_3), 187 (43, $M^+-CO_2CH_3$), 105 (100), 77 (56), 59 (19). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.61; H, 5.79; N, 11.23.

4.2.11. *Trimethyl 1-benzoyl-3-methyl-8-phenyl-1,2-diazabicyclo[3.3.0]octane-3,6,6-tricarboxylate (**5e**).*

4.2.11.1. Method A. Benzoyl chloride (84 mg, 0.6 mmol) was added to a solution of pure *anti*-**5a** (120 mg, 0.32 mmol) in anhydrous pyridine (3 mL) and the mixture was stirred at 80 °C for 2 h. After cooling and removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (5 mL) and washed with 10% aq $NaHCO_3$ (3 mL) at 30–35 °C. Then aqueous solution was extracted with CH_2Cl_2 (5 mL), the combined organic layer was washed with 1% aq HCl (5 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to afford compound *anti*-**5e** (144 mg, 94%) as colorless crystals; mp 162–164 °C; IR (KBr) 1740 br (O=C–O), 1636 (O=C–N), 1576, 1540, 1496, 1436 cm^{-1}; ^1H NMR δ 2.00 (s, 3H, CH_3), 2.11 (dd, 1H, $H_{anti}(7)$, ^2J=14.3, ^3J=10.4 Hz), 2.27 (dd, 1H, $H_{syn}(4)$, ^2J=13.2, ^3J=11.9 Hz), 2.52 (dd, 1H, $H_{anti}(4)$, ^2J=13.2, ^3J=6.7 Hz), 3.16 (dd, 1H, $H_{syn}(7)$, ^2J=14.3, ^3J=7.7 Hz), 3.72 (s, 3H, OCH_3 at C(3)), 3.80 and 3.84 (both s, 2×3H, $2OCH_3$), 4.06 (dd, 1H, H(8), ^3J=10.4 and 7.7 Hz), 4.86 (dd, 1H, H(5), ^3J=11.9 and 6.7 Hz), 6.71 (br dd, 2H, 2 *o*-CH, ^3J=7.9 and 1.3 Hz), 6.86 (dd, 2H, *m*-CH, ^3J=7.9 and 7.5 Hz), 7.01 (tt, 1H, *p*-CH, ^3J=7.5 and 1.3 Hz), 7.12 (br dd, 2H, 2 *m*-CH, ^3J=7.7 and 7.3 Hz), 7.19 (br dd, 2H, *o*-CH, ^3J=7.7 and 1.5 Hz), 7.24 (tt, 1H, *p*-CH, ^3J=7.3 and 1.5 Hz); ^{13}C NMR δ 26.4 (CH_3), 39.5 (C(7)), 43.0 (C(4)), 52.9 (OCH_3 at C(3)), 53.3 and 53.4 ($2OCH_3$), 58.6 (C(6)), 66.5 (C(5)), 68.5 (C(3)), 69.9 (C(8)), 127.2 (2 *m*-C from Bz), 127.7 (*p*-C), 128.1 (2 *m*-C), 128.2 (2×2 *o*-C), 129.3 (*p*-C from Bz), 135.8 (*i*-C from Bz), 137.0 (*i*-C), 169.7 and 170.9 (2COO), 169.9 (C=O), 172.8 (COO at C(3)). HRMS calcd for $C_{26}H_{28}N_2O_7$: M+H, 481.1969; M+Na, 503.1789. Found: *m*/*z* 481.1960, 503.1783.

Similarly, from pure *syn*-**5a** (119 mg, 0.32 mmol) and benzoyl chloride (82 mg, 0.6 mmol) compound *syn*-**5e** (141 mg, 92%) was obtained as colorless thick oil; ^1H NMR δ 1.74 (s, 3H, CH_3), 2.17 (dd, 1H, $H_a(7)$, ^2J=14.1, ^3J=10.6 Hz), 2.19 (dd, 1H, $H_a(4)$, ^2J=12.2, ^3J=5.9 Hz), 2.50 (dd, 1H, $H_b(4)$, ^2J=12.2, ^3J=11.8 Hz), 3.14 (dd, 1H, $H_b(7)$, ^2J=14.1, ^3J=7.8 Hz), 3.80, 3.85 and 3.90 (all s, 3×3H, $3OCH_3$), 4.56 (dd, 1H, H(8), ^3J=10.6 and 7.8 Hz), 4.74 (dd, 1H, H(5), ^3J=11.8 and 5.9 Hz), 6.82 (br dd, 2H, 2 *m*-CH, ^3J=7.7 and 6.9 Hz), 6.85 (dd, 2H, *o*-CH, ^3J=7.7 and 1.8 Hz), 6.94 (tt, 1H, *p*-CH, ^3J=6.9 and 1.8 Hz), 7.02 (br dd, 2H, 2 *m*-CH, ^3J=7.9 and 7.3 Hz), 7.15 (br t, 1H, *p*-CH, ^3J=7.3 Hz), 7.17 (br d, 2H, *o*-CH, ^3J=7.9 Hz); ^{13}C NMR δ 21.1 (CH_3), 39.0 and 41.5 (C(4) and C(7)), 53.1, 53.3 and 53.4 ($3OCH_3$), 58.3 (C(6)), 66.8 and 68.4 (C(5) and C(8)), 68.5 (C(3)), 127.1, 127.9, 128.6 and 128.7 (2×2 *o*-C and 2×2 *m*-C), 127.5 and 129.5 (2 *p*-C), 135.4 and 136.9 (2 *i*-C), 166.7, 169.3, 170.9 and 173.4 (3COO and C=O). Anal. Calcd for $C_{26}H_{28}N_2O_7$: C, 64.99; H, 5.87; N, 5.83. Found: C, 64.78; H, 5.94; N, 5.62.

4.2.11.2. Method B. A mixture of cyclopropane **1a** (281 mg, 1.2 mmol), pyrazoline **3e** (99 mg, 0.4 mmol), and $Sc(OTf)_3$ (20 mg, 0.04 mmol) in 3 mL dichloroethane was refluxed for 12 h. After cooling and removal of the solvent, the residue was separated by silica gel column chromatography (benzene–EtOAc, 5:1) to give unreacted pyrazoline **3e** (74 mg, 75%) and a mixture of *anti*- and *syn*-**5e** (42 mg, 22%), which ^1H and ^{13}C NMR spectra were the same as for the samples prepared above.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.09.092.

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