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trans-Directing Ability of the Amide Group: Enabling the Enantiocontrol in the Synthesis of 1,1-Dicarboxy Cyclopropanes. Reaction Development, Scope, and Synthetic Applications

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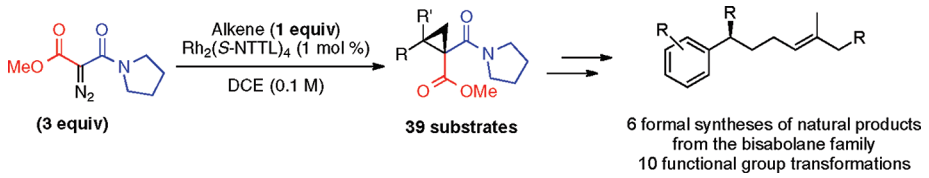

In this article, we describe our efforts toward the enantioselective formation of 1,1-cyclopropane diesters via the metal-catalyzed cyclopropanation of olefins. The strategies envisioned to achieve such a goal are discussed as well as the results that led us to the discovery of the powerful *trans*-directing ability of the amide group in Rh(II)-catalyzed cyclopropanation reactions. We show how this feature enables a solution for the stereoselective synthesis of 1,1-dicarboxy cyclopropane derivatives. The scope and limitations are discussed as well as the demonstration that these newly formed cyclopropanes display reactivity similar to that of 1,1-cyclopropane diesters. Conversely, 1,1-cyclopropane diesters could be accessed in two steps from commercially available alkenes. The potential utility of this methodology is illustrated by several functional group transformations and its use in the expedient stereoselective formal synthesis of (*S*)-(+)-curcumene, (*S*)-(+)-nuciferal, (*S*)-(+)-nuciferol, (+)-erogorgiaene, (±)-xanthorrhizol, and (±)-2-hydroxycalamenene.

1. Introduction

The cyclopropane ring has been shown to undergo a wide variety of transformations due to its high Baeyer strain.[1] Of all cyclopropanes, those bearing two geminal acceptor groups have been widely studied due to their ability to react with different nucleophiles and, thus, are known as electrophilic cyclopropanes.[2] Recently, there has been a growing interest in the reactivity of 1,1-cyclopropane diesters. Indeed, they have been exploited in cycloaddition reactions with imines,[3] aldehydes,[4] nitrones,[5] and others[6] to afford a variety of useful building blocks (Scheme 1). Cylopropane **1** has also been shown to react with nucleophiles[7] such as organocuprate

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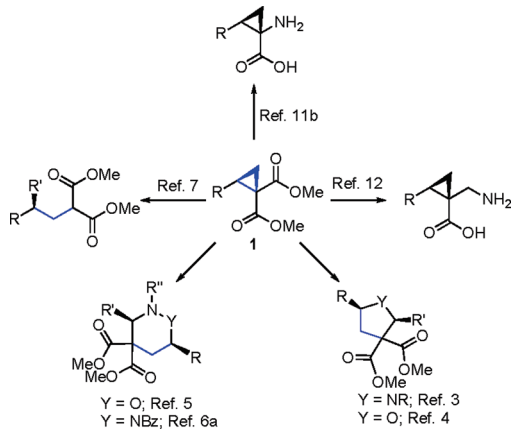
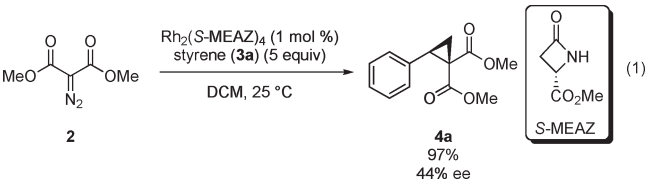
SCHEME 1. Reactivity and Synthetic Applications of 1,1-Cyclopropane Diesters

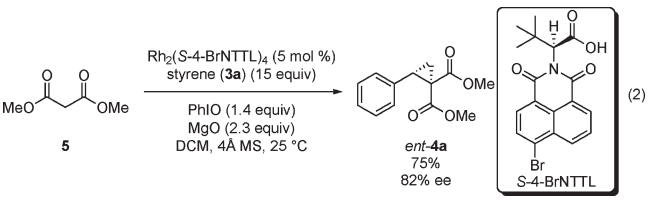


reagents (Scheme 1).[8] This unique reactivity has been utilized as a key step in the efficient synthesis of structurally complex molecules (Figure 1).[9] Cyclopropane **1** is also a useful intermediate for the synthesis of biologically relevant molecules such as α-amino acid[10] and *β*-amino acid cyclopropanes (Scheme 1).[11,12] Importantly, all of these derivatizations and reactivities are realized with preservation of the stereochemical information, further validating **1** as a very attractive target.

Although 1,1-cyclopropane diesters have been shown to be valuable chiral intermediates, their asymmetric synthesis still remains an important challenge. Several multistep syntheses have been reported (Scheme 2). For example, they can be accessed through the asymmetric Simmons−Smith cyclopropanation[13] or the Davies Rh(II)-catalyzed cyclopropanation[14] in four and three steps from the corresponding alkene, respectively. Likewise, the Sharpless dihydroxylation has also been utilized to afford enantioenriched 1,1-cyclopropane diesters in three steps.[15] Kinetic resolution of **1**[5a] and cocrystallization of the 1,1-diacid derivatives with a chiral amine[4f] have also been described. In these cases, the overall yields range from 15 to 48%.

Even though the metal-catalyzed cyclopropanation between diazomalonate **2** and commercially available olefins is the most straightforward route to **1**,[16] no highly enantioselective methods have been reported to date.[17] Indeed, the best catalyst, Rh_2(*S*-MEAZ)$_4$, performs this reaction with only 44% ee on styrene (eq 1).[18] Müller has also described the in situ formation of the phenyliodonium ylide variants and obtained 82% ee on styrene employing Rh_2(*S*-4-BrNTTL)$_4$ as the catalyst (eq 2).[19]





Herein, we report the discovery of the powerful *trans*-directing ability of the amide group that led to the first highly enantio- and diastereoselective Rh(II)-catalyzed cyclopropanation with diazo reagents bearing two acceptor groups. The *trans*-directing ability of different groups in Rh(II)-catalyzed cyclopropanation is detailed, and the demonstration that the *trans*-directing group must adopt an out-of-plane conformation is described. We demonstrate how this feature can be applied to enable a solution to the enantiocontrol issue in the synthesis of 1,1-cyclopropane diesters. Finally, the scope of this new reaction as well as the synthetic utility of these novel cyclopropanes is discussed.[20,21]

2. Results and Discussion

Because of the growing interest in chiral, nonracemic 1,1-cyclopropane diesters, we investigated the transition metal-catalyzed formation of **4a**. According to the literature precedent (vide supra), rhodium-based catalysts were unsuitable for the highly enantioselective synthesis of 1,1-cyclopropane diesters from diazomalonates.[18,19] Recently, we reported a highly enantio- and diastereoselective formation of 1-nitro-1-cyclopropane

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(19) Müller, P.; Ghanem, A. *Org. Lett*. **2004**, *6*, 4347. In our hands, we obtained 10% ee in the cyclopropanation of styrene with Rh_2(4-Br-*S*-NTTL)$_4$. A screening of Rh(II) catalyst did not improve the enantioselectivity.
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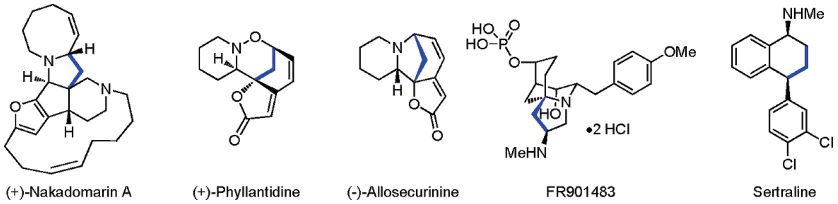
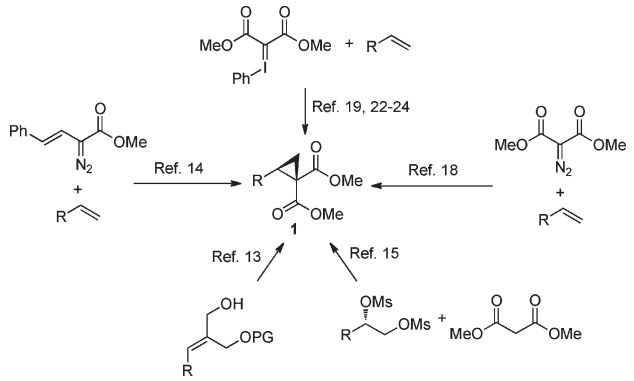


FIGURE 1. Structurally diverse products synthesized from a substituted 1,1-cyclopropane diesters.

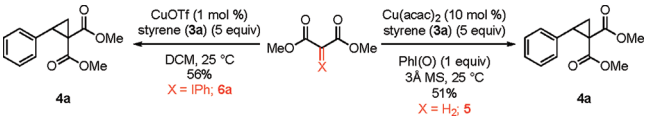
SCHEME 2. Asymmetric Synthesis of 1,1-Cyclopropane Diesters



carboxylates using a Cu(I)/bisoxazoline complex.[11a] We, therefore, envisioned that such complexes could enable a solution for the enantiocontrol issue in preparing cyclopropane **4a**. Unfortunately, Cu(I)OTf was not effective at decomposing diazomalonate **2**, affording < 10% of the desired cyclopropane with recovery of the unreacted diazo reagent. We thus turned our attention toward the use of the phenyliodonium ylide derivatives, as they are known to be more prone to metal-catalyzed decomposition.[22] As shown by Dauban, $Cu(acac)_2$ successfully catalyzed the reaction using the in situ generated iodonium ylides (Scheme 3).[22l] This strategy required a large quantity of molecular sieves that makes the reaction difficult to perform on larger scale and may explain the requirement for high catalyst loading (10 mol %) (Scheme 3). We recently reported an efficient method to isolate the corresponding phenyliodonium ylide.[23] The use of this isolated phenyliodonium ylide afforded a promising result toward the development of an asymmetric variant using only 1 mol % of catalyst (Scheme 3).

2.1. Cu(I)-Catalyzed Asymmetric Cyclopropanation. With our previously developed conditions,[11a] several symmetric and asymmetric bisoxazoline and Pybox ligands were first tested (entries 1−9, Table 1). Bisoxazolines L1 and L2 were both effective, affording the desired cyclopropane in 60% ee (entries 1 and 2). We presume that the decreased yield

SCHEME 3. Cu(I)-Catalyzed Formation of 4a via Iodonium Ylide Reagents



obtained with L2 (31 vs 71%) is a result of the ligand's greater steric hindrance. Further optimization demonstrated that L7 gave improved enantioselectivity (60%, 66% ee). Among all solvents studied with L7 (entries 10−17), no significant increase in enantioselectivity was observed, though the yield improved to 70% when the reaction was performed in toluene (entry 12). A variety of Cu sources and counterions were next considered (entries 18−24). Cu(II)SbF_6 did not catalyze the reaction, while the counterion of Cu(I) played an important role, with SbF_6^- providing the best results. A control experiment showed that CuCl did catalyze the reaction, though it yielded a racemic product (entry 24). This result suggests an important background reaction if the complex is not suitably preformed. It should also be highlighted that $AgSbF_6$ is not an effective catalyst in this reaction. Finally, lowering the temperature to 0 °C afforded the desired cyclopropane in 88% yield and 75% ee (entry 25), while lower temperature led to decreased yield (< 20%). Different symmetrical and asymmetrical malonates were considered, but none led to a better enantioselectivity (entries 25−29). Nonetheless, the result obtained with L7 (entry 25) represents the highest enantioselectivity reported to date for the Cu(I)-catalyzed cyclopropanation of styrene with a malonate carbene precursor. To achieve a more enantioselective process, we envisioned the use of different transition metals. However, Co(II)/Salen[24] and Ru(II)/Pybox[25] complexes were found to be ineffective at decomposing diazo **2** or iodonium ylides **6a** at room temperature.

2.2. Mechanistic Considerations. Cu(I) and Rh(II) do not seem suitable for the highly enantioselective formation of 1,1-cyclopropane diesters from malonates using known ligands. As such, we decided to go back on the proposed mechanism to fully understand this problem. Both the

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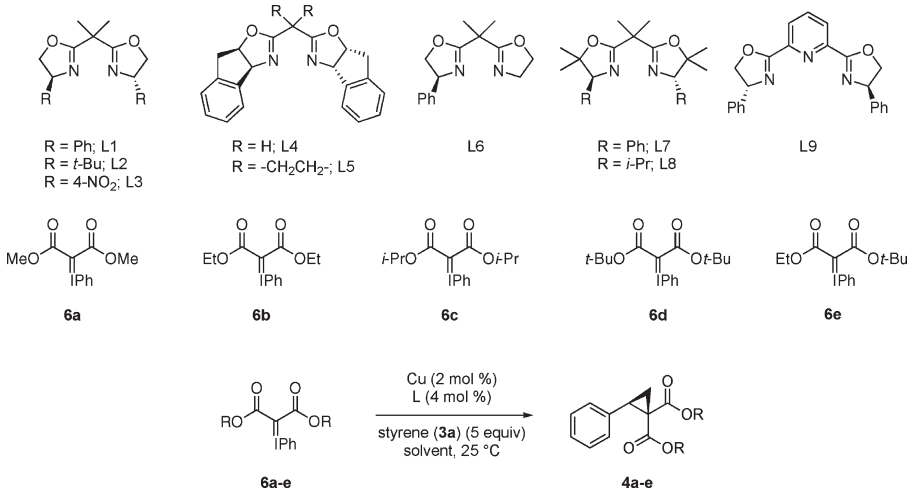
TABLE 1. Optimization of the Cu(I)-Catalyzed Cyclopropanation



entry	6[a]	Cu[b]	L	solvent	yield (%)[c]	ee (%)[d]
1	**6a**	$CuSbF_6$	L1	PhH	71	60
2	**6a**	$CuSbF_6$	L2	PhH	31	60
3	**6a**	$CuSbF_6$	L3	PhH	12	47
4	**6a**	$CuSbF_6$	L4	PhH	17	50
5	**6a**	$CuSbF_6$	L5	PhH	21	62
6	**6a**	$CuSbF_6$	L6	PhH	88	17
7	**6a**	**$CuSbF_6$**	**L7**	**PhH**	**60**	**66**
8	**6a**	$CuSbF_6$	L8	PhH	56	42
9	**6a**	$CuSbF_6$	L9	PhH	38	0
10	**6a**	$CuSbF_6$	L7	DCM	60	51
11	**6a**	$CuSbF_6$	L7	DCE	53	48
12	**6a**	**$CuSbF_6$**	**L7**	**PhMe**	**70**	**67**
13	**6a**	$CuSbF_6$	L7	PhCl	49	60
14	**6a**	$CuSbF_6$	L7	$PhCF_3$	55	63
15	**6a**	$CuSbF_6$	L7	$PhNO_2$	53	51
16	**6a**	$CuSbF_6$	L7	THF	6	59
17	**6a**	$CuSbF_6$	L7	dioxane	38	57
18	**6a**	$Cu(SbF_6)_2$	L7	PhMe	< 5	–
19	**6a**	$CuClO_4$	L7	PhMe	43	59
20	**6a**	$CuOOCCF_3$	L7	PhMe	12	0
21	**6a**	CuOTf	L7	PhMe	81	63
22	**6a**	$CuBF_4$	L7	PhMe	5	50
23	**6a**	$CuPF_6$	L7	PhMe	55	57
24	**6a**	CuCl	L7	PhMe	65	0
25[e]	**6a**	**$CuSbF_6$**	**L7**	**PhMe**	**88**	**75**
26[e]	**6b**	$CuSbF_6$	L7	PhMe	23	34
27[e]	**6c**	$CuSbF_6$	L7	PhMe	41	35
28[e]	**6d**	$CuSbF_6$	L7	PhMe	77	7
29[e,f]	**6e**	$CuSbF_6$	L7	PhMe	60	54

[a]Added in one portion. [b]Made from CuCl (2 mol %) and AgX (2.4 mol %). [c]Isolated yield. [d]Determined by SFC analysis on chiral stationary phase. [e]Reaction performed at 0 °C. [f]A 85:15 dr mixture was isolated.

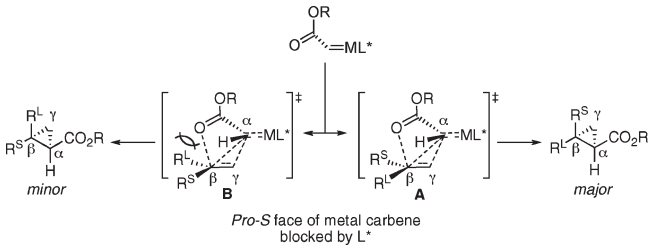
Cu- and Rh(II)-catalyzed decompositions of diazo reagents are known to proceed via a metal carbene that reacts in an asynchronous [2 + 1] transition state with an olefin (Scheme 4).[16] With diazoacetate reagents, it has been postulated that the ester on the metal carbene adopts an out-of-plane conformation[26] that places the carbonyl group in a position that stabilizes the developing Markovnikov positive charge in the transition state.[27,28] The largest substituent on the alkene is oriented to minimize steric interactions, affording the major *trans*-isomer. The ester can thus be seen as a *trans*-directing group. This situation is more complicated for carbenes possessing two electron-withdrawing groups, as at least three different conformations can be envisioned for carbenes derived from malonates (out−out, in−out, in−in, Figure 2). The out−out

(26) This out-of-plane conformation has been demonstrated by different calculation for Cu(I)- and Rh(II)-catalyzed cyclopropanation. For examples, see: (a) Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616. (b) Straub, B. F.; Gruber, I.; Rominger, F.; Hofmann, P. *J. Organomet. Chem.* **2003**, *684*, 124. (c) Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902.

(27) (a) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53. (b) See ref [16b].

(28) Although we are not aware of any calculation that validates this *trans*-directing ability neither for Cu(I)- nor Rh(II)-catalyzed cyclopropanation, we believe that this stabilization has not been explicitly searched (see ref 26). Work toward the demonstration of this stabilization by calculation is ongoing in our group.

SCHEME 4. Cu(I)- and Rh(II)-Catalyzed Cyclopropanation Transition State Structures with Diazoacetates as Carbene Precursor



conformation is believed to constitute the ground state, as corroborated by Nishiyama's X-ray structure of a Ru-malonate carbene.[29] We also postulate that this conformation is nonreactive due to steric repulsion with an approaching alkene. We hypothesize that the in−out conformation is operative as placing one group in the same plane of the metal carbene liberates space for an alkene to approach and enhances the

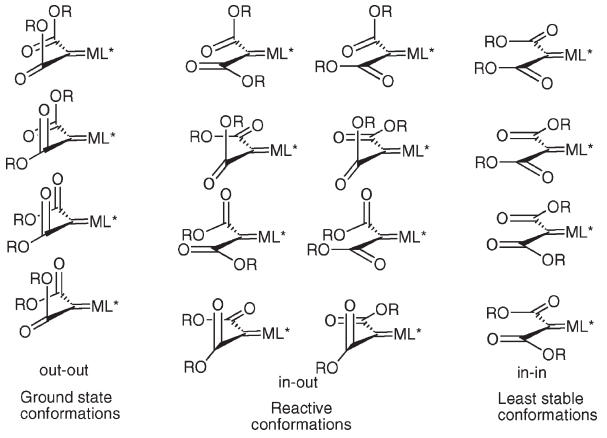
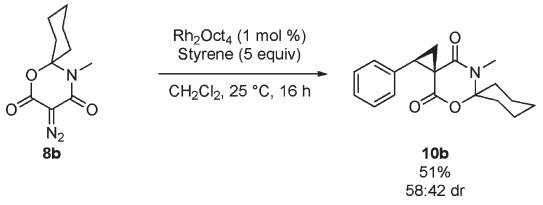


FIGURE 2. Different possible conformations of a malonate-derived metal carbene with chiral ligands.

electrophilicity of the metal carbene. The out-of-plane substituent can act as a *trans*-directing group, and in the case of malonates, transition state structures **C**−**F** would be plausible (Scheme 5). Assuming that the use of a chiral catalyst would be effective at blocking the *pro-S* face, we found that the four possible transition state structures would lead to a pair of enantiomers (Scheme 5). This may explain the low enantiocontrol obtained to date with malonates. Therefore, we envisioned several strategies for the development of a highly enantioselective version of this reaction: (1) The use of a chiral ligand that would be large enough to efficiently control the selectivity of the longer C−C bond formation in the asynchronous [2 + 1] transition state. This would probably be detrimental to the isolated yield as can be seen with the bulkier catalyst derived from L2 (entry 2, Table 1). (2) The use of a chiral ligand that would control the conformation of the carbene as well as favor reaction on one of the two prochiral faces (discrimination between **C**,**D** and **E**,**F**, Scheme 5). (3) The use of a carbene possessing two different groups that have different *trans*-directing abilities in combination with a catalyst that would be effective at blocking one of the two prochiral faces (Scheme 6). Transition state structures **I**,**J** would not be accessible due to the greater *trans*-directing ability of the COR group. (4) The use of a metal that reacts in a more synchronous matter or through a different mechanism. From these four hypotheses, it appeared to us that the use of a carbene precursor possessing two groups with different *trans*-directing abilities was the most promising, and we decided to investigate it further (Scheme 6).

2.2.1. *trans*-Directing Ability of the Amide Group. Our initial work focused on establishing a relative trend of the *trans*-directing ability of various carboxyl groups. As such, we investigated the $Rh_2(oct)_4$-catalyzed cyclopropanation of styrene with a variety of substituted α-carbonyl diazaoacetate reagents (Scheme 7). We were excited by the result obtained with α-amido-α-diazoacetate derivatives **8**. Indeed, this class of compounds led to very high levels of diastereocontrol. The *trans*-relationship between the phenyl group and the ketone has been unambiguously established by X-ray analysis of cyclopropane **9c**.[30] Interestingly, it was found that, as postulated, the polarity of the carbonyl has an important influence on the diastereoselectivities of the reactions. By varying the *p*-substituent on the phenylketone (diazo **7b**−**d**), different levels of diastereocontrol were observed. Since all three phenylketone derivatives possess similar steric constraints around the metal carbene, the interpretation of these results must rely on electronic considerations. It is known that C=O IR stretching vibration gives insight into the polarity of the C=O bond, and it was found that it also gives a qualitative prediction of the *trans*-directing ability of different groups. Indeed, the more polar the C=O bond, the better the diastereoselectivity (Figure 3).[31] Interestingly, the methyl ketone **7a** follows the diastereoselectivity trend even though it is sterically less congested than phenyl ketones **7b**−**d**. To demonstrate further reliability of this *trans*-directing ability, we envisioned the synthesis of a carbene precursor that would not be capable to adopt an out-of-plane conformation. Strikingly, the submission of diazo **8b** led to a low diastereoselectivity (58:42 dr), indicating that the *trans*-directing group *must adopt an out-of-plane conformation* to induce high diastereoselectivities (eq 3).



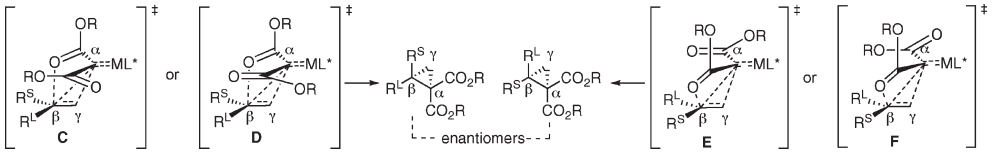
2.3. Optimization of the Reaction. Now that we did succeed in finding a carbene precursor possessing two different acceptor groups with different *trans*-directing abilities and exhibiting outstanding levels of diastereocontrol, we studied different chiral catalysts. In our first attempt, Cu(I)/bisoxazolines were ineffective at decomposing diazo **8a**. The use of the in situ generated iodonium ylides did not afford the corresponding cyclopropane, and we have not been successful in isolating the corresponding iodonium ylides in good yield and purity. The use of Rh(II) dimers, known to be more reactive catalysts than the copper-based system, was therefore investigated despite the fact that these complexes have never been reported to produce high enantioselectivities in

(29) Nishiyama, H.; Aoki, K.; Itoh, H.; Iwamura, T.; Sakata, N.; Kurihara, O.; Motoyama, Y. *Chem. Lett.* **1996**, 1071.

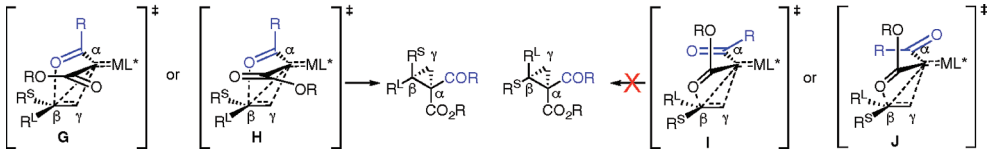
(30) See Supporting Information for further details.

(31) IR stretching vibration according to the Sadtler database.

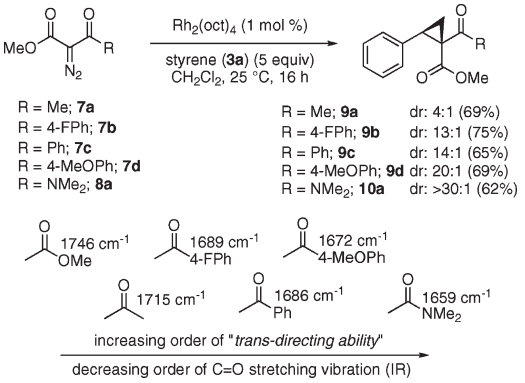
SCHEME 5. Cu(I)- and Rh(II)-Catalyzed Cyclopropanation Transition State Structures with Diazomalonates as Carbene Precursor



SCHEME 6. Proposed Strategy with a Metal Carbene Possessing Two Different Groups with Different *trans*-Directing Abilities



SCHEME 7. Cyclopropanation of Styrene with a Variety of Carboxy Diazoacetate Reagents



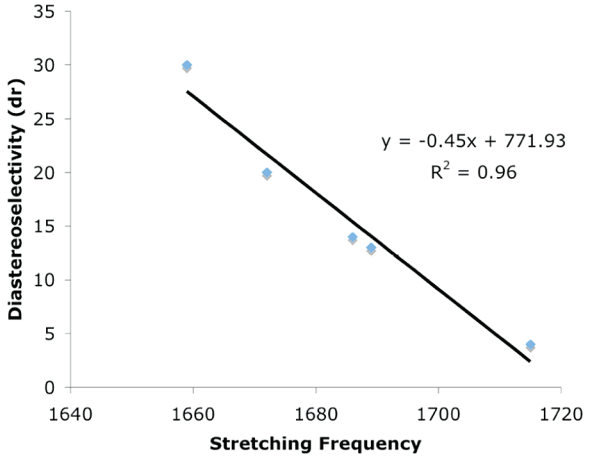


FIGURE 3. Graphical representation of the diastereoselectivity of the reaction as a function of the carbonyl IR stretching frequency of the *trans*-directing group.

reactions involving metal carbenes bearing two acceptor groups. We first considered the effect of a variety of chiral ligands using diazo reagent **8a** in CH_2Cl_2 at 25 °C (entries 1−10, Table 2). Though the diastereoselectivity remained high in all cases, the different ligands had a drastic effect on both the yield and the enantioselectivity. Hashimoto's[32] (L13−L15) and Müller's[33] (L10−L12) ligands were found to be the most promising. In general, increasing the size of the side chain from Bn to *t*-Bu led to improved enantiocontrol, with L12 and L15 being the most interesting, affording the corresponding cyclopropane in 75 and 70% ee, respectively (entries 3 and 6). Many solvents were tested, but none was found to have a significant positive effect on the selectivity compared to CH_2Cl_2. Decreasing the temperature to 0 °C led to no conversion, and the diazo could be recovered. This is a particular feature as Rh(II)-based catalysts have been shown to be highly effective at decomposing diazo reagents even at low temperatures.[16] The time of addition of the diazo reagent had little or no impact on the efficiency of the reaction, as similar results were obtained when the reagent was added over a 2, 10, or 24 h period, but 10 h was chosen for the optimization. We next turned our attention to study structurally different α-amido diazoacetate reagents **8**, and it was found that their structure greatly affected the enantioselectivity and yield of the reaction (entries 11−19). More precisely, we were pleased to find that the pyrrolidine amide **8h** gave excellent enantiocontrol (95% ee) regardless of the structure of the ester (entries 17−19). To the best of our knowledge, these results represent the first example of a highly selective Rh(II)-catalyzed cyclopropanation with a carbene possessing two acceptor groups. The reduced yield with the Et and *i*-Pr ester (entries 18 and 19) is explained by the presence of a secondary and tertiary carbon that undergoes C−H insertion to form the corresponding β-lactone (eq 4).[34] Interestingly, diazo **8h** did not undergo this type of reaction when mixed alone with Rh_2(*S*-NTTL)$_4$, and the unreacted diazo was recovered. This special feature has also been reported by Box using diazo **8h** and $Rh_2(OAc)_4$ as catalyst.[35] Surprisingly, changing the amide for the piperidine amide **8e** and azepane amide **8f** led to very low

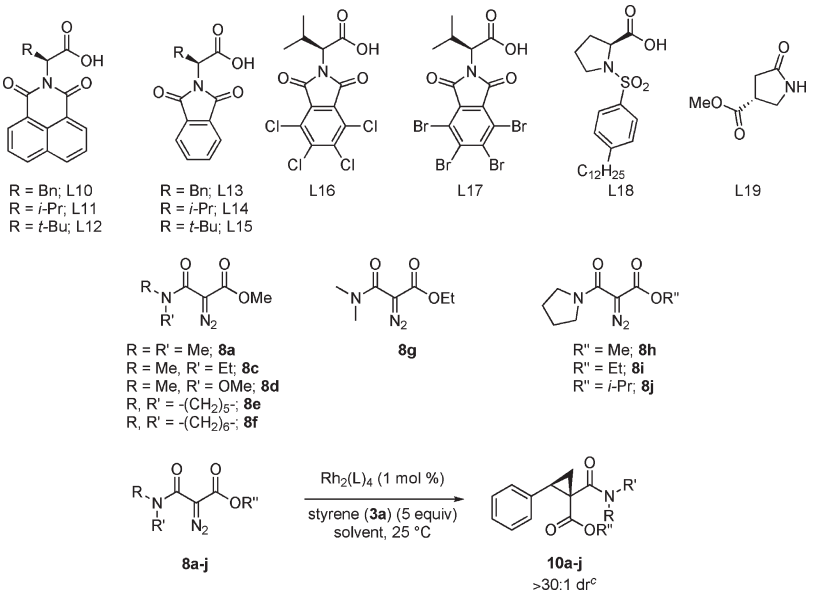
(32) (a) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173. (b) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Synlett* **1994**, 353. (c) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561.

(33) Müller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Flack, H. D. *Org. Lett.* **2004**, *6*, 1725.

(34) Unfortunately, enantiomeric excesses of these β-lactones could not be determined.

(35) Box, V. G. S.; Marinovic, N.; Yiannikouros, G. P. *Heterocycles* **1991**, *32*, 245.

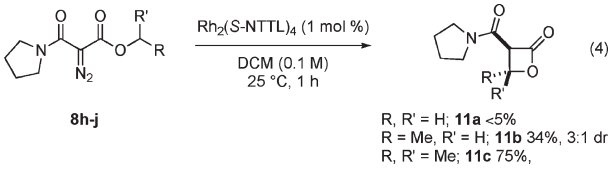
TABLE 2. Optimization of the Rh(II)-Catalyzed Cyclopropanation



entry	8[a]	L	solvent	yield (%)[b]	ee (%)[d]
1	**8a**	L10	DCM	61	33
2	**8a**	L11	DCM	83	54
3	**8a**	L12	DCM	71	75
4	**8a**	L13	DCM	63	45
5	**8a**	L14	DCM	69	30
6	**8a**	L15	DCM	76	70
7	**8a**	L16	DCM	52	−30
8	**8a**	L17	DCM	45	−23
9	**8a**	L18	DCM	67	0
10	**8a**	L19	DCM	NR	–
11	**8b**	L12	DCM	< 10	–
12	**8c**	L12	DCM	35	85
13	**8d**	L12	DCM	24	80
14	**8e**	L12	DCM	29	15
15	**8f**	L12	DCM	< 10	–
16	**8g**	L12	DCM	48	54
17	**8h**	L12	DCM	71	95
18	**8i**	L12	DCM	45	94
19	**8j**	L12	DCM	19	97
20	**8a**	L12	EtOAc	54	86
21	**8a**	L12	PhMe	49	81
22	**8a**	L12	DCE	75 (77)[e]	96 (96)[e]
23[f]	**8a**	**L12**	**DCE**	**79**	**96**
24	**8a**	L12	THF	< 10	–

[a]Addition over 10 h. [b]Isolated yields. [c]Determined by ^{1}H NMR and GC/MS analysis of the crude reaction mixture. [d]Determined by SFC analysis on chiral stationary phase. [e]Yield and ee in parentheses correspond to a 5 mmol scale reaction. [f]3 equiv of **9h** and 1 equiv of **3a** were used.

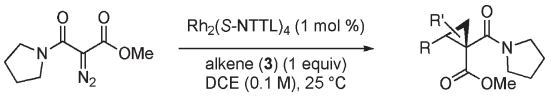
asymmetric induction and no conversion, respectively (entries 15 and 16). Optimization of the solvent (entries 20−22 and 24) showed that DCE gave a slight increase in enantioselectivity to 96% ee. When expensive olefins are cyclopropanated, the alkene can be used as the limiting reagent with 3 equiv of **8h** to afford the desired cyclopropane with a slightly increased yield (79 vs 75%) and with the same level of selectivity (entry 23). Conversely, when the olefin is inexpensive as styrene (**3a**), a 5-fold excess was used. In both cases, the unreacted olefin was recovered in nearly quantitative yield following completion of the reaction. Using 5-fold excess of styrene (**3a**) (entry 22), cyclopropane **10h** could be obtained in 77% yield (96% ee, > 30:1 dr) using 1 g (ca. 5 mmol) of diazo **8h** when added over a 10 h period.



(4)

2.3.1. Scope of the Cyclopropanation Reaction. With these optimal conditions in hand (entry 23, Table 2), we studied the scope of the reaction beginning with the effect of different *p*-substituted styrenes (entries 1−13, Table 3). Electron-rich

TABLE 3. Scope of the Reaction



8h 10h, k-am

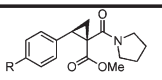
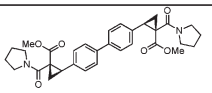
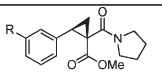
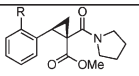
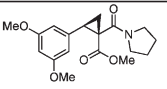
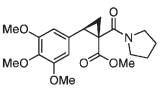
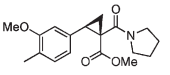
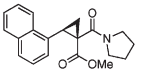
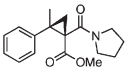
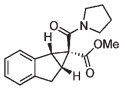
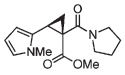
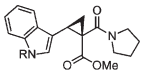
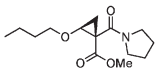
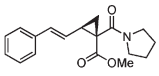
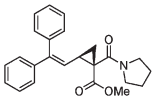
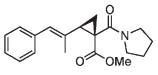
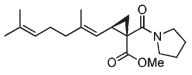
entry	products		yield (%)[a]	dr[b]	% ee[c]
1		R = H (**10h**)	79	>30:1	96
2[d]			83	>30:1	97
3		R = *t*-Bu (**10k**)	89	>30:1	96
4[d]			90	>30:1	96
5		R = F (**10l**)	77	>30:1	97
6[d]			84	>30:1	97
7		R = Cl (**10m**)	81	>30:1	96
8[d]			84	>30:1	97
9		R = Me (**10n**)	82	>30:1	96
10		R = OMe (**10o**)	92	>30:1	93
11[e]		R = NO_2 (**10p**)	31	>30:1	95
12[e]		R = CF_3 (**10q**)	55	>30:1	95
13[f]		(**10r**)	62	25:1	>99
14[e]		R = OMe (**10s**)	78	>30:1	96
15[e]		R = NO_2 (**10t**)	51	>30:1	96
16[e]		R = CF_3 (**10u**)	49	>30:1	95
17[e]		R = F (**10v**)	43	>30:1	94
18[eg]			72	>30:1	96
19[e]		R = Cl (**10w**)	35	>30:1	94
20[eg]			52	>30:1	96
21[e]		R = Br (**10x**)	24	>30:1	94
22[e]		(**10y**)	54	22:1	90
23[e]		(**10z**)	29	24:1	59
24[e]		(**10aa**)	64	25:1	81
25		(**10ab**)	86	>30:1	95
26		(**10ac**)	63	>30:1	95

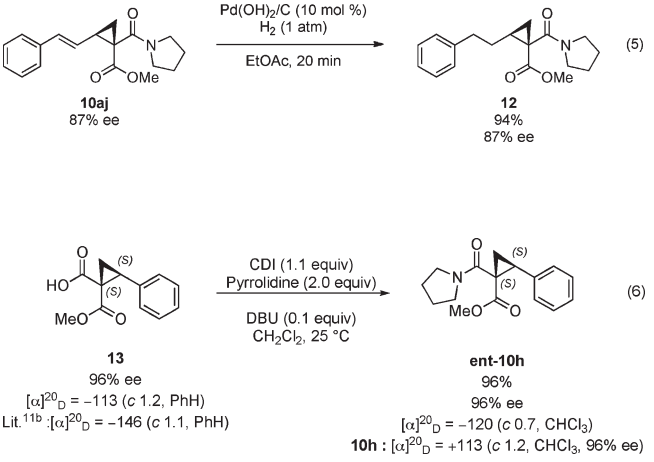
TABLE 3. Continued

entry	products	yield (%)[a]	dr[b]	% ee[c]
27	 (**10ad**)	51	>30:1	84
28[d]		63	>30:1	89
29[h]		62	>30:1	89
30	 (**10ae**)	31	>30:1	90
31	 R = Boc (**10af**)	54[i]	1.2:1	96(88)[j]
32	R = Ts (**10ag**)	58[i]	1:1	95(83)[j]
33	R = Bn (**10ah**)	88[i]	1.5:1	50(41)[j]
34	 (**10ai**)	70	9:1	89
35	 (**10aj**)	78	9:1	87
36	 (**10ak**)	90	6:1	75(53)
37	 (**10al**)	73	14:1	85
38	 (**10am**)	45	22:1	90

[a]Isolated yields. [b]Determined by ^{1}H NMR and GC/MS analysis of the crude reaction mixture. [c]Determined by SFC analysis on chiral stationary phase. [d]2 mol % of catalyst was used. [e]Reaction performed at 50 °C. [f]6 equiv of **8h** were used. [g]The diazo reagent was added over 48 h. [h]5 mol % of catalyst was used. [i]Yield of the mixture of diastereomer. [j]ee of the *trans*-isomer is in parentheses.

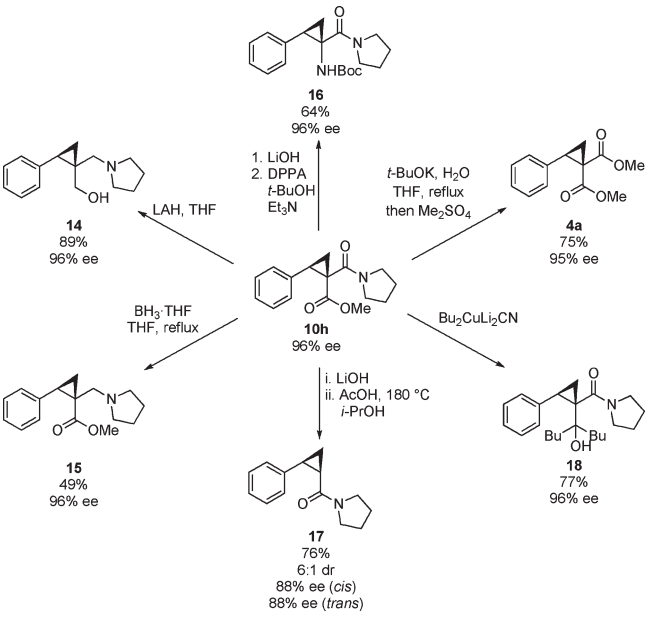
(entries 10, 23, and 24) and electron-neutral styrenes (entries 1−9 and 13) underwent the reaction in high yields (75−92%) and high enantioselectivities (93−97% ee). Electron-poor styrenes did give the corresponding cyclopropane derivatives in high enantioselectivities (95% ee) but were found to be less reactive as decreased yields were observed (31−55%) (entries 11 and 12). Moving the electron-withdrawing group from the *para* to the *meta* position led to a better isolated yield in the case of the nitro group (51%) (entry 15) while having no significant effect for the CF_3 group (49%) (entry 16). Sterically hindered *o*-substituted styrenes reacted in yields ranging from 24 to 43% but with high enantiocontrol (entries 17−21). Even the presence of an *o*-basic Br group did not affect the selectivity. The same substrate was reported to give low enantiocontrol as a result of the proximity to the double bond.[33] It should be noted that, in the cases of less reactive styrenes, a non-negligible amount of unreacted diazo **8h** was recovered after a reaction time of 16 h. This unusual feature can, in part, account for the decreased isolated yields due to the similar R_f of diazo **8h** and the corresponding cyclopropanes. To overcome this, the use of 2 mol % of catalyst or longer addition time can be used to fully consume diazo **8h** and increase the isolated yield. For example, with *o*-fluorostyrene (entries 17 and 18) and *o*-chlorostyrene (entries 19 and 20), the yield can be improved if the addition time is increased to 48 h (from 43 to 72% and from 35 to 52%, respectively). It is believed that a high concentration of unreacted diazo **8h** poisons the catalyst by complexation with the highly basic amide oxygen that bears a negative charge on the α-carbon. Interesting results were encountered when *m*-MeO styrene derivatives were submitted to the reaction (entries 14 and 22−24), as both the selectivity and the isolated yields were lower even when the reaction was performed at 50 °C. 1-Naphthyl-substituted olefins also reacted in 86% and high enantioselectivity (entry 25). The 1,1- and 1,2-(*Z*)-disubstituted styrene derivatives afforded the corresponding cyclopropanes in moderate yields (51−63%) and excellent to good enantioselectivities (84−95% ee) (entries 26−29). Non-styryl olefins also reacted under these optimal conditions. Indeed, *N*-Me-2-vinylpyrrole and

butylvinyl ether both reacted in low and good yields, respectively, to afford the desired cyclopropanes with good selectivities (entries 30 and 34). Surprising results were observed using *N*-protected 3-vinylindole (entries 31−33) as low diastereoselectivities (1:1 dr) were found with Ts, Boc, and Bn as protecting groups, though excellent enantioselectivities (95−96% ee) were observed in the cases of the *N*-Boc- and *N*-Ts-protected adducts. The exact explanation for the low diastereoselectivity remains unclear. Aryl-substituted dienes as well as an alkyl-substituted diene provided the corresponding cyclopropanes in moderate to excellent yields (45−90%) and with selectivities ranging from 6:1 dr and 75% ee to 22:1 dr and 85% ee (entries 35−38). Aliphatic olefins, which are less reactive substrates in Rh(II)-catalyzed cyclopropanation, did not react under these conditions. However, they can be accessed after cyclopropanation of the less hindered double bond of a diene followed by hydrogenation (eq 5). $Pd(OH)_2$ and EtOAc were found to be crucial in this hydrogenation as other solvents and Pd sources gave competing side reactions leading to the opened cyclopropane presumably through π-allyl chemistry.[36] Finally, the absolute and relative stereochemistry of these cyclopropanes was determined using known acid **13** (eq 6).[30]



2.3.2. Synthetic Utility. As we validated the efficiency of the reaction, we wished to demonstrate the versatility of these newly formed cyclopropanes (Scheme 8). The amino alcohol **14** was obtained upon treatment with LAH. Interestingly, such cyclopropanes possess biological activity as selective serotonin reuptake inhibitors.[12] The amide could be reduced with excellent chemoselectively using $BH_3 \cdot THF$ in moderate yield.[37] β-Aminoester derivatives such as **15** are important derivatives extensively used in peptide mimetic chemistry[10,11] and as selective serotonin reuptake inhibitors.[12] The ester could be selectively hydrolyzed and converted to the *N*-Boc cyclopropyl amine **16** following a Curtius rearrangement.[38] Cyclopropane **16** was recrystallized from Et_2O, and X-ray analysis unambiguously showed the *cis*-relationship between the amine and the phenyl group.[30] Such α-amino acid derivatives have also

SCHEME 8. Functional Group Transformations on Cyclopropane 10h



been widely used for their biological properties.[10,11] The acid obtained after ester hydrolysis was decarboxylated under heating at 180 °C to afford **17** in 76% yield (85:15 dr). The *cis*-stereochemistry of the major product was assigned by converting the amide to the known ethyl ester **19** using a methodology previously reported by our group (Scheme 9).[39] The *cis*-stereochemistry obtained can be explained by a protonation from the less sterically hindered face since that the reaction is not under thermodynamic control. Indeed, treating cyclopropane *cis*-**17** in *i*-PrOH/AcOH at 180 °C for 1 h did not lead to the *trans*-isomer. However, epimerization could be performed in basic medium (Scheme 9).[40] Unfortunately, the decarboxylation reaction afforded **17** with loss of the stereochemical information. We know that **17** does not racemize under the reaction conditions and that the ester hydrolysis is performed with complete retention of ee. Conversely, the amide acid intermediate is configurationally unstable at 180 °C and racemizes prior to decarboxylation.[4f,15] The amide could also be hydrolyzed to afford the valuable 1,1-cyclopropane diesters **4a** in 75% yield after in situ methylation with Me_2SO_4.[41] Though cyclopropane **4a** could be rapidly accessed, we wondered if the presence of the amide on cyclopropane **10h** affected its electrophilicity.

We therefore studied its reactivity toward organocuprate reagents. The reaction of **10h** with 2 equiv of Bu_2CuLi_2CN did not afford the desired product. Instead, the organocuprate reagent reacted with the ester, affording the tertiary alcohol **18** in 77% yield (Scheme 8). As shown in eq 7, this reagent reacted smoothly with diester **4a** to afford the linear product. Different Cu sources and cuprates were investigated, and we were pleased to observe that BuCu·LiCN reacted with cyclopropane **10h** to give **21** in 70% yield with

(36) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541.
(37) (a) Kornet, M. J.; Thio, P. A.; Tan, S. I. *J. Org. Chem.* **1968**, *33*, 3637. (b) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.
(38) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
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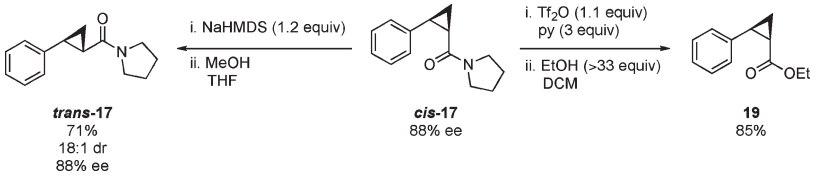
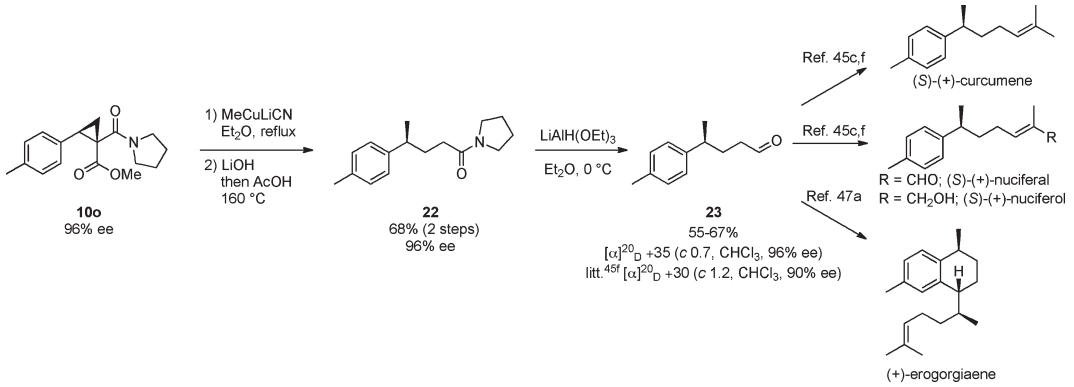
(40) Yamaguchi, K.; Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 9255.
(41) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.

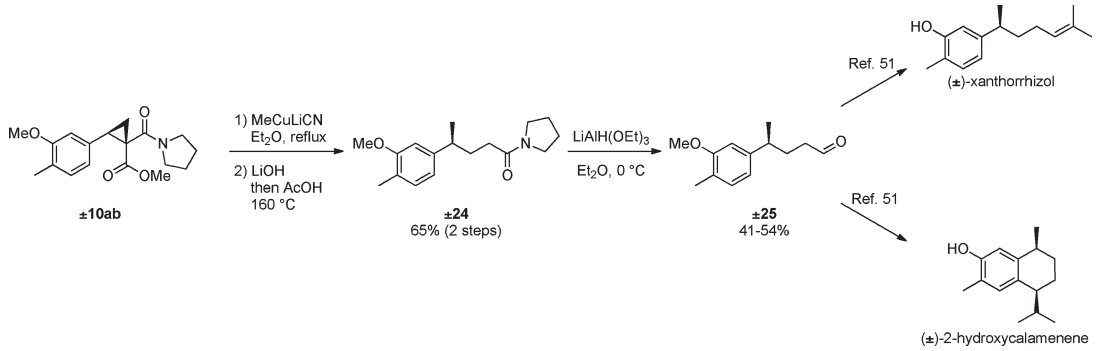
SCHEME 9. Epimerization of Amide 17 and Its Conversion to an Ethyl Ester



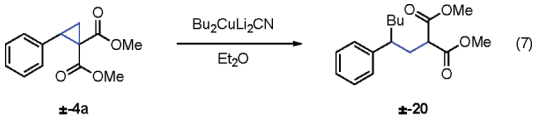
SCHEME 10. Formal Synthesis of Bisabolane-Type Natural Products

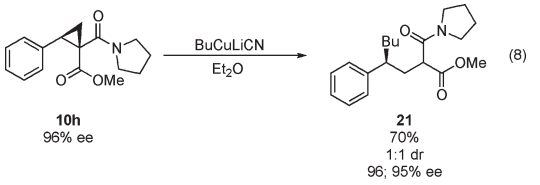


SCHEME 11. Formal Synthesis of (±)-Xanthorrhizol and (±)-3-Hydroxycalamenene



trace amounts of alcohol **18** (eq 8). We thus believe that cyclopropanes **10** have a similar reactivity to diester **1** and **4a**, therefore making them a good alternative to study the reactivity of electrophilic cyclopropanes bearing *gem*-dicarboxy groups.





We were excited by this result, as it provides a route to the expedient synthesis of a variety of molecules from the bisabolane family. These natural products are sesquiterpenes characterized by a chiral benzylic aliphatic substituent. They have been found in many different natural sources[42] and displayed a myriad of biological features ranging from olfactive properties[43] to antibabesial activities.[44] Their simple structures have captured the attention of synthetic chemists as exemplified by the large number of reported

(42) (a) Sakai, T.; Nishimura, K.; Hirose, Y. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 381. (b) Honwad, V. K.; Rao, A. S. *Tetrahedron* **1964**, *20*, 2921. (c) Damodaran, N. P.; Dev, S. *Tetrahedron* **1968**, *24*, 4113. (d) Nagumo, S.; Irie, S.; Hayashi, K.; Akita, H. *Heterocycles* **1996**, *43*, 1175. (e) Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S. *J. Org. Chem.* **2004**, *69*, 2461.

(43) (a) Stevens, K. L.; Lundin, R. E.; Teranishi, R. *J. Org. Chem.* **1965**, *30*, 381. (b) Flath, R. A.; Lundin, R. E.; Teranishi, R. *Tetrahedron Lett.* **1966**, 295. (c) Thomas, A. F. *Chem. Commun.* **1967**, 947. (d) Bertele, E.; Schudei, P. *Helv. Chim. Acta* **1967**, *50*, 2445.

(44) (a) Bohlman, F.; Lonitz, M. *Chem. Ber* **1978**, *111*, 843. (b) McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661. (c) Fusetani, N.; Sugano, M.; Matsunaga, S.; Hashimoto, K. *Experientia* **1987**, *43*, 1234. (d) Wright, A. E.; Pomponi, S. A.; McConnell, O. J.; Kohmoto, S.; McCarthy, P. J. *J. Nat. Prod.* **1987**, *50*, 976. (e) Ohno, M.; Todoriki, R.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1994**, *42*, 1590. (f) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757. (g) Rucker, G.; Breitmaier, E.; Manns, D.; Maier, W.; Marek, A.; Heinzmann, B.; Heiden, K.; Seggewies, S. *Arch. Pharm.* **1997**, *330*, 12. (h) Mayer, A. M. S.; Jacobson, P. B.; Fenical, W.; Jacobs, R. S.; Glaser, K. B. *Life Sci.* **1998**, *62*, 401.

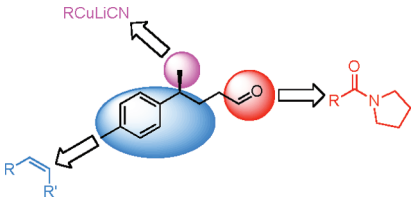


FIGURE 4. Versatility of chiral, nonracemic cyclopropane amide esters.

total syntheses. Within the bisabolane family, (*S*)-(+)-curcumene,[45] (*S*)-(+)-nuciferal,[46] (*S*)-(+)-nuciferol,[46] and (+)-erogorgiaene[47] attracted our attention. Indeed, it was found that all four natural products could be accessed from the same intermediate **23**. To date, the fastest route to form **23** was reported by Pan and required six steps from *p*-methylstyrene (90% ee).[46d] We envisioned that **23** could come from a three-step sequence involving the MeCu·LiCN ring opening of cyclopropane **10o**, decarboxylation, and reduction of the amide **22** to aldehyde **23** using $LiAlH(OEt)_3$, a reagent developed by Brown (Scheme 10).[48] Aldehyde **23** was thus accessed in four steps (37% overall yield) from commercially available *p*-methylstyrene. To the best of our knowledge, this synthetic sequence represents to date the fastest route to **23**.

Interestingly, this synthetic route appears to be extremely versatile for SAR studies (Figure 4). Indeed, the aldehyde group comes from an amide that is a highly useful functional group that can be converted into several other useful functionalities.[49] The aliphatic side chain at the benzylic position can be installed using the appropriate organocuprate reagent (eq 8). Finally, the aromatic moiety can be modified as shown in Table 3. For example, treatment of cyclopropane (±)-**10ab** through the same synthetic sequence gave access to the formal synthesis of (±)-xanthorrhizol[50] and (±)-2-hydroxycalamenene[51] (Scheme 11).

3. Conclusion

Herein we have described our efforts toward the highly enantio- and diastereoselective synthesis of 1,1-dicarboxy cyclopropane derivatives. We elaborated the concept of the *trans*-directing ability of different groups in Rh(II)-catalyzed cyclopropanation and demonstrated that the *trans*-directing group must adopt an out-of-plane conformation. The scope and the limitations of the reaction between diazo reagent **8h** and a variety of mono- and disubstituted alkenes were also studied, which represents the first highly stereoselective Rh-(II)-catalyzed cyclopropanation with a carbene possessing two acceptor groups. Finally, the resulting cyclopropanes have been used in further synthetic transformations as well as in the formal synthesis of six natural products. Other applications of this *trans*-directing ability of amides in cyclopropanation will be reported in due course.

Experimental Section

General Procedure of the Optimized Condition for the Synthesis of Enantioenriched Cyclopropanes (Table 3). A 10 mL microwave tube was charged with Rh_2(*S*-NTTL)$_4$ (2.9 mg, 0.002 mmol, 1 mol %) and a magnetic stir bar. The tube was sealed with a Teflon septum and purged with argon. DCE (1 mL) and the corresponding alkene (0.20 mmol, 1.00 equiv) were then added. The diazo compound (0.60 mmol, 3.00 equiv) dissolved in 1 mL of DCE was added to the reaction mixture over a period of 10 h using a syringe pump at 25 °C. Following complete addition, the resulting mixture was stirred for an additional 6 h at 25 °C. After complete consumption of the diazo reagent, the reaction mixture was put directly on a silica gel column and eluted with 100% hexane to 100% Et_2O. In ases where the rhodium dimer is complexed to the product, the green mixture was dissolved in DCM and poly(4-vinylpyridine) (≈20 mg) was added. The color of the mixture turned from green to red, and the mixture was then filtered through Celite to afford a rhodium-free product following concentration under reduced pressure.

(1*R*,2*R*)-Methyl 2-phenyl-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10h). Prepared according to the general procedure. The product was isolated as a white solid: yield 79%; diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 32.3 min, t_r (major) 33.3 min); enantiomeric excess (96% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 4% *i*-PrOH, 5 mL/min, 30 °C, 200 psi, t_r (major) 13.9 min, t_r (minor) 16.8 min); mp 73−75 °C; R_f 0.35 (100%, Et_2O); $[\alpha]^{20}_D$ = +113 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.22 (m, 5H), 3.78−3.50 (m, 3H), 3.42 (s, 3H), 3.41−3.27 (m, 2H), 2.21 (dd, J = 4.7 Hz, J = 7.9 Hz, 1H), 2.01−1.87 (m, 4H), 1.53 (dd, J = 4.7 Hz, J = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 166.5, 135.4, 129.2 (2C), 128.1 (2C), 127.2, 52.4, 46.6, 46.5, 38.8, 31.5, 26.2, 24.3, 17.8; IR (film) 3039, 3008, 2946, 2884, 1715, 1638, 1511, 1434, 1334, 1135 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{19}N_1O_3$ $[M + H]^+$ 274.1438, found 274.1437.

Methyl 2-(4-*tert*-butylphenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10k). Prepared according to the general

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(47) (a) Harmata, M.; Hong, X.; Schreiner, P. R. *J. Org. Chem.* **2008**, *73*, 1290. (b) Yadav, J. S.; Basak, A. K.; Srihari, P. *Tetrahedron Lett.* **2007**, *48*, 2841. (c) Harmata, M.; Hong, X. C. *Tetrahedron Lett.* **2005**, *46*, 3847. (d) Davies, H. M. L.; Walji, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1733. (e) Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96.

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(51) Krause, W.; Bohlmann, F. *Tetrahedron Lett.* **1987**, *28*, 2575.

procedure. The product was isolated as a white solide: yield 89%; diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 37.3 min, t_r (major) 38.7 min); enantiomeric excess (96% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 5% MeOH, 3 mL/min, 30 °C, 200 psi, t_r (minor) 5.4 min, t_r (major) 6.6 min); mp 78−80 °C; R_f 0.36 (100%, Et_2O); $[\alpha]^{20}_D$ = +124 (*c* 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 6.4 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 2H), 3.71−3.54 (m, 3H), 3.42 (s, 3H), 3.38−3.28 (m, 2H), 2.19 (dd, *J* = 4.9 Hz, *J* = 8.1 Hz, 1H), 2.01−1.85 (m, 4H), 1.54 (dd, *J* = 4.9 Hz, *J* = 9.2 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.6, 150.0, 132.3, 128.9 (2C), 125.0 (2C), 52.3, 46.7, 46.6, 38.8, 34.6, 31.5 (3C), 31.3, 26.3, 24.4, 17.9; IR (film) 3038, 3009, 2956, 2879, 1729, 1644, 1432, 1319, 1139 cm^{-1}; HRMS (ES, Pos) calcd for $C_{20}H_{27}N_1O_3$ $[M + H]^+$ 330.2064, found 330.2062.

Methyl 2-(4-fluorophenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10l). Prepared according to the general procedure. The product was isolated as a white solid: yield 77%; diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 34.4 min, t_r (major) 35.5 min); enantiomeric excess (97% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 4% MeOH, 3 mL/min, 40 °C, 210 psi, t_r (minor) 5.8 min, t_r (major) 6.9 min); mp 68−72 °C; R_f 0.36 (100%, Et_2O); $[\alpha]^{20}_D$ = +79 (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.26 (m, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.53−3.49 (m, 3H), 3.45 (s, 3H), 3.37−3.28 (m, 2H), 2.17 (dd, *J* = 4.9 Hz, *J* = 8.0 Hz, 1H), 2.03−1.87 (m, 4H), 1.54 (dd, *J* = 4.9 Hz, *J* = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 166.9, 162.7 (d, *J* = 243.9 Hz, 1C), 131.8 (d, *J* = 3.2 Hz, 1C), 131.5 (d, *J* = 8.1 Hz, 2C), 115.7 (d, *J* = 21.3 Hz, 2C), 53.1, 47.3, 47.2, 39.5, 31.4, 26.9, 25.0, 18.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.95; IR (film) 3050, 3012, 2953, 2878, 1728, 1632, 1513, 1434, 1316, 1145 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{18}N_1O_3F_1$ $[M + Na]^+$ 314.1163, found 314.1162.

Methyl 2-(4-chlorophenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10m). Prepared according to the general procedure. The product was isolated as a white solid; yield 81%; diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 36.0 min, t_r (major) 36.6 min); enantiomeric excess (96% ee) was determined by SFC analysis on chiral phase (Chiralcel OD-H 25 cm, 10% MeOH, 2 mL/min, 30 °C, 150 psi, t_r (minor) 3.7 min, t_r (major) 4.8 min); mp 72−75 °C; R_f 0.36 (100%, Et_2O); $[\alpha]^{20}_D$ = +88 (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.19 (m, 4H), 3.62−3.49 (m, 3H), 3.45 (s, 3H), 3.33−3.24 (m, 2H), 2.16 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 1H), 2.00−1.86 (m, 4H), 1.54 (dd, *J* = 5.0 Hz, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 166.2, 134.0, 133.1, 130.6 (2C), 128.4 (2C), 52.6, 46.7, 46.6, 39.0, 30.9, 26.3, 24.3, 17.9; IR (film) 3050, 3010, 2951, 2876, 1727, 1635, 1427, 1314, 1143 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{18}N_1O_3Cl_1$ $[M + H]^+$ 308.1048, found 308.1048.

Methyl 1-(pyrrolidine-1-carbonyl)-2-*p*-tolylcyclopropanecarboxylate (10n). Prepared according to the general procedure. The product was isolated as a white solid: yield 82%; diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 33.8 min, t_r (major) 35.2 min); enantiomeric excess (96% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 5% MeOH, 3 mL/min, 30 °C, 200 psi, t_r (minor) 7.5 min, t_r (major) 9.2 min); mp 72−74 °C; R_f 0.35 (100%, Et_2O); $[\alpha]^{20}_D$ = +85 (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 3.68−3.49 (m, 3H), 3.45 (s, 3H), 3.38−3.28 (m, 2H), 2.33 (s, 3H), 2.18 (dd, *J* = 4.9 Hz, *J* = 8.1 Hz, 1H), 2.03−1.87 (m, 4H), 1.54 (dd, *J* = 4.9 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.6, 136.7, 132.3, 129.1 (2C), 128.9 (2C), 52.4, 46.7, 46.6, 38.8, 31.3, 26.3, 24.3, 21.3, 17.8; IR (film) 3050, 3010, 2951, 2876, 1731, 1641, 1429, 1317, 1144 cm^{-1}; HRMS (ES, Pos) calcd for $C_{17}H_{21}N_1O_3$ $[M + H]^+$ 288.1594, found 288.1593.

Methyl 2-(4-methoxyphenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10o). Prepared according to the general procedure. The product was isolated as a white solid: yield 92%; diastereomeric ratio (50:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 36.5 min, t_r (major) 37.9 min); enantiomeric excess (93% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 10% *i*-PrOH, 3 mL/min, 25 °C, 200 psi, t_r (minor) 6.7 min, t_r (major) 7.8 min); mp 78−81 °C; R_f 0.28 (100%, Et_2O); $[\alpha]^{20}_D$ = +70 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 3.76−3.48 (m, 3H), 3.43 (s, 3H), 3.32−3.25 (m, 2H), 2.14 (dd, *J* = 4.9 Hz, *J* = 8.0 Hz, 1H), 2.03−1.82 (m, 4H), 1.51 (dd, *J* = 4.9 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.6, 158.7, 130.3 (2C), 127.4, 113.6 (2C), 55.3, 52.4, 46.6, 46.5, 38.8, 31.0, 26.3, 24.3, 18.0 ; IR (film) 3050, 3010, 2952, 2877, 1729, 1638, 1516, 1429, 1316, 1248, 1143 cm^{-1}; HRMS (ES, Pos) calcd for $C_{17}H_{21}N_1O_4$ $[M + Na]^+$ 326.1363, found 326.1359.

Methyl 2-(4-nitrophenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10p). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a colorless oil: yield 31%; diastereomeric ratio (> 30:1) was determined by ^1H NMR of the crude mixture, and enantiomeric excess (95% ee) was determined by SFC analysis on chiral phase (Chiralpak OD-H 25 cm, 5% MeOH, 3 mL/min, 30 °C, 210 psi, t_r (minor) 6.9 min, t_r (major) 7.8 min); R_f 0.25 (100%, Et_2O); $[\alpha]^{20}_D$ = +99 (*c* 1.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 3.63−3.49 (m, 3H), 3.47−3.38 (m, 4H), 3.31−3.20 (m, 1H), 2.26 (dd, *J* = 5.1 Hz, *J* = 8.1 Hz, 1H), 2.07−1.84 (m, 4H), 1.64 (dd, *J* = 5.1 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.3, 147.8, 144.0, 130.8 (2C), 124.0 (2C), 53.4, 47.4, 47.2, 40.2, 31.7, 26.9, 25.0, 18.8; IR (film) 3050, 3010, 2951, 2876, 1731, 1641, 1521, 1429, 1317, 1144, 870 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{18}N_2O_5$ $[M + H]^+$ 319.1289, found 319.1289.

Methyl 1-(pyrrolidine-1-carbonyl)-2-(4-(trifluoromethyl)phenyl)-cyclopropanecarboxylate (10q). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a colorless oil: yield 55%; diastereomeric ratio (> 30:1) was determined by ^1H NMR of the crude mixture, and enantiomeric excess (95% ee) was determined by SFC analysis on chiral phase (Whelk-O 25 cm, 7% *i*-PrOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 9.8 min, t_r (major) 12.1 min); R_f 0.42 (100%, Et_2O); $[\alpha]^{20}_D$ = +79 (*c* 1.91, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2H), 7.38−7.34 (m, 2H), 3.54−3.49 (m, 3H), 3.47−3.38 (m, 4H), 3.31−3.20 (m, 1H), 2.19 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 1H), 1.93−1.84 (m, 4H), 1.54 (dd, *J* = 5.0 Hz, *J* = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.0, 139.7, 129.6 (2C), 126.3 (q, *J* = , 1C), 125.0 (m, 1C), 122.6 (2C), 52.6, 46.7, 46.5, 39.2, 31.1, 26.3, 24.3, 17.9; IR (film) 2954, 2878, 1730, 1640, 1433, 1324, 1116, 1068 cm^{-1}; HRMS (ES, Pos) calcd for $C_{17}H_{18}N_1O_3F_3$ $[M + H]^+$ 342.1312, found 342.1319.

Dimethyl 2,2′-(biphenyl-4,4′-diyl)bis((pyrrolidine-1-carbonyl)-cyclopropanecarboxylate) (10r). Prepared according to the general procedure. The product was isolated as a white solid: yield 62%; diastereomeric ratio (25:1) was determined by ^1H NMR of the crude mixture, and enantiomeric excess (> 99% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 20% MeOH, 3 mL/min, 30 °C, 210 psi, t_r (minor) 13.9 min, t_r (major) 16.4 min); mp 194−197 °C; R_f 0.35 (100%,

EtOAc); $[\alpha]^{20}_D$ = +209 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.2 Hz, 4H), 7.35 (d, *J* = 8.2 Hz, 4H), 3.54−3.49 (m, 6H), 3.47−3.34 (m, 8H), 3.31−3.19 (m, 2H), 2.23 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 2H), 2.06−1.87 (m, 8H), 1.54 (dd, *J* = 5.0 Hz, *J* = 9.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (2C), 166.5 (2C), 139.5 (2C), 134.5 (2C), 129.7 (4C), 126.7 (4C), 52.5 (2C), 46.7 (2C), 46.6 (2C), 39.1 (2C), 31.4 (2C), 26.3 (2C), 24.4 (2C), 18.0 (2C); IR (film) 3044, 2952, 2877, 1727, 1629, 1433, 1312, 1144, 908 cm^{-1}; HRMS (ES, Pos) calcd for $C_{32}H_{36}N_2O_6$ $[M + H]^+$ 545.2646, found 545.2642.

Methyl 2-(3-methoxyphenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10s). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a colorless oil: yield 78%; diastereomeric ratio (> 30:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (96% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 7% *i*-PrOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 13.8 min, t_r (major) 14.9 min); R_f 0.34 (100%, Et_2O); $[\alpha]^{20}_D$ = +73 (*c* 1.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.13 (m, 1H), 6,85−6.80 (m, 2H), 6.76−6.72 (m, 1H), 3.75 (s, 3H), 3.54−3.49 (m, 3H), 3.41 (s, 3H), 3.31−3.218 (m, 2H), 2.13 (dd, *J* = 5.1 Hz, *J* = 8.1 Hz, 1H), 1.94−1.84 (m, 4H), 1.44 (dd, *J* = 5.1 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 166.5, 159.5, 137.2, 129.2, 121.6, 114.8, 113.1, 55.4, 52.5, 46.7, 46.6, 38.9, 31.6, 26.3, 24.4, 18.0; IR (film) 2951, 2876, 1730, 1638, 1429, 1315, 1143, 1046 cm^{-1}; HRMS (ES, Pos) calcd for $C_{17}H_{21}N_1O_4$ $[M + H]^+$ 304.1543, found 304.1551.

Methyl 2-(3-nitrophenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10t). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a colorless oil: yield 51%; diastereomeric ratio (> 30:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (96% ee) was determined by SFC analysis on chiral phase (Whelk-O 25 cm, 5% MeOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 13.8 min, t_r (major) 21.8 min); R_f 0.21 (100%, Et_2O); $[\alpha]^{20}_D$ = +42 (*c* 2.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.43 (t, *J* = 8.8 Hz, 1H), 3.57−3.43 (m, 3H), 3.42 (s, 3H), 3.38 (app t, *J* = 8.0 Hz, 1H), 3.31−3.20 (m, 1H), 2.21 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 1H), 1.97−1.84 (m, 4H), 1.61 (dd, *J* = 5.0 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 165.7, 148.2, 137.9, 135.7, 129.1, 124.2, 122.4, 52.8, 46.8, 46.5, 39.1, 30.8, 26.3, 24.3, 18.1; IR (film) 2953, 2877, 1728, 1640, 1529, 1432, 1349, 1147 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{18}N_2O_5$ $[M + H]^+$ 319.1289, found 319.1297.

Methyl 1-(pyrrolidine-1-carbonyl)-2-(3-(trifluoromethyl)phenyl)-cyclopropanecarboxlate (10u). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a colorless oil: yield 49%; diastereomeric ratio (> 30:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (95% ee) was determined by SFC analysis on chiral phase (Whelk-O 25 cm, 7% *i*-PrOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 8.6 min, t_r (major) 13.4 min); R_f 0.25 (100%, Et_2O); $[\alpha]^{20}_D$ = +70 (*c* 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.46−7.43 (m, 2H), 7.38−7.34 (m, 1H), 3.57−3.46 (m, 3H), 3.42−3.36 (m, 4H), 3.31−3.24 (m, 1H), 2.17 (dd, *J* = 5.1 Hz, *J* = 8.1 Hz, 1H), 1.97−1.86 (m, 4H), 1.52 (dd, *J* = 5.1 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.0, 136.7, 132.7, 130.7 (q, *J* = Hz, 1C), 128.6, 126.1, 124.0, 122.4, 52.5, 46.7, 46.5, 39.0, 30.9, 26.2, 24.3, 17.8; ^{19}F NMR (182 MHz, $CDCl_3$) δ −117.0; IR (film) 2953, 2878, 1730, 1640, 1429, 1326, 1122 cm^{-1}; HRMS (ES, Pos) calcd for $C_{17}H_{18}N_1O_3F_3$ $[M + H]^+$ 342.1312, found 342.1319.

Methyl 2-(2-fluorophenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10v). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a white solid: yield 43%; diastereomeric ratio (> 30:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (94% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 7% *i*-PrOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 9.8 min, t_r (major) 11.4 min); R_f 0.35 (100%, Et_2O); mp 88−91 °C; $[\alpha]^{20}_D$ = +121 (*c* 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.16 (m, 2H), 7.06−6.95 (m, 2H), 3.60−3.45 (m, 3H), 3.44 (s, 3H), 3.43−3.38 (m, 1H), 3.22 (app t, *J* = 8.8 Hz, 1H), 2.13 (dd, *J* = 5.0 Hz, *J* = 8.1 Hz, 1H), 1.97−1.87 (m, 4H), 1.63 (dd, *J* = 5.1 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 166.2, 162.0 (d, *J* = 1C), 130.8 (d, *J* = 1C), 129.0 (d, *J* = 1C), 123.6 (d, *J* = 1C), 122.8 (d, *J* = 1C), 115.2 (d, *J* = 1C), 52.5, 46.7, 46.4, 37.9, 26.3, 26.2, 24.3, 18.3; IR (film) 2952, 2876, 1727, 1637, 1428, 1319, 1145 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{18}N_1O_3F_1$ $[M + H]^+$ 292.1344, found 292.1349.

Methyl 2-(2-chlorophenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10w). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a white solid: yield 35%; diastereomeric ratio (> 30:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (94% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 7% *i*-PrOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 14.1 min, t_r (major) 22.8 min); R_f 0.35 (100%, Et_2O); mp 96−98 °C; $[\alpha]^{20}_D$ = +49 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.33 (m, 1H), 7.23−7.19 (m, 3H), 3.88−3.54 (m, 3H), 3.52−3.45 (m, 4H), 3.32−3.28 (m, 1H), 2.21 (dd, *J* = 5.1 Hz, *J* = 8.1 Hz, 1H), 2.01−1.85 (m, 4H), 1.60 (dd, *J* = 5.1 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.1, 136.2, 133.8, 130.6, 129.4, 128.6, 126.3, 52.5, 46.7, 46.4, 38.1, 30.4, 26.3, 24.3, 18.5; IR (film) 2951, 2877, 1728, 1642, 1432, 1317, 1148 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{18}N_1O_3Cl_1$ $[M + H]^+$ 308.1048, found 308.1054.

Methyl 2-(2-bromophenyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10x). Prepared according to the general procedure at 50 °C instead of 25 °C. The product was isolated as a colorless oil: yield 24% (85% brsm); diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 36.2 min, t_r (major) 37.3 min); enantiomeric excess (94% ee) was determined by SFC analysis on chiral phase (Chiralpak AS-H 25 cm, 10% *i*-PrOH, 2 mL/min, 25 °C, 150 psi, t_r (minor) 8.4 min, t_r (major) 10.2 min); R_f 0.32 (100%, Et_2O); $[\alpha]^{20}_D$ = +73 (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 1.1 Hz, *J* = 7.9 Hz, 1H), 7.29−7.20 (m, 2H), 7.15−7.09 (m, 1H), 3.66−3.52 (m, 3H), 3.50−3.43 (m, 4H), 3.33−3.24 (m, 1H), 2.20 (dd, *J* = 4.8 Hz, *J* = 8.1 Hz, 1H), 2.04−1.82 (m, 4H), 1.59 (dd, *J* = 4.8 Hz, *J* = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.0, 135.5, 132.5, 130.8, 128.9, 126.9, 126.4, 52.5, 46.7, 46.4, 38.3, 32.7, 26.3, 24.3, 18.9; IR (film) 3050, 3010, 2950, 2877, 1731, 1639, 1413, 1297, 1148 cm^{-1}; HRMS (ES, Pos) calcd for $C_{16}H_{18}Br_1N_1O_3$ $[M + H]^+$ 351.0470, found 351.0475.

Methyl 2-(3,5-dimethoxyphenyl)-1-(pyrrolidine-1-carbonyl)-cyclopropanecarboxylate (10y). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a colorless oil: yield 54%; diastereomeric ratio (22:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (90% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 7% MeOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 6.0 min, t_r (major) 12.5 min); R_f 0.22 (100%, Et_2O); $[\alpha]^{20}_D$ = +89 (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 8.8 Hz, *J* = 1.1 Hz, 2H), 6.29 (t, *J* = 8.8 Hz, 1H), 3.72 (s, 6H), 3.60−3.44 (m, 3H), 3.44 (s, 3H), 3.33−3.19 (m, 2H), 2.10 (dd, *J* = 5.0 Hz, *J* = 8.0 Hz, 1H), 2.07−1.84 (m, 4H), 1.44 (dd, *J* = 5.0 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 166.4, 160.5 (2C), 138.0, 107.2 (2C), 99.6, 55.5 (2C), 52.5, 46.7, 46.5, 38.8, 31.6, 26.2, 24.3, 18.0;

IR (film) 2951, 2877, 2840, 1729, 1636, 1594, 1425, 1425, 1310, 1203, 1151 cm^{-1}; HRMS (ES, Pos) calcd for $C_{18}H_{23}N_1O_5$ $[M + H]^+$ 334.1649, found 334.1660.

Methyl 1-(pyrrolidine-1-carbonyl)-2-(3,4,5-trimethoxyphenyl)-cyclopropanecarboxylate (10z). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a colorless oil: yield 29%; diastereomeric ratio (24:1) was determined by ^1H NMR of the crude mixture, and enantiomeric excess (59% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 15% MeOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 2.3 min, t_r (major) 3.1 min); R_f 0.21 (100%, Et_2O); $[\alpha]^{20}_D = +47$ (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 2H), 3.78 (s, 6H), 3.75 (s, 3H), 3.60−3.43 (m, 3H), 3.42 (s, 3H), 3.42 (app t, $J = 8.8$ Hz, 1H), 3.38−3.24 (m, 1H), 2.10 (dd, $J = 5.1$ Hz, $J = 8.1$ Hz, 1H), 1.92−1.84 (m, 4H), 1.42 (dd, $J = 5.1$ Hz, $J = 9.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 166.4, 153.1 (2C), 137.1, 131.3, 106.1 (2C), 61.0, 56.4 (2C), 52.5, 46.7, 46.4, 38.9, 31.6, 26.2, 24.3, 18.0; IR (film) 3050, 3010, 2951, 2876, 1731, 1641, 1521, 1429, 1317, 1144, 870 cm^{-1}; HRMS (ES, Pos) calcd for $C_{19}H_{25}N_1O_6$ $[M + H]^+$ 363.1760, found 363.1764.

Methyl 2-(3-methoxy-4-methylphenyl)-1-(pyrrolidine-1-carbonyl)-cyclopropanecarboxylate (10aa). Prepared according to the general procedure with a reaction temperature of 50 °C. The product was isolated as a white solid: yield 64%; diastereomeric ratio (25:1) was determined by ^1H NMR of the crude mixture, and enantiomeric excess (81% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 15% MeOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 2.3 min, t_r (major) 4.3 min); mp 105−108 °C; R_f 0.29 (100%, Et_2O); $[\alpha]^{20}_D = +49$ (*c* 2.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, $J = 8.8$ Hz, 1H), 6.76−6.70 (m, 2H), 3.77 (s, 3H), 3.61−3.48 (m, 3H), 3.48 (s, 3H), 3.36−3.19 (m, 2H), 2.18−2.10 (m, 4H), 1.97−1.80 (m, 4H), 1.44 (dd, $J = 5.1$ Hz, $J = 9.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 166.6, 157.5, 134.2, 130.2, 125.5, 120.8, 111.1, 55.4, 52.5, 46.6, 46.5, 38.8, 31.6, 26.2, 24.3, 18.0, 16.1; IR (film) 3050, 3010, 2951, 2876, 1731, 1641, 1521, 1429, 1317, 1144, 870 cm^{-1}; HRMS (ES, Pos) calcd for $C_{18}H_{23}N_1O_4$ $[M + H]^+$ 318.1700, found 318.1700.

Methyl 2-(naphthalen-1-yl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10ab). Prepared according to the general procedure. The product was isolated as a white foam: yield 86%; diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 37.7 min, t_r (major) 38.2 min); enantiomeric excess (95% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 15% MeOH, 3 mL/min, 30 °C, 200 psi, t_r (minor) 3.6 min, t_r (major) 7.8 min); mp 83−85 °C; R_f 0.39 (100%, Et_2O); $[\alpha]^{20}_D = -28$ (*c* 1.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, $J = 8.5$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.60 (t, $J = 1.4$ Hz, 1H), 7.50−7.28 (m, 3H), 3.77 (app t, $J = 8.5$ Hz, 1H), 3.65−3.53 (m, 3H), 3.27−3.22 (m, 1H), 3.11 (s, 3H), 2.42 (dd, $J = 4.7$ Hz, $J = 8.1$ Hz, 1H), 2.03−1.89 (m, 4H), 1.64 (dd, $J = 4.7$ Hz, $J = 8.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 166.8, 133.5, 133.3, 132.0, 128.2, 128.0, 126.5, 126.4, 126.0, 125.3, 125.1, 52.2, 46.6, 46.3, 38.3, 30.3, 26.2, 24.4, 17.9; IR (film) 3050, 3010, 2951, 2875, 1733, 1639, 1429, 1315, 1140 cm^{-1}; HRMS (ES, Pos) calcd for $C_{20}H_{21}N_1O_3$ $[M + H]^+$ 324.1594, found 324.1597.

Methyl 2-methyl-2-phenyl-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10ac). Prepared according to the general procedure. The product was isolated as a colorless oil after purification by HPLC prep: yield 63%; diastereomeric ratio (> 20:1) was determined by ^1H NMR of the crude mixture, and enantiomeric excess (95% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 5% MeOH, 3 mL/min, 30 °C, 210 psi, t_r (major) 7.7 min, t_r (minor) 9.3 min); R_f 0.33 (100%, Et_2O); $[\alpha]^{20}_D = +90$ (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 3.76−3.72 (m, 1H), 3.64−3.59 (m, 3H), 3.42 (s, 3H), 2.16 (d, $J = 4.6$ Hz, 1H), 2.05−1.96 (m, 4H), 1.66 (d, $J = 4.6$, 1H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 166.5, 142.6, 129.1 (2C), 129.1 (2C), 127.9, 52.9, 48.1, 47.2, 42.1, 38.9, 27.1, 26.5, 26.3, 25.0; IR (film) 3038, 3009, 2956, 2879, 1729, 1644, 1432, 1319, 1139 cm^{-1}; HRMS (ES, Pos) calcd for $C_{17}H_{21}N_1O_3$ $[M + H]^+$ 288.1594, found 288.1593.

Methyl-1-(pyrrolidine-1-carbonyl)-1,1a,6,6a-tetrahydrocyclopropana[*a*]indene-1-carboxylate (10ad). Prepared according to the general procedure. The product was isolated as a white solid: yield 51%; diastereomeric ratio (> 30:1) was determined by GC/MS analysis of the crude mixture (30 m × 0.25 mm, 5 °C/min from 40 to 270 °C, 63 psi H_2, t_r (minor) 37.8 min, t_r (major) 38.5 min); enantiomeric excess (84% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 5% MeOH, 3 mL/min, 30 °C, 200 psi, t_r (minor) 6.0 min, t_r (major) 7.0 min); mp 71−73 °C; R_f 0.37 (100%, Et_2O); $[\alpha]^{20}_D = +43$ (*c* 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.37 (m, 1H), 7.18−7.12 (m, 3H), 3.71−3.60 (m, 1H), 3.60−3.46 (m, 4H), 3.43−3.24 (m, 5H), 2.50 (t, $J = 6.5$ Hz, 1H), 2.01−1.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 166.8, 145.5, 139.8, 127.8, 127.1, 125.9, 124.7, 52.7, 47.5, 47.4, 40.6, 38.9, 34.0, 31.4, 27.0, 24.9; IR (film) 3050, 3010, 2950, 2877, 1731, 1639, 1413, 1297, 1148 cm^{-1}; HRMS (ES, Pos) calcd for $C_{17}H_{19}N_1O_3$ $[M + Na]^+$ 308.1257, found 308.1258.

Methyl 2-(1-methyl-1*H*-pyrrol-2-yl)-1-(pyrrolidine-1-carbonyl)-cyclopropanecarboxylate (10ae). Prepared according to the general procedure. The product was isolated as a colorless oil: yield 31%; diastereomeric ratio (> 30:1) was determined by ^1H NMR analysis of the crude mixture, and enantiomeric excess (90% ee) was determined by SFC analysis on chiral phase (R,R-Welko 25 cm, 7% MeOH, 3 mL/min, 40 °C, 160 psi, t_r (minor) 14.3 min, t_r (major) 17.9 min); R_f 0.37 (100%, Et_2O); $[\alpha]^{20}_D = +97$ (*c* 0.93, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (t, $J = 2.2$ Hz, 1H), 6.10−6.00 (m, 1H), 5.95−5.90 (m, 1H), 3.68 (s, 3H), 3.64−3.49 (m, 3H), 3.48 (s, 3H), 3.28−3.15 (m, 2H), 2.16 (dd, $J = 4.7$ Hz, $J = 7.8$ Hz, 1H), 2.02−1.86 (m, 4H), 1.50 (dd, $J = 4.7$ Hz, $J = 9.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.3, 127.4, 122.5, 108.0, 106.7, 52.5, 46.6, 46.3, 38.2, 33.8, 26.2, 24.3, 23.9, 17.7; IR (film) 2951, 2876, 1723, 1635, 1430, 1313, 1295, 1142 cm^{-1}; HRMS (ES, Pos) calcd for $C_{15}H_{20}N_2O_3$ $[M + H]^+$ 277.1558, found 277.1547.

***tert*-Butyl 3-(2-(methoxycarbonyl)-2-(pyrrolidine-1-carbonyl)-cyclopropyl)-1*H*-indole-1-carboxylate (10af).** Prepared according to the general procedure. The product was isolated as a white solid: yield 54%; diastereomeric ratio (1.2:1) was determined by ^1H NMR of the crude mixture, and enantiomeric excess (96 and 88% ee) was determined by SFC analysis on chiral phase ((major) Chiralcel AS-H 25 cm, 5% MeOH, 3 mL/min, 35 °C, 150 psi, t_r (minor) 9.7 min, t_r (major) 11.7 min; (minor) Chiralcel OB-H 25 cm, 5% MeOH, 3 mL/min, 40 °C, 150 psi, t_r (minor) 3.0 min, t_r (major) 3.8 min); mp 165−168 °C; R_f 0.15 (100%, Et_2O); $[\alpha]^{20}_D = +28$ (*c* 0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 8.08 (br s, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.43 (br s, 1H), 7.33−7.22 (m, 2H), 3.67−3.51 (m, 3H), 3.37 (s, 3H), 3.34−3.22 (m, 2H), 2.16 (dd, $J = 4.6$ Hz, $J = 8.0$ Hz, 1H), 2.07−1.84 (m, 4H), 1.68 (s, 9H), 1.58 (dd, $J = 4.6$ Hz, $J = 9.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 171.3, 168.8, 166.5, 130.8, 124.6, 122.7, 119.8, 116.1, 115.2, 83.7, 66.0, 53.6, 46.6, 46.4, 37.6, 28.4 (3C), 26.2, 35.5, 22.8, 18.1; IR (film) 2975, 2877, 1725, 1631, 1451, 1371, 1309, 1179 cm^{-1}; HRMS (ES, Pos) calcd for $C_{23}H_{28}N_2O_5$ $[M + H]^+$ 413.2071, found 413.2078.

Methyl 1-(pyrrolidine-1-carbonyl)-2-(1-tosyl-1*H*-indol-3-yl)-cyclopropanecarboxylate (10ag). Prepared according to the general procedure. The product was isolated as a white solid: yield 58%; diastereomeric ratio (1.2:1) was determined by ^1H NMR

of the crude mixture, and enantiomeric excess (95 and 83% ee) was determined by SFC analysis on chiral phase (Chiralpak OD-H 25 cm, 10% MeOH, 3 mL/min, 30 °C, 150 psi, t_r (minor *trans*) 6.7 min, t_r (major *trans*) 7.9 min, t_r (major *cis*) 9.3 min, t_r (minor *cis*) 12.6 min); mp 125−127 °C; R_f 0.25 (100%, EtOAc); mp 180−183 °C; $[\alpha]^{20}_D = -26$ (*c* 2.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major + minor) 8.05−8.00 (m, 1H), 7.89−7.85 (m, 1H), 7.78−7.65 (m, 5H), 7.63−7.55 (m, 1H), 7.35−7.09 (m, 10H), 3.74 (s, 3.74), 3.58−3.47 (m, 4H), 3.24−3.09 (m, 3H), 3.12 (s, 3H), 3.07−2.91 (m, 2H), 2.61−2.50 (m, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.16−2.04 (m, 2H), 1.96−1.84 (m, 4H), 1.81 (dd, *J*= 5.1 Hz, *J* = 8.1 Hz, 1H), 1.53 (dd, *J* = 5.1 Hz, *J* = 9.2 Hz, 1H), 1.45−1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 168.3, 166.2, 163.3, 135.4, 135.3, 135.1, 135.0, 131.3, 130.9, 130.0 (2C), 129.9 (2C), 127.1 (2C), 127.0 (2C), 125.7, 125.1, 125.0, 123.5, 123.4, 121.9, 120.3, 118.9, 118.0, 117.3, 113.9, 113.6, 53.6, 52.9, 52.3, 46.6, 46.4, 46.3, 45.8, 39.6, 38.2, 30.5, 26.2, 25.3, 24.3, 23.7, 23.0, 22.4, 21.7, 21.1, 17.9; IR (film) 3050, 3010, 2951, 2876, 1731, 1641, 1600, 1521, 1429, 1317, 1144, 870 cm^{-1}; HRMS (ES, Pos) calcd for $C_{25}H_{26}N_2O_5S_1$ $[M + H]^+$ 467.1634, found 467.1635.

Methyl 2-(1-benzyl-1*H*-indol-3-yl)-1-(pyrrolidine-1-carbonyl)-cyclopropanecarboxylate (10ah). Prepared according to the general procedure. The product was isolated as a colorless oil: yield 88%; diastereomeric ratio (1.5:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (50 and 41% ee) was determined by SFC analysis on chiral phase ((major) Chiralpak AD-H 25 cm, 20% MeOH, 3 mL/min, 35 °C, 150 psi, t_r (minor) 5.7 min, t_r (major) 12.2 min; (minor) Chiralpak AD-H 25 cm, 20% MeOH, 3 mL/min, 35 °C, 150 psi, t_r (minor) 3.7 min, t_r (major) 4.2 min); R_f 0.25 (100%, Et_2O); $[\alpha]^{20}_D = +39$ (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (Major) 7.80 (d, *J* = 8.8 Hz, 1H), 7.78−6.93 (m, 9H), 5.29−5.23 (m, 2H), 3.61−3.3.52 (m, 3H), 3.39 (app t, *J* = 8.7 Hz, 1H), 3.30−3.20 (m, 4H), 2.08 (dd, *J* = 4.9 Hz, *J* = 8.0 Hz, 1H), 1.95−1.83 (m, 4H), 1.57 (dd, *J* = 4.9 Hz, *J* = 9.2 Hz, 1H), (minor) 7.77 (d, *J* = 8.8 Hz, 1H), 7.48−7.07 (m, 8H), 6.84 (s, 1H), 5.24 (dd, *J* = 4.5 Hz, *J* = 9.2, 2H), 3.79 (s, 3H), 3.40 (app t, *J* = 8.9 Hz, 1H), 3.33−3.14 (m, 2H), 3.08−2.94 (m, 1H), 2.77−2.70 (m, 1H), 2.14 (dd, *J* = 4.9 Hz, *J* = 8.0 Hz, 1H), 1.88 (dd, *J* = 4.9 Hz, *J* = 9.2 Hz, 1H), 1.57−1.35 (m, 3H), 0.52−0.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 169.0, 166.9, 137.9, 136.6, 129.0, 128.9 (2C), 127.7, 127.3, 126.9 (2C), 122.0, 119.8, 119.5, 110.2, 109.7, 52.3, 50.1, 46.6, 46.5, 38.4, 26.2, 24.4, 23.7, 18.6; IR (film) 2949, 2874, 1726, 1630, 1432, 1308, 1145, 732 cm^{-1}; HRMS (ES, Pos) calcd for $C_{25}H_{26}N_2O_3$ $[M + H]^+$ 403.2016, found 403.2031.

Methyl 2-butoxy-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10ai). Prepared according to the general procedure using the alkene with a 10-fold excess. The product was isolated as a colorless oil: yield 70%; diastereomeric ratio (89:11) was determined by ^{1}H NMR analysis of the crude mixture, and enantiomeric excess (89% ee) was determined by SFC analysis on chiral phase (R,R-Welko 25 cm, 7% MeOH, 3 mL/min, 40 °C, 160 psi, t_r (minor) 10.3 min, t_r (major) 15.7 min); R_f 0.38 (100%, Et_2O); $[\alpha]^{20}_D = +64$ (*c* 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (dd, *J* = 5.4 Hz, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 3.65−3.60 (m, 1H), 3.56−3.42 (m, 3H), 3.26−3.23 (m, 1H), 2.06 (app t, *J* = 5.4 Hz, 1H), 1.97−1.86 (m, 4H), 1.58−1.51 (m, 2H), 1.37−1.22 (m, 4 H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 165.8, 71.5, 64.1, 52.7, 46.4, 46.2, 37.1, 31.6, 26.1, 24.3, 20.3, 19.4, 14.0; IR (film) 2955, 2873, 1732, 1634, 1433, 1307, 1147 cm^{-1}; HRMS (ES, Pos) calcd for $C_{14}H_{23}N_1O_4$ $[M + H]^+$ 270.1700, found 270.1703.

Methyl 1-(pyrrolidine-1-carbonyl)-2-styrylcyclopropanecarboxylate (10aj). Prepared according to the general procedure. The product was isolated as a white solid: yield 77%; diastereomeric ratio (9:1) was determined by ^{1}H NMR analysis of the crude mixture, and enantiomeric excess (87% ee) was determined by SFC analysis on chiral phase (Chiralpak OD-H 25 cm, 5% MeOH, 3 mL/min, 30 °C, 150 psi, t_r (major) 10.2 min, t_r (minor) 23.8 min); R_f 0.48 (100%, Et_2O); mp 72−75 °C; $[\alpha]^{20}_D = +116$ (*c* 0.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.21 (dd, *J* = 9.3 Hz, *J* = 15.9 Hz, 1H), 3.75 (s, 3H), 3.54−3.50 (m, 3H), 3.41−3.37 (m, 1H), 2.62 (app q, *J* = 9.3 Hz, *J* = 15.6 Hz, 1H), 1.97−1.91 (m, 4H), 1.84 (dd, *J* = 4.8 Hz, *J* = 7.5 Hz, 1H), 1.68 (dd, *J* = 4.8 Hz, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 166.4, 137.2, 133.3, 128.7 (2C), 127.6, 126.3 (2C), 125.7, 52.8, 46.8, 46.5, 37.8, 31.7, 26.2, 24.4, 21.5; IR (film) 3024, 2959, 2874, 1726, 1633, 1416, 1312, 1139 cm^{-1}; HRMS (ES, Pos) calcd for $C_{18}H_{21}N_1O_3$ $[M + H]^+$ 300.1594, found 300.1596.

Methyl 2-(2,2-diphenylvinyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10ak). Prepared according to the general procedure. The product was isolated as a white solid: yield 90%; diastereomeric ratio (6:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (75 and 53% ee) was determined by SFC analysis on chiral phase (Chiralpak OD-H 25 cm, 7% *i*-PrOH, 2 mL/min, 35 °C, 150 psi, t_r (minor *trans*) 15.7 min, t_r (major *trans*) 18.8 min, t_r (minor *cis*) 20.3 min, t_r (major *cis*) 23.4 min); mp 115−118 °C; R_f 0.45 (100%, Et_2O); $[\alpha]^{20}_D = +44$ (*c* 1.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 7.51−7.21 (m, 10H), 6.13 (d, *J* = 13.1 Hz, 1H), 3.79 (s, 3H), 3.42−3.31 (m, 3H), 3.20−3.09 (m, 1H), 2.64−2.53 (m, 1H), 1.97−1.63 (m, 6H), (minor) 7.51−7.21 (m, 10H), 5.44 (d, *J* = 13.1 Hz, 1H), 3.69 (s, 3H), 3.45−3.34 (m, 3H), 3.34−3.19 (m, 1H), 2.81−2.70 (m, 1H), 1.97−1.63 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major + minor) 171.6, 171.5, 170.6, 167.0, 145.7, 145.6, 142.9, 142.7, 140.2, 140.0, 131.1 (2C), 130.7, 139.4, 129.2 (2C), 129.1, 128.9 (2C), 128.4, 128.4, 128.3, 128.2 (2C), 128.1, 128.0, 126.1, 125.2, 53.5, 53.4, 47.3, 47.2, 47.1, 47.0, 38.7, 38.4, 29.9, 29.2, 26.9, 26.7, 26.9, 26.7, 25.1, 24.9, 23.7, 23.1; IR (film) 3057, 3010, 2952, 2877, 1726, 1639 cm^{-1}; HRMS (ES, Pos) calcd for $C_{24}H_{25}N_1O_3$ $[M + H]^+$ 376.1907, found 376.1919.

Methyl 2-((*E*)-1-phenylprop-1-en-2-yl)-1-(pyrrolidine-1-carbonyl)-cyclopropanecarboxylate (10al). Prepared according to the general procedure. The product was isolated as a colorless oil: yield 73%; diastereomeric ratio (14:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (85% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 3% MeOH, 3 mL/min, 40 °C, 150 psi, t_r (major) 5.7 min, t_r (minor) 6.9 min); R_f 0.33 (100%, Et_2O); $[\alpha]^{20}_D = -83$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.12 (m, 5H), 6.36 (s, 1H),3.63 (s, 3H), 3.60−3.39 (m, 3H), 3.29−3.17 (m, 1H), 2.85 (app t, *J* = 9.2 Hz, 1H), 2.03 (dd, *J* = 4.8 Hz, *J* = 8.1 Hz, 1H), 1.96−1.78 (m, 7H), 1.32 (dd, *J* = 4.8 Hz, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 166.6, 137.9, 132.4, 129.0 (2C), 128.5, 128.3 (2C), 126.5, 52.6, 46.7, 46.4, 37.8, 35.7, 30.5, 26.3, 24.3, 18.6; IR (film) 3057, 3010, 2952, 2877, 1726, 1639 cm^{-1}; HRMS (ES, Pos) calcd for $C_{19}H_{23}N_1O_3$ $[M + H]^+$ 314.1756, found 314.1760.

Methyl 2-((*E*)-2,6-dimethylhepta-1,5-dienyl)-1-(pyrrolidine-1-carbonyl)cyclopropanecarboxylate (10am). Prepared according to the general procedure. The product was isolated as a colorless oil: yield 45%; diastereomeric ratio (22:1) was determined by ^{1}H NMR of the crude mixture, and enantiomeric excess (90% ee) was determined by SFC analysis on chiral phase (Chiralpak AD-H 25 cm, 5% MeOH, 10 mL/min, 40 °C, 150 psi, t_r (minor) 3.9 min, t_r (major) 5.2 min); R_f 0.54 (100%, Et_2O); $[\alpha]^{20}_D = -32$ (*c* 2.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05−5.00 (m, 2H), 3.67 (s, 3H), 3.53−3.39 (m, 3H), 3.29−3.15 (m, 1H), 2.52−2.50 (m, 1H), 2.10−1.76 (m, 8H), 1.74 (s, 3H), 1.67−1.60 (m, 4H), 1.56 (s, 3H), 1.43 (dd, *J* = 4.5 Hz, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 166.8, 140.7, 131.6, 124.1, 119.7, 52.4, 46.5, 46.3, 39.7, 37.6, 27.1, 26.7, 26.1, 25.8, 24.3, 21.1, 17.8, 16.8; IR (film) 2970, 2890, 1729, 1643,

1434, 1310, 1138, 911 cm^{-1}; HRMS (ES, Pos) calcd for $C_{19}H_{29}N_1O_3$ $[M + H]^+$ 320.2223, found 320.2220.

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Supporting Information Available: Experimental procedures for the preparation of all the compounds and characterization data for each reaction and detailed structural assignment. This material is available free of charge via the Internet at http://pubs.acs.org.