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Palladium-Catalyzed Diastereo- and Enantioselective Formal [3+2]-Cycloadditions of Substituted Vinylcyclopropanes

Barry M. Trost*, Patrick J. Morris, and Simon J. Sprague

Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

Abstract

We describe a palladium-catalyzed diastereo- and enantioselective formal [3+2]-cycloaddition between substituted vinyl-cyclopropanes and electron deficient olefins in the form of azlactone- and Meldrum's acid alkylidenes to give highly-substituted cyclopentane products. By modulation of the electronic properties of the vinylcyclopropane and the electron-deficient olefin, high levels of stereoselectivity were obtained. The remote stereoinduction afforded by the catalyst, distal from the chiral pocket generated by the ligand, is proposed to be the result of a new mechanism invoking the Curtin-Hammett principle.

Keywords

asymmetric catalysis; palladium; cyclopentane synthesis; cycloaddition

Introduction

The preparation of functionalized cyclopentane-containing compounds from simple precursors in a stereocontrolled fashion has received a great deal of attention from the synthetic community in recent years.¹ Methods involving [3+2]-cycloaddition reactions – or reactions which may be formally considered as such – have featured fairly frequently in the strategies being added to the chemical lexicon.² Such approaches are attractive since they satisfy a desirable ambition of modern synthesis; that of atom economy.³

While cycloadditions of 1,3-dipoles such as azides with unsaturated compounds may typically occur under mild conditions,⁴ the generation and controlled reaction of a 1,3-dipole for the synthesis of carbocyclic products presents a formidable challenge. The well-established reaction of so-called tri-methylenemethane with olefins under palladium catalysis has allowed access to a range of cyclopentane products [Figure 1],⁵ and in recent years has been rendered asymmetric through the development of new classes of chiral ligands.⁶

The addition of all-carbon 1,3-dipoles to olefins under mild conditions requires that substrates and/or reaction conditions are selected such that the dipole is stabilized to allow time for the desired intermolecular reaction to take place before dipole recombination or polymerization can occur. As such, substituted cyclopropanes have featured widely as dipole precursors, with the release of strain energy providing a thermodynamic driving force for dipole generation. Stabilization of the dipole is generally achieved through substitution of the cyclopropane ring with an electron-donating group capable of stabilizing the cation and

Corresponding Author: bmtrost@stanford.edu.

Supporting Information. Full experimental procedures and spectral data for all new compounds, as well as crystallographic data for cycloadducts **5c** and derivative **15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

an electron-withdrawing group for anion-stabilization; hence, so-called “donor-acceptor” cyclopropanes have emerged as dipole precursors.⁷ To date, three main methods by which donor-acceptor cyclopropanes may be activated to unmask the 1,3-dipole [Figure 2] have been reported. In perhaps the simplest case, thermal activation can lead to C-C bond scission to afford the dipole.⁸ Alternatively, a Lewis acid may bind to the acceptor group,⁹ further stabilizing the anionic charge and favoring dipole formation. This method of activation has been expanded to the use of chiral Lewis acids, to give high levels of enantioinduction in the synthesis of *cis*-substituted tetrahydrofurans.⁹ⁱ Finally, low valent metals including palladium(0),¹⁰ nickel(0),¹¹ iron(0)¹² and iridium(0)¹³ have been used to stabilize the resulting cation through interaction with the donor group. The interaction of the resulting dipoles with an olefin represents a formal [3+2]-cycloaddition reaction, leads to the construction of two new C-C bonds and results in the creation of up to four stereocenters.

A subset of reactions in this latter class employs cyclopropanes bearing a vinyl substituent as donor group. Interaction of the vinyl group with either palladium(0) or nickel(0) leads to π -allyl formation with resulting cation stabilization, with an electron-withdrawing substituent positioned to stabilize the anion.¹⁴ Tsuji and co-workers first reported the addition reaction of vinylcyclopropane **1** with methyl vinyl ketone **2** to give the cyclopentane product **3** in 66% yield as a mixture of diastereomers [Figure 3].^{10a} The reaction is proposed to proceed *via* a π -allyl-palladium intermediate in which the dipole is stabilized long enough to allow conjugate addition of the anion into the enone, with the resulting enolate trapping onto the π -allyl species to complete the cyclization with concomitant ejection of the Pd⁰ catalyst.

Until recently, few of the processes disclosed delivered the desired carbocyclic products with control of absolute stereochemistry; many processes were also found to give mixtures of diastereomers. Based on our previous exploits in the field of asymmetric palladium π -allyl chemistry, we wondered whether the use of our chiral DPPBA bisphosphine ligands¹⁵ [Figure 4] might be able to create chiral space around a metal center capable of influencing the stereoselectivity of annulation reactions based on vinylcyclopropane substrates.

Results and Discussion

Based on exploratory studies within our group, we determined that Meldrum's acid alkylidenes¹⁶ might prove a suitable class of substrates, presumably owing to the highly electron-withdrawing nature of the substituents. Stereocontrol of the proposed reaction is not so readily achieved as it might first appear. Whilst the DPPBA bisphosphine ligands have been extensively used for control of nucleophilic attack onto attached π -allyl species, they have not been widely used for more remote stereoinduction. In order to achieve both diastereo- and enantiocontrol, two possible scenarios are conceivable [Figure 5]. In the first case (pathway **A**), the ligand could control both the facial selectivity of the conjugate addition of the enolate onto the Meldrum's acid alkylidene and facial selectivity of the ring closing reaction, setting both of the resulting stereocenters. Alternatively (pathway **B**), if the initial conjugate addition were unselective (owing to the remote nature of the chiral pocket created by the ligand-metal complex) but reversible, it could be that one of the two resulting epimeric complexes underwent stereocontrolled ring-closure more rapidly than the other, such that overall high stereoselectivity would be obtained, in accordance with the Curtin-Hammett principle. Given the significant distance between the chiral pocket provided by the ligand and the site of conjugate addition, it was anticipated that a reaction proceeding *via* pathway **B** in which conjugate addition is reversible would offer a greater opportunity for enantioinduction.

In order to investigate the proposed transformation, Meldrum's acid adduct **4** was reacted with a range of vinylcyclopropanes substituted with electron-withdrawing groups [Table 1]. Dimethylmalonyl substrate **1** was found to undergo the formal cycloaddition process in near quantitative yield to give product **5a** (entry 1), but the control over both absolute and relative stereochemistry was found to be rather poor for the major diastereomer, but encouraging for the minor diastereomer.

Use of the di(trifluoroethyl) ester analogue **6** (entry 2) led to slightly improved diastereocontrol, and again gave an excellent yield of the desired product **5b**; however, the control of absolute stereochemistry was similarly poor for the major diastereomer but good for the minor diastereomer. In an attempt to render the conjugate addition step more reversible, the substituent on the vinylcyclopropane was further modified. Switching to the Meldrum's acid derivative **7** (entry 3) gave the corresponding product **5c** with excellent diastereo- and enantiocontrol, albeit with room for optimization in terms of yield. Given the impressive levels of stereocontrol, in our further studies we investigated further the use of Meldrum's acid-substituted vinyl-cyclopropane **7**.

Encouraged by this early result, we next brought to bear our armory of bisphosphine ligands, with the aim of increasing the yield to a synthetically-useful level while maintaining the high levels of stereocontrol. A screen of our four standard chiral bisphosphine ligands identified **L₃** as beneficial to the yield of the process [Table 2], without appreciable loss of diastereo- or enantiocontrol. A screen of solvents similarly allowed us to select dioxane for our further studies, giving formal cycloaddition product **5c** in 62% yield, with a 17:1 mixture of diastereomers and a 96% e.e. for the major diastereomer.

With these conditions identified, our attention turned to examination of the scope of the reaction. Pleasingly, we found that a range of aryl and heteroaryl Meldrum's acid alkylidenes were tolerated in the reaction [Table 3], affording the corresponding addition products in generally excellent yields and with impressive control of both relative and absolute stereochemistry. A variety of substituted benzaldehyde-derived alkylidenes bearing both electron-donating and electron-withdrawing substituents gave the corresponding cycloadducts **9a–9e** in up to 78% yield, up to 17:1 d.r. and up to 96% e.e. 2-Thienyl-substituted cyclopentane **9f** product was also prepared with excellent stereocontrol, albeit in modest yield, whereas the corresponding 2-furyl compound **9g** was obtained in 52% yield, as a 7:1 mixture of diastereomers and an 85% e.e. for the major diastereomer. 2-Naphthyl-substituted cyclopentane **9h** was also prepared with excellent stereocontrol, as was enyne-derived product **9i**, which was obtained solely as the result of 1,4-, rather than 1,6-conjugate addition. The selectivity for 1,4-addition is attributed to the steric bulk of the triisopropylsilyl group; if this group is replaced by a methyl substituent, a mixture of products arising from both 1,4- and 1,6-addition are obtained. Throughout our studies, alkyl-substituted Meldrum's acid alkylidenes were found to be poor substrates for the reaction, as exemplified by isopropyl-substituted cyclopentane **9j**, which was formed in only trace amount. On the other hand, the successful preparation of the alkynyl-substituted product **9i**, wherein this substituent can be readily converted into numerous types of alkyl group, helps to obviate this problem.

The relative and absolute stereochemistry of cycloadduct **5c** were confirmed unambiguously by X-ray crystallography [Figure 6]. The unit cell was found to contain three molecules, each with slightly different conformation but all with the same absolute configuration.¹⁷

The stereoconvergence of both enantiomers of starting material to enantioenriched products can be explained by the ability of the the palladium-bound allyl species to isomerize between η^1 and η^3 haptomers – so-called π - σ - π interconversion [Figure 7].

Furthermore, the absolute configuration of the product is what would be expected from the ‘wall and flap’ mnemonic [Figure 8].¹⁸ The ‘wall and flap’ mnemonic proposes that the two phenyl rings on each phosphine have their spatial arrangements dictated by the diamine backbone, such that a C₂-symmetric chiral pocket is created around the metal center. Both enantiomers of the starting vinylcyclopropane ((*R*)-**7** and (*S*)-**7**) undergo ionization in either a matched or mismatched event to give the corresponding π -allyl species **A** and **F**, which may be interconverted *via* π - σ - π isomerization [Figure 7] to favor that complex (**A**) in which steric clashes with the phosphine ‘walls’ are avoided. Attack of this palladium-complex onto the Meldrum’s acid alkylidene then occurs. It may be that the attack occurs so as to minimize interactions between the R group and the ligand (**B** rather than **D**). Alternatively, it may be that attack is reversible and that the relative rates of ring closure (**E** and **C**) drive enantioinduction. This latter scenario would seem to be the more likely for two reasons. Firstly, as previously described, the chiral environment of the ligand is rather too far from the site of conjugate addition to afford a controlling influence. Secondly, there is a plausible structural reason why ring closure of complex **C** might be faster than that of complex **E**. In the case of complex **E**, the sterically bulky R group is pushed towards the bulky metal-ligand complex; in complex **C** the R group is held away. Either way, the enolate closes down onto the π -allyl species to afford the major product **9** with the observed stereochemistry. The intermediates *en route* to the products derived from complex **F** (**G**, **H**, **I** and **J**) each involve steric clashes between the reactants and the ligand backbone and hence are disfavored. However, the steric clashes may be alleviated as before by π - σ - π rotation – such interconversions may serve to enhance the enantiomeric excess of the two diastereomers (**H** \rightarrow **C**, **J** \rightarrow **E**), since molecules which would otherwise form the minor enantiomer of one diastereomer go on to form the major enantiomer of the other diastereomer.

It proved possible to carry out chemoselective differentiation of the two Meldrum’s acid moieties in cycloadduct **9h**, to afford further functionalized cyclopentane-containing products [Scheme 1]. In the presence of one equivalent of sodium methoxide, the more sterically-accessible Meldrum’s acid motif was opened to give diester **10** after treatment with TMS-diazomethane. By contrast, if two equivalents of sodium methoxide were employed in the transformation, tetramethyl ester **11** was formed in good yield after the same TMS-diazomethane treatment. Further elaboration of the tetraester *via* a hydroboration-oxidation-lactonization sequence afforded the highly-substituted δ -lactone **12** in 40% over three steps from the tetraester **11**.

With the formal cycloaddition of Meldrum’s acid alkylidenes fairly rigorously explored, we sought to investigate other dipolariphiles which might undergo a related process to afford further functionalized cyclopentane products.

We identified azlactone alkylidenes as possible candidate substrates, reasoning that the cycloadducts formed would not only contain three stereocenters over which we might be able to exert stereocontrol; they would also represent desirable highly-functionalized amino acid derivatives.

We were delighted to discover that the enantioselective addition of substituted vinylcyclopropane **6** and a range of azlactone alkylidenes **13a–o** [Table 4] gave the corresponding functionalized cyclopentane products **14a–o**, generally in good to excellent yields with control of both the relative and absolute stereochemistry.¹⁹

Our chiral diphosphine ligands [Figure 4] were found to create suitable chiral space to allow highly enantioselective addition. A range of aryl azlactone alkylidenes performed particularly well, although very electron-rich substituents, exemplified by substrates **13e** and

13f were found to be either unreactive or to deliver the desired product in low yield. By contrast, electron-poor alkylidene **13g** gave the product **14g** in good yield with good diastereo- and enantiocontrol, and naphthyl compound **13h** also performed very well. Beyond alkylidenes substituted with aryl rings, functionalized cinnamyl compound **14i** was also prepared in good yield and impressive stereocontrol, and heterocyclic substituents were also tolerated on the alkylidene, as demonstrated by the reactions to form thienyl and furyl compounds **14j** and **14k**. In both cases, the degree of stereocontrol was excellent. Moving to more challenging substrates, cyclopentane products bearing heteroatom substituents (**14l**) alkyl substituents (**14m** – **14o**) were found to be either inaccessible under the reaction conditions (**14m**) or to be formed with somewhat lower stereoselectivity (**14l, n, o**).

The absolute and relative stereochemistry was confirmed by single crystal X-ray diffraction analysis of a derivative of 4-bromo compound **14b** [Figure 9].¹⁹

As before, the degree of stereocontrol is surprising, since the initial bond-forming process occurs some distance from the metal-ligand complex bearing the chiral information – this suggests that in an analogous manner to that previously described, addition of the enolate formed by ionization of the vinylcyclopropane into the azlactone may be reversible and that the final stereochemistry observed may be explained by considering which of the complexes is able to achieve ring closure most rapidly [Figure 10]. As before, both enantiomers of the starting vinylcyclopropane **6** undergo ionization to afford π -allyl species (**A** and **D**), which may interconvert *via* π - σ - π isomerization so as to minimize steric clashes (favoring **A** in this case). Attack of the enolate into the azlactone alkylidene is then reversible and closure occurs under ligand control to deliver the observed product. The particular diastereomer and enantiomer observed may be rationalized on the basis of the ring closure event which leads to its formation. Structure **C** appears to minimize steric repulsions in that the alkylidene substituent is held away from the metal-ligand complex as bond formation occurs; moreover, the phenyl substituent on the azlactone ring interacts with the ‘flap’ portion in the far quadrant, rather than with the ‘wall’ (if the other face of the azlactone enolate were to attack).

In order to explore the synthetic utility of the products, we sought to use the compounds as precursors to fused cyclopentane-lactones [Scheme 2]. Pleasingly, azlactone adduct **14h** was found to react cleanly in a one-pot transformation to give δ -lactone **16** in excellent yield without trans-esterification of the residual trifluoroethyl esters.

Buoyed by a number of highly successful results, we sought to improve the reaction of those substrates where the reaction was not so successful. A major challenge of the reaction is to out-compete polymerisation of the opened vinylcyclopropane, which occurs readily²⁰ to form insoluble material unless the desired addition process is relatively rapid [Figure 11].

We reasoned that modification of the azlactone substituent might allow unreactive substrates to be rendered more reactive. Specifically, if the azlactone substituent were electron-withdrawing, the (reversible) conjugate addition step should be faster (preventing polymerization) and the stereodetermining ring-closing step should be slower – and therefore potentially more selective. Such a strategy was also considered attractive on account of the fact that the azlactone would typically be deprotected to reveal the corresponding amino acid following the reaction; hence from a strategic perspective the substituents on its aryl ring might be considered to be structurally unimportant.

Accordingly, a variety of differently-substituted azlactone alkylidenes were prepared and subjected to the reaction conditions [Table 5]. Initially, alkylidene **17a** (R = Ph, Ar = 3,4-Cl₂C₆H₃) was employed as an investigation of the overall concept. Using the reaction with

azlactone **13a** (R = Ph, Ar = Ph) as a benchmark, it was found that switching to a slightly more electron-poor azlactone substituent did indeed give a slight increase in yield without any drop in e.e. (**18a**).²¹ Attention was next switched to improving the yield of the 2-methoxy-substituted azlactone, which had failed to deliver the desired product **14e**. 3,4-Dichlorophenyl-substituted azlactone **17b** gave improved reactivity and delivered the addition product **18b** in a modest 29% yield but with excellent stereocontrol. The use of 4-(trifluoromethyl)phenyl-substituted azlactone **17c** gave a further improved 64% yield and maintaining the excellent stereocontrol. The use of the electron-poor azlactone **17d** also allowed the preparation of 4-methoxyphenyl-substituted product **18d** in excellent yield and with impressive stereocontrol, showing a marked improvement over the modest 36% yield of phenyl-substituted azlactone derivative **14f** previously obtained. Earlier studies had demonstrated alkyl-substituted azlactones to be challenging substrates. Specifically, cyclohexyl-substituted azlactone **13j** failed to deliver the corresponding addition product **14j**. By contrast, 3,4-dichlorophenyl-substituted azlactone **17e** delivered cyclopentane **18e** in 31% yield and with excellent diastereocontrol, albeit in a modest 70% e.e.

Such results vindicate the use of electron-poor azlactones as a means for increasing the yield. Such results may be comprehended in terms of the proposed mechanism of the reaction. If the azlactone substituent is electron-poor, the first addition step should be faster, allowing the desired reaction to outcompete the polymerization of the dipole and enhancing the reaction yield.

Conclusion

In conclusion, we have explored a range of diastereo- and enantioselective formal cycloaddition reactions between substituted vinylcyclopropanes and electron-deficient olefins. The formal cycloaddition of Meldrum's acid-substituted vinylcyclopropane **7** with a range of Meldrum's acid alkylidenes has been shown to afford substituted cyclopentane products with excellent levels of stereoselectivity. The stereochemistry of the major product was verified by X-ray crystallography, and was confirmed as that predicted by the 'wall and flap' mnemonic. It was demonstrated that the two Meldrum's acid residues could be chemodifferentiated to give highly-functionalized cyclopentane-containing products.

Furthermore, building on our work with azlactone alkylidenes, we have demonstrated that variation of the azlactone substituent can be used to enhance the yield of substrates which had been previously proven problematic, allowing access to highly functionalized constrained amino acid derivatives in enantioenriched form. We have validated the utility of the DPPBA ligands for asymmetric induction, likely by a new mechanism invoking a Curtin-Hammett process *via* a 1,3-dipolar palladium complex.

Experimental Detail

General Information

Glassware was oven-dried for at least 6 h at 110 °C or flame dried prior to use. All reactions were performed under inert atmosphere (dry nitrogen or argon) unless otherwise noted. Analytical thin-layer chromatography was performed using 0.25 nm coated commercial silica gel plates (EMD Chemicals, silica gel 60 F254). Silica gel flash chromatography was performed using Silicycle silica gel (230–400 Mesh). Proton and carbon nuclear magnetic resonance spectra (¹H NMR and ¹³C NMR) were acquired on an Inova-300 (300 MHz), Mercury 400 (400 MHz), or Varian Unity Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) relative to deuteriochloroform (7.26 ppm for ¹H NMR and 77.23 ppm for ¹³C NMR). Coupling constants (*J*) are quoted in Hz to the nearest 0.5 Hz. Splitting patterns are reported as: s, singlet; d, doublet; t, triplet; q, quartet, m,

multiplet, etc. Melting points (uncorrected) were measured using a Thomas Hoover Capillary Melting Point Analysis. Infrared (IR) spectra were recorded as a thin film on NaCl plates with a Thermo Scientific Nicolet IR 100 FT-IR. Chiral HPLC analyses were performed on a Thermo Separation Products spectra series P-100 or P-200 pump and a UV100 detector (254 nm or 220 nm) using a Chiralpak IA, IB, or IC column eluted with the indicated solvent mixture and a flow rate of 1 mL min⁻¹. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter using 5 cm cells and the sodium D line (589 nm) at ambient temperature in methylene chloride. High resolution mass spectra were obtained from Stanford University using positive electrospray ionization (ESI+). Dioxane and toluene were distilled from sodium metal under nitrogen prior to use.

Synthesis of 5c

An oven-dried reaction tube equipped with a stir bar was charged with palladium dibenzylideneacetone-chloroform complex (4.0 mg, 0.004 mmol) and (*R,R*)-**L**₃ chiral ligand, (8.0 mg, 0.010 mmol). A second reaction tube, also equipped with a stir bar, was charged with 6,6-dimethyl-1-vinyl-5,7-dioxaspiro[2.5]octane-4,8-dione **7** (35.0 mg, 0.178 mmol) and 5-(4-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **4** (60.0 mg, 0.229 mmol). Both tubes were sealed with a septum, evacuated, and backfilled with dry nitrogen. Dioxane (degassed by sparging with nitrogen for 30 min) was added to the first tube (1 mL) and second tube (2 mL), and the tubes were stirred 20 min. The contents of the first reaction tube were transferred to the second test tube via syringe, and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into sat. aq. sodium bicarbonate solution, and extracted with methylene chloride. The combined organic extracts were dried (MgSO₄) and the solvent was removed in vacuo to give the crude product, which was purified by flash column chromatography (30% to 35% diethyl ether in petroleum ether) to give the title compound **5c** as a white solid (50.8 mg, 0.111 mmol, 62%), as a 17:1 mixture of diastereomers (by crude ¹H NMR) and with a 96% e.e. for the major diastereomer (by chiral HPLC, Chiralpak IC column, 0.7% ethanol, 27% methylene chloride, 72.3% heptanes, UV wavelength 254 nm; retention times: 7.83 min (minor enantiomer, major diastereomer), 10.07 min (minor diastereomer), 10.60 min (minor diastereomer), 12.54 min (major enantiomer, major diastereomer)); ¹H NMR (500 MHz, CDCl₃): δ = 7.26 (d, *J* = 6.5 Hz, 2H), 6.81 (d, *J* = 6.5 Hz, 2H), 5.80 (ddd, *J* = 17.5, 10.5, 8.5 Hz, 1H), 5.35 (d, *J* = 17.5 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.94 (ddd, *J* = 13.0, 8.5, 6.0 Hz, 1H), 4.86 (s, 1H), 3.78 (s, 3H), 3.19 (dd, *J* = 13.0, 12.5 Hz, 1H), 2.47 (dd, *J* = 12.5, 6.0 Hz, 1H), 1.63 (s, 3H), 1.57 (s, 3H), 1.19 (s, 3H), 0.92 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 170.4, 170.1, 167.1, 166.6, 160.6, 133.9, 132.9, 125.0, 121.2, 114.6, 105.6, 105.3, 66.2, 64.7, 62.1, 56.2, 55.5, 42.2, 29.6, 29.4, 29.3, 28.5; IR (cm⁻¹): 3583, 3001, 2944, 1769, 1746, 1609, 1514, 1393, 1382, 1275, 1205, 1186, 1091, 1029, 929, 732; HRMS (ESI+) observed 481.1468; calculated 481.1479 (C₂₄H₂₆NaO₉, [M+Na]⁺); [α]_D²³ = +27.55° (c = 1.0, CH₂Cl₂); m.p. 148 °C (decomposes).

Synthesis of 14a

An oven-dried reaction tube equipped with a stir bar was charged with palladium dibenzylideneacetone-chloroform complex (4 mg, 0.004 mmol) and (*S,S*)-**L**₁ chiral ligand, (8 mg, 0.010 mmol). A second reaction tube, also equipped with a stir bar, was charged with bis(2,2,2-trifluoroethyl) 2-vinylcyclopropane-1,1-dicarboxylate (40 mg, 0.12 mmol) and (*Z*)-4-benzylidene-2-phenyloxazol-5(4*H*)-one **13a** (40 mg, 0.160 mmol). Both tubes were sealed with a septum, evacuated, and backfilled with dry nitrogen. Toluene (degassed by sparging with nitrogen for 30 min, 1 mL) was added to each tube, and the tubes were stirred 20 min. The contents of the first reaction tube were transferred to the second test tube via syringe, and the mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo to give the crude product, which was purified by flash column

chromatography (5% to 10% diethyl ether in petroleum ether) to give the title compound **14a** as a colorless oil (45 mg, 0.079 mmol, 66%), as a 19:1 mixture of diastereomers (by crude ^1H NMR) and with a 96% e.e. for the major diastereomer (by chiral HPLC, Chiralpak OD-H column, 5% isopropanol, 95% heptanes, UV wavelength 254 nm; retention times: 5.74 min (major enantiomer), 7.30 min (minor enantiomer)); ^1H NMR (500 MHz, CDCl_3): δ = 7.89 (dd, J = 8.5, 1.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.36 (m, 2H), 7.22 (m, 3H), 5.79 (ddd, J = 17.5, 10.5, 8.0 Hz, 1H), 5.23 (d, J = 17.5 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 4.78 (s, 1H), 4.66 (dq, J = 12.5, 8.0 Hz, 1H), 4.43 (dq, J = 12.5, 8.0 Hz, 1H), 4.40 (dq, J = 12.5, 8.0 Hz, 1H), 3.66 (ddd, J = 9.5, 8.0, 6.5 Hz, 1H), 3.41 (dq, J = 12.5, 8.0 Hz, 1H), 3.19 (dd, J = 13.5, 6.5 Hz, 1H), 2.51 (dd, J = 13.5, 9.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ = 178.6, 169.1, 168.1, 160.3, 136.4, 134.0, 133.3, 133.1, 131.2, 128.9, 128.3, 128.1, 125.7, 122.7 (q, $J_{\text{C-F}}$ = 276 Hz), 122.4 (q, $J_{\text{C-F}}$ = 276 Hz), 120.5, 91.2, 80.3, 78.6, 65.1, 61.7 (q, $J_{\text{C-F}}$ = 36 Hz), 61.5 (q, $J_{\text{C-F}}$ = 37 Hz), 58.1, 53.4, 38.0; ^{19}F NMR (376 MHz, CDCl_3): δ = -74.20–74.24 (m, 3F), -74.30–74.35 (m, 3F); IR (cm^{-1}): 2965, 1812, 1752, 1652, 1495, 1451, 1413, 1283, 1236, 1168, 871, 697; HRMS (ESI+): observed 570.1336; calculated 570.1351 ($\text{C}_{27}\text{H}_{22}\text{F}_6\text{NO}_6$, $[\text{M}+\text{H}]^+$); $[\alpha]_{\text{D}}^{23}$ = +15.61° (c = 1.0, CH_2Cl_2).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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17. See supporting information for full details of the X-ray crystal structure, including full details of the unit cell. It was not possible to unambiguously assign the absolute stereochemistry of the minor diastereomer, although this is in part testament to the highly diastereoselective nature of the reaction. On the basis of the 'wall and flap' mnemonic, it seems plausible that 1-*epi*-**9** (see Figure 8) is the major enantiomer of the minor diastereomer, although this cannot be verified at the present time.
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20. For the use of palladium catalysis in the polymerization of a donor-acceptor vinylcyclopropane, see: Suzuki M, Sawada S, Yoshida S, Eberhardt A, Saegusa T. *Macromolecules.* 1993; 26:4748–4750.
21. The corresponding 4-methoxyphenyl-substituted azlactone alkylidene (X = OMe) gave no reaction.

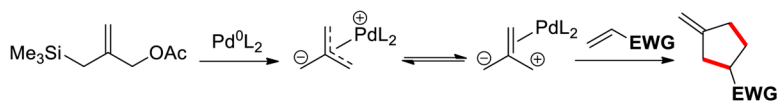


Figure 1.
Trimethylenemethane Addition Reaction

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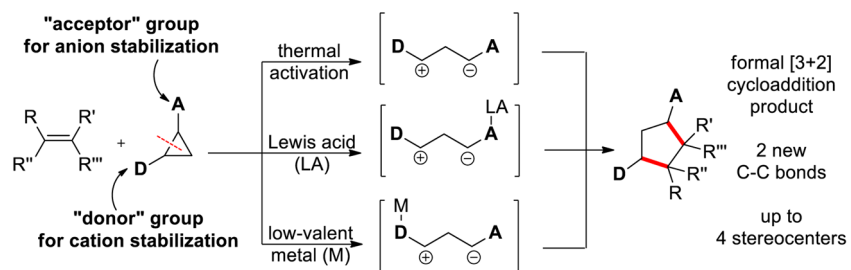


Figure 2.
 Methods of Activation of Donor-Acceptor Cyclopropanes

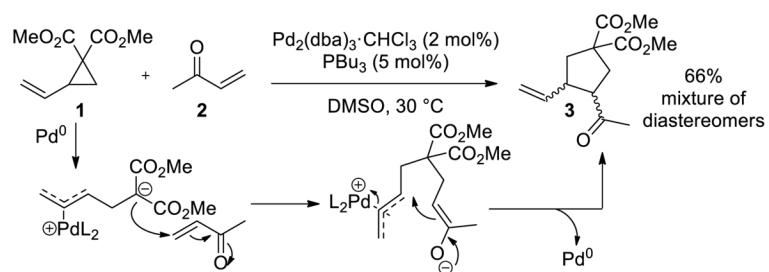


Figure 3.
Tsuji's Palladium-catalyzed Annulation of methyl vinyl ketone

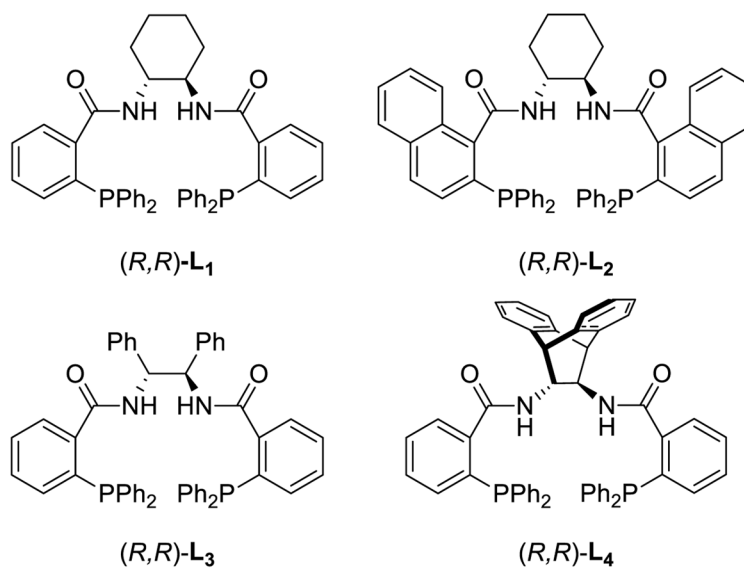


Figure 4.
Chiral Ligands for Asymmetric Palladium Catalysis

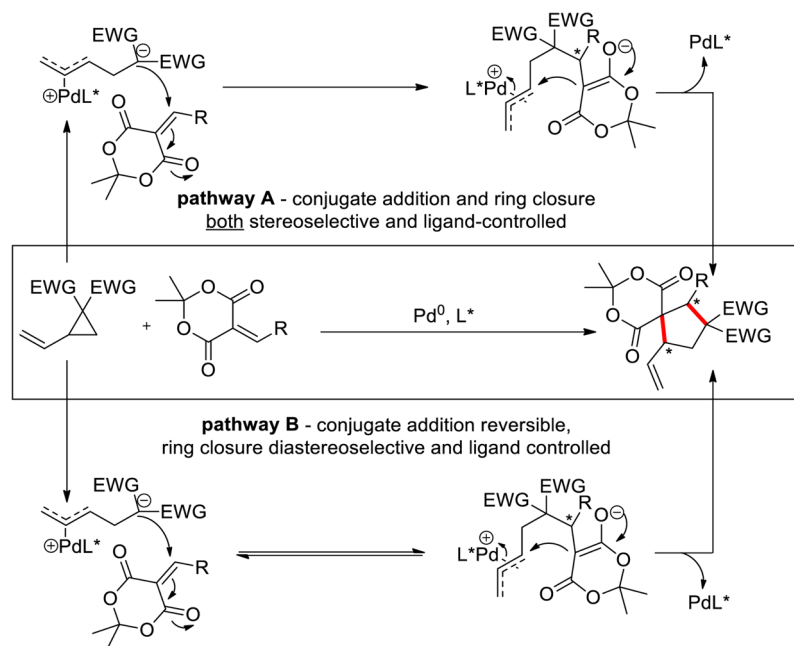


Figure 5.
Possible Mechanisms for Stereocontrol of the Proposed Annulation Reactions

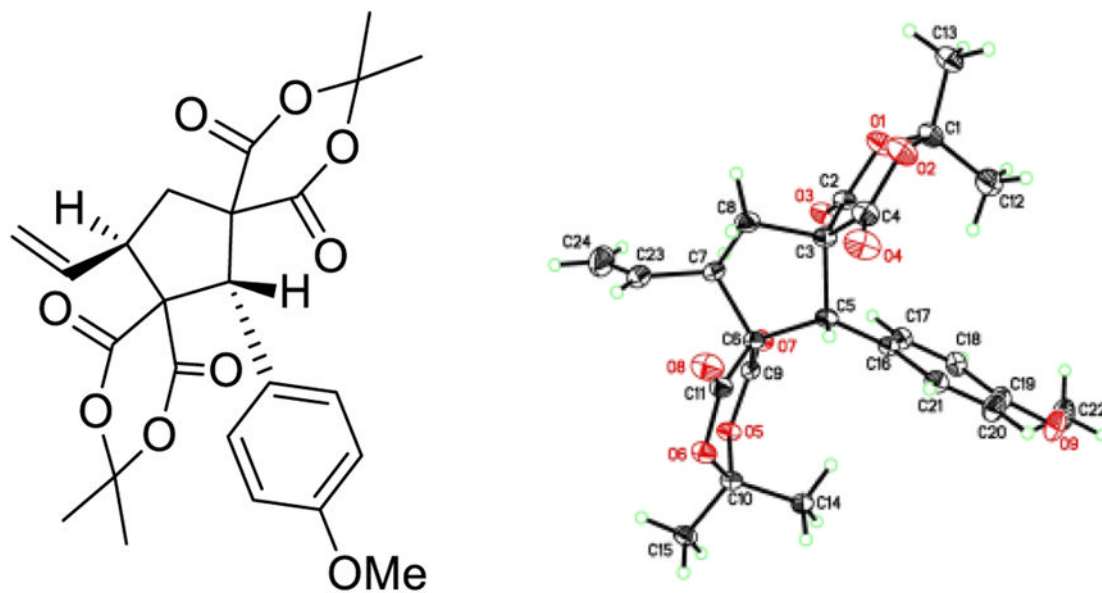


Figure 6.
X-ray crystal structure of addition product 5c

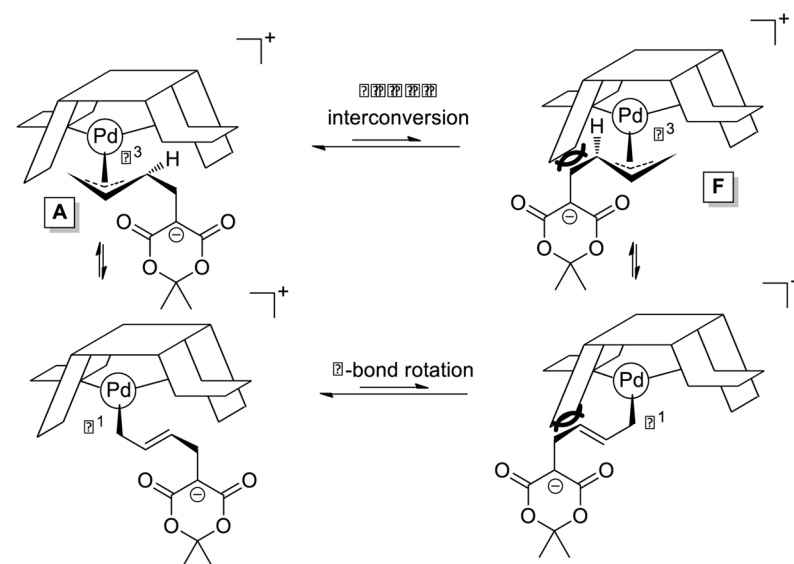


Figure 7.
Explanation of π - σ - π interconversion for stereoconvergence

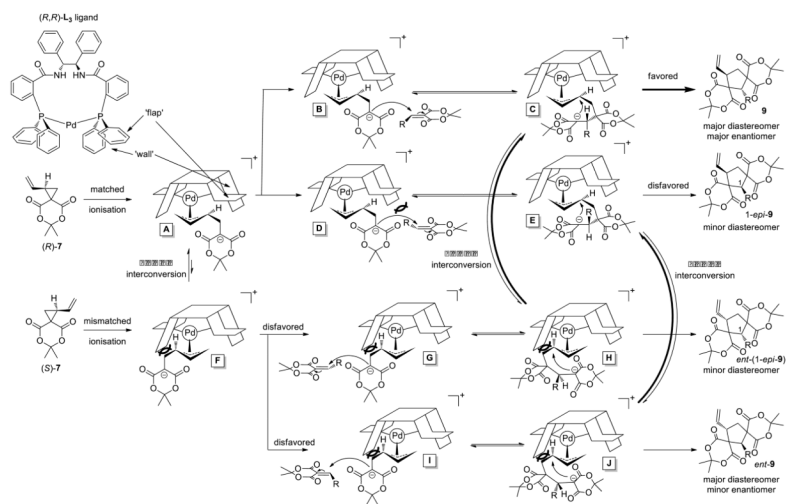


Figure 8.
Rationalization of the observed stereochemistry in terms of the 'wall and flap' mnemonic

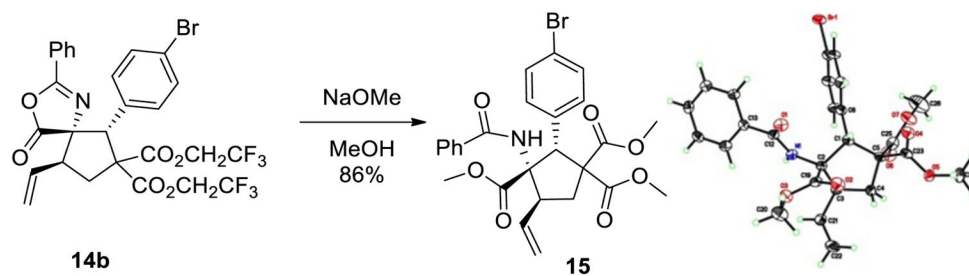


Figure 9. Assignment of Absolute Stereochemistry of cycloadduct 14b by Derivatization and X-ray Diffraction Analysis

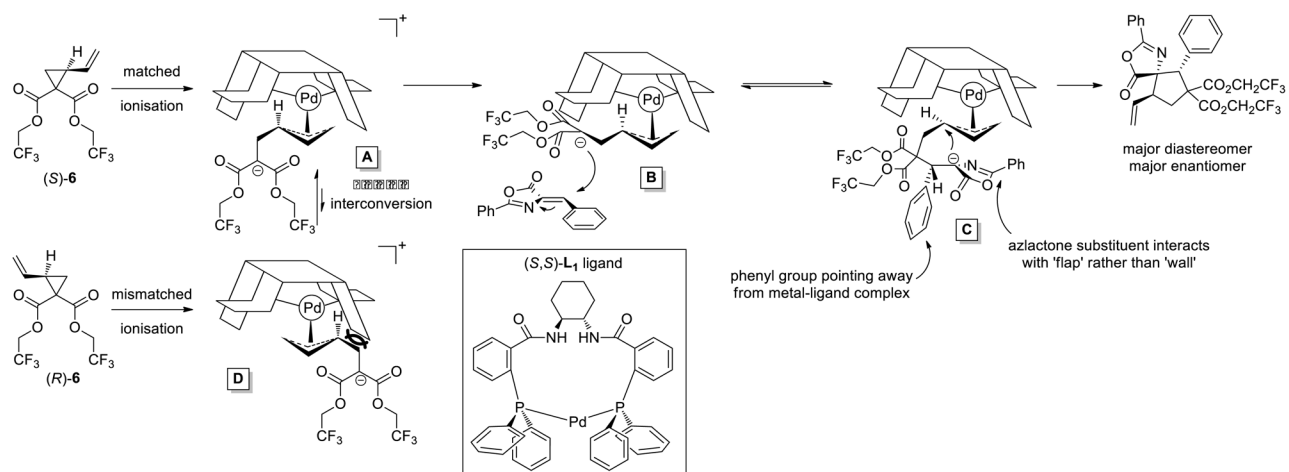


Figure 10.
Rationalization of the observed stereochemistry in terms of the 'wall and flap' mnemonic

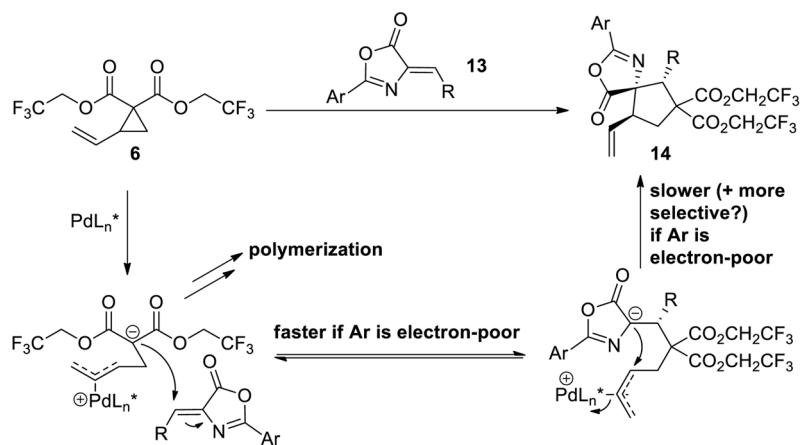
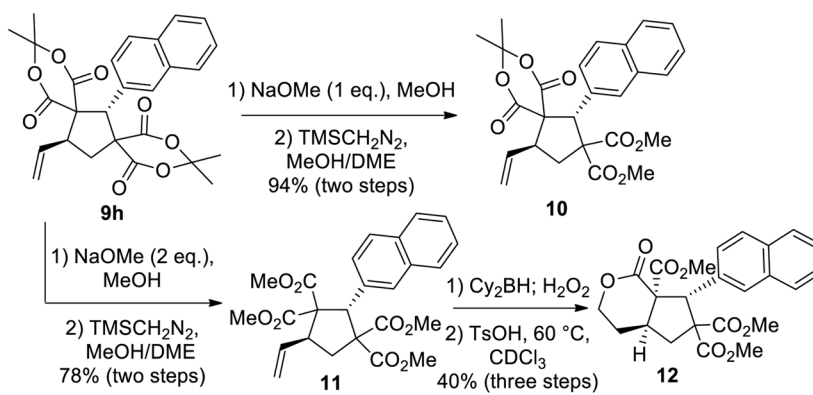
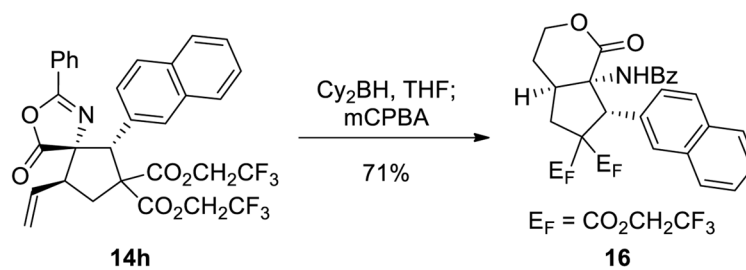


Figure 11.
Possible Impact of Variation of Azlactone Substituents



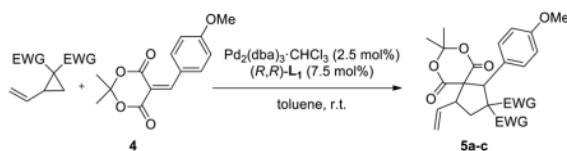
Scheme 1.
Derivatization of cycloadduct 9h

**Scheme 2.**

One-pot Transformation of the Cycloaddition Product 15h

Table 1

Screening of Various Vinylcyclopropanes



entry	substrate	product
1	 1	 5a 97% ^a , 1.5:1 d.r. ^b 39% e.e. (major) ^c 72% e.e. (minor) ^c
2	 6	 5b 84% ^a , 2.1:1 d.r. ^b 29% e.e. (major) ^c 79% e.e. (minor) ^c
3	 7	 5c 22% ^a , >20:1 d.r. ^b 94% e.e. (major) ^c

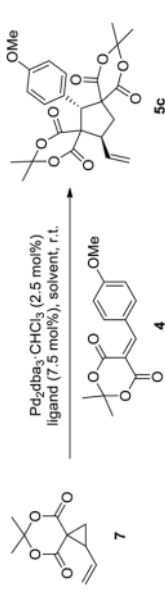
^a Isolated yield.

^b Diastereomeric ratio (d.r.) determined by ¹H NMR.

^c Enantiomeric excess (e.e.) of major and minor diastereomer, respectively, determined by chiral HPLC.

Table 2

Selected Optimization Results

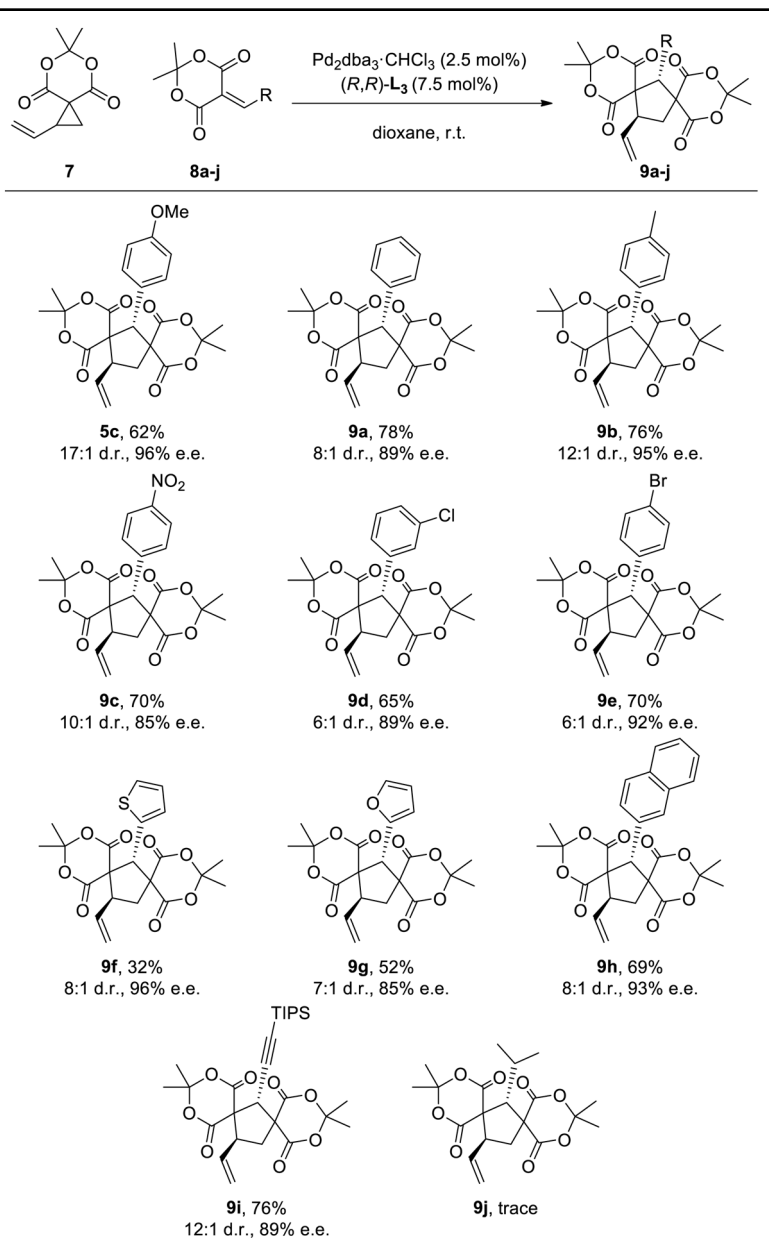


entry	ligand	solvent	yield ^a	d.r. ^b	e.e. ^c
1	(<i>S,S</i>)-L ₁	DME	48%	5.4:1	-60%
2	(<i>S,S</i>)-L ₂	DME	27%	2.2:1	-82%
3	(<i>R,R</i>)-L ₃	DME	50%	6.5:1	87%
4	(<i>R,R</i>)-L ₄	DME	54%	3.2:1	33%
5	(<i>R,R</i>)-L ₃	THF	49%	6.1:1	88%
6	(<i>R,R</i>)-L ₃	MeOH	26%	14:1	84%
7	(<i>R,R</i>)-L ₃	DMF	53%	2.7:1	30%
8	(<i>R,R</i>)-L ₃	toluene	22%	24:1	94%
9	(<i>R,R</i>)-L ₃	dioxane	62%	17:1	96%

^a Isolated yields.^b Diastereomeric ratio (d.r.) determined by ¹H NMR.^c Enantiomeric excess (e.e.) of the major diastereomer, determined by chiral HPLC.

Table 3

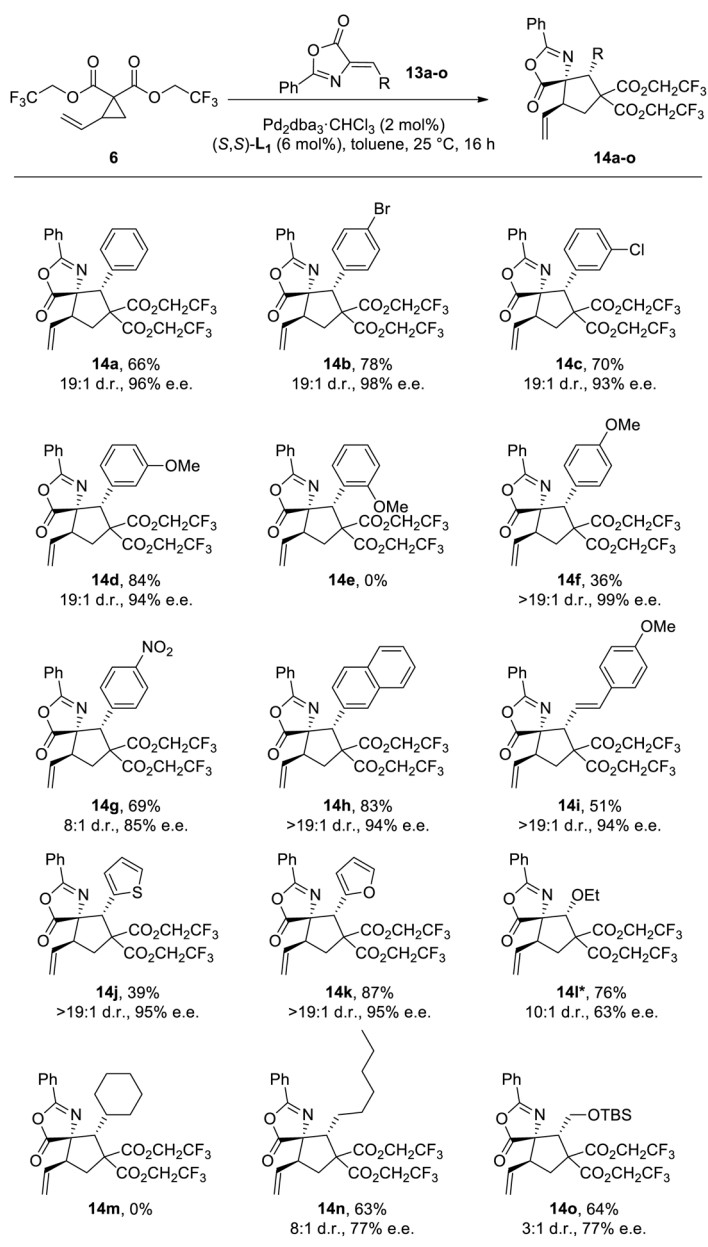
Cycloaddition with Meldrum's Acid Alkylidenes



Yields given are of the isolated products. Diastereomeric ratios (d.r.) determined by ^1H NMR. Enantiomeric excesses (e.e.) of the major diastereomer determined by chiral HPLC.

Table 4

Scope and Limitations of the Cycloaddition of Substituted Vinylcyclopropanes with Azlactone Alkylidenes

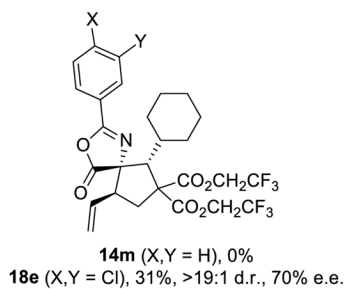
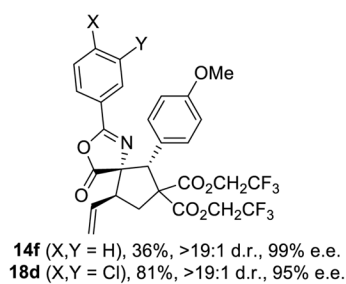
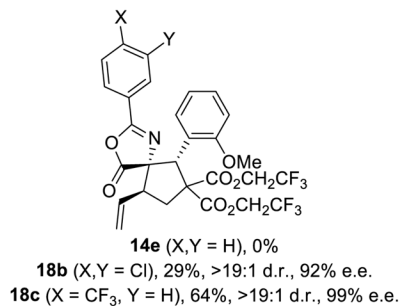
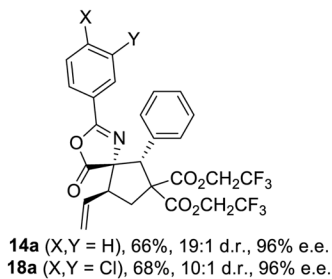
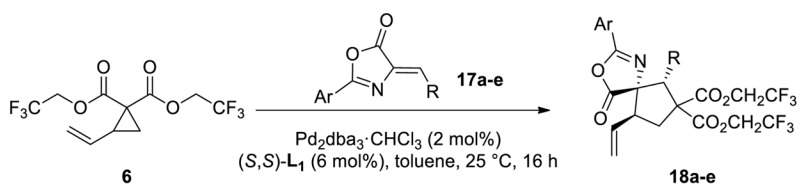


Yields given are for the isolated products. Diastereomeric ratios (d.r.) determined by ¹H NMR. Enantiomeric excesses of the major diastereomer (e.e.) determined by chiral HPLC.

* A 3:1 mixture of *EIZ* isomers of the azlactone alkylidene **13l** was used in the reaction; the e.e. of compound **14l** was determined on a derivative of the compound to aid separation on the chiral HPLC.

Table 5

Variation of Azlactone Substituents to Improve Yield of the Cyclization Products



Yields given are for the isolated products. Diastereomeric ratios (d.r.) determined by ¹H NMR. Enantiomeric excesses of the major diastereomer (e.e.) determined by chiral HPLC.