Asymmetric Synthesis

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Palladium-Catalyzed Diastereo- and Enantioselective Synthesis of Substituted Cyclopentanes through a Dynamic Kinetic Asymmetric Formal [3+2]-Cycloaddition of Vinyl Cyclopropanes and Alkylidene Azlactones**

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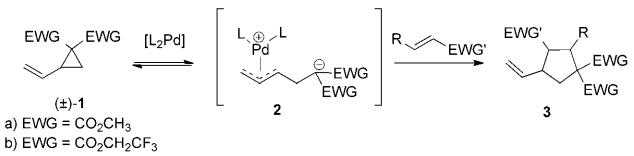
The development of new enantioselective methods for the formation of cyclopentane rings containing multiple stereocenters is of importance both in organic and medicinal chemistry.[1] A powerful approach would be a metal-catalyzed asymmetric formal [3+2]-cycloaddition between a 1,3-dipole and an olefin; it would allow for the construction of the cyclopentane and form multiple stereocenters in a single synthetic step. Additionally, development of this methodology would identify new "three-carbon-atom" precursors for asymmetric cycloadditions, beyond the relatively small number that currently exist in the literature.[2]

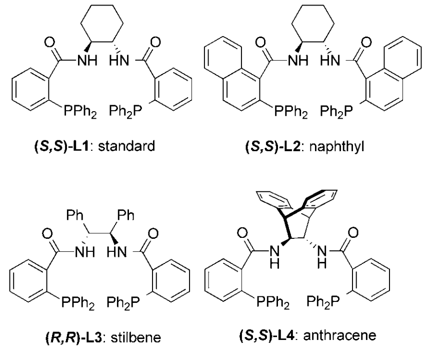
Vinyl epoxides, aziridines, and cyclopropanes bearing electron-withdrawing groups are known to open into 1,3-dipoles in the presence of palladium(0) catalysts. The resulting Pd^{II} complexes add across olefins,[3] isocyanates,[4,5] carbodiimides,[6] and aldehydes[7] to afford five-membered rings. We hypothesized that we could use 1,3-dipoles generated from vinyl cyclopropanes as a novel three carbon fragment to generate cyclopentanes in an asymmetric fashion through palladium catalysis.

Tsuji et al. have reported that vinylcyclopropane **1a** adds across methyl vinyl ketone in the presence of $[Pd_2dba_3]$ (dba = dibenzylideneacetone) and bis(diphenylphosphino)ethane to afford vinylcyclopentane **3** (Scheme 1).[3] Later, Johnson et al. demonstrated the Pd-catalyzed additions of the vinyl cyclopropane **1a** to aldehydes.[7] However, they needed to employ an alternative strategy using chiral Lewis acid catalysts to achieve asymmetric induction, a process that has not been expanded to electron-poor olefins.[8,9]



Scheme 1. Palladium-catalyzed addition of vinyl cyclopropanes **1** to electron poor olefins. EWG = electron-withdrawing group.

Previously, the chiral ligands developed in our laboratory (**L1**–**L4**; Scheme 2) for the Pd-catalyzed asymmetric allylic alkylation have been employed to induce asymmetry at both



Scheme 2. Trost asymmetric allylic alkylation ligands.

the prochiral nucleophile and/or at the carbon of the π-allyl which is being attacked.[10a–c] However, it has not been demonstrated for these ligands to be able to control stereochemistry in a bond-forming event distal to the π-allyl Pd-complex. Our proposed Pd-catalyzed formal [3+2]-cycloaddition is a new challenge for these chiral ligands, in that it is requisite for them to control the stereochemistry of the Michael addition by the malonate carbanion, in addition to the stereochemistry at the nucleophile and the allyl center.

To explore the prospect of this new class of asymmetric 1,3-dipole donors, we chose alkylidene azlactones as acceptors since these olefins should represent a reactive and useful class that would generate an interesting family of conformationally constrained α-amino acids.[11] Promisingly, when **1a** and **4a** were combined with $[Pd_2(dba)_3]\cdot CHCl_3$ (3 mol%) and **L1** (9 mol%) in toluene at room temperature, the desired [3+2]-cycloadduct was observed, albeit in only a 16% yield with a 10:1 d.r. and 60% *ee*.

Attributing the low reactivity of the dipole **2** derived from precursor **1a** to its low lifetime, we speculated that the trifluoroester **1b** might possess sufficiently greater stability to increase its lifetime, while at the same time maintaining reactivity.[12] Indeed, by combining our more reactive vinyl

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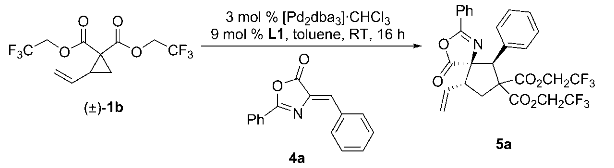
Table 1: Selected optimization results.



Entry	Ligand	Solvent	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**L1**	toluene	64	19:1	96
2	**L2**	toluene	61	19:1	92
3	**L3**	toluene	66	15:1	−87
4	**L4**	toluene	21	4:1	23
5	**L1**	α,α,α-trifluorotoluene	69	4:1	83
6	**L1**	THF	14	15:1	89
7	**L1**	CH_2Cl_2	77	8:1	91
8	**L1**	dioxane	82	14:1	94

[a] Yields of isolated products. [b] Diastereomeric ratios determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC.

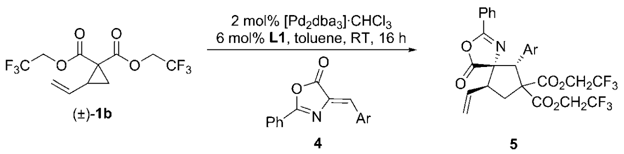
cyclopropane **1b** and Michael acceptor **4a**, we were able to observe the desired product in 64% yield, 19:1 d.r., and 96% *ee* (Table 1, entry 1). Notably, only two of four possible diastereomers were observed, one of which was heavily favored. Furthermore, the reactions proceeded well at room temperature.

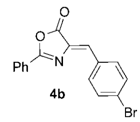
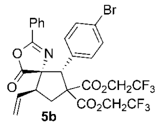
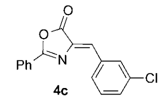
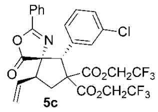
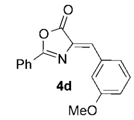
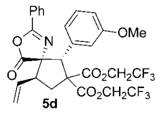
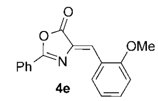
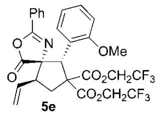
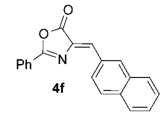
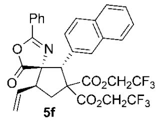
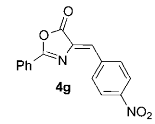
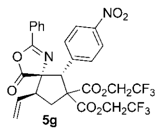
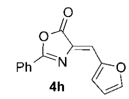
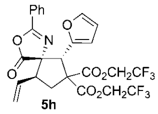
Further ligand (Table 1, entries 2–4) and solvent optimization (Table 1, entries 5–8) confirmed that ligand **L1** was differential, and the highest selectivities were observed with toluene. Dioxane provided higher yields at only a modest decrease in stereoselectivity (Table 1, entry 8). We also found the catalyst loading could be reduced from 6% to 4%.

We then sought to evaluate the scope of the reaction with a variety of aryl-substituted azlactones, using the conditions for optimal diastereoselectivity (Table 2). Moderately election-withdrawing substituents in the *meta*- and *para*- positions (entries 1–3) were well tolerated, maintaining high levels of enantioselectivity and diastereoselectivity. However, when a substituent was introduced in the *ortho*-position (entry 4), no product was obtained, presumably due to the additional steric bulk. The moderately electron-rich 2-naphthyl system was also well tolerated (entry 5). A substrate bearing a highly electron-withdrawing substituent (entry 6) proved slightly detrimental to the enantioselectivity and diastereoselectivity, while electron-rich furan (entry 7) gave excellent diastereoselectivity, enantioselectivity and yield.

Next, we examined non-aromatic substituents on the azlactone electrophile (Table 3). The cinnamyl derivative (entry 1) gave excellent selectivities, albeit in a slightly reduced yield. Notably, only 1,4-addition was observed. The *n*-hexyl derivative (entry 2) reacted well, affording a 63% yield of the desired product, with somewhat reduced diastereo- and enantioselectivity. Increasing the steric bulk to cyclohexyl led to no product formation (entry 3), suggesting sensitivity to steric effects on the electrophile, similar to the *ortho*-methoxyphenyl group (Table 2, entry 4). Finally, both a protected alcohol in the alkyl chain (entry 4) and a heteroatom were well tolerated, with no elimination products observed in the latter case (entry 5). Those azlactones which

Table 2: Cycloaddition of vinyl cyclopropanes with aryl alkylidene azlactones.



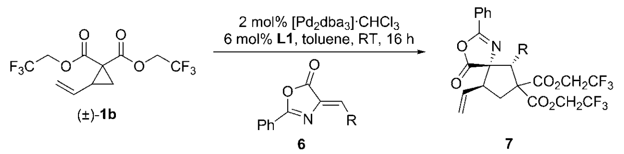
Entry	Substrate	Product	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	 **4b**	 **5b**	78	19:1	98
2	 **4c**	 **5c**	70	>19:1	93
3	 **4d**	 **5d**	83	19:1	94
4	 **4e**	 **5e**	0	n.d.	n.d.
5	 **4f**	 **5f**	84	>19:1	94
6	 **4g**	 **5g**	72	8:1	85
7	 **4h**	 **5h**	87	>19:1	95

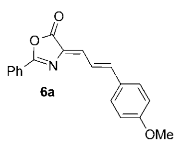
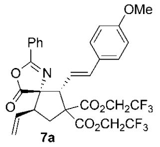
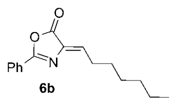
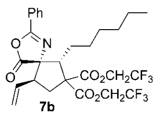
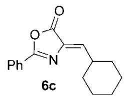
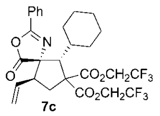
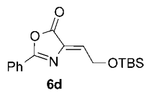
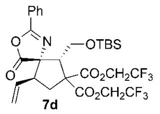
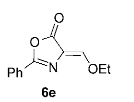
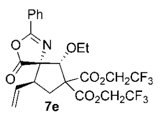
[a] Yields of isolated products. [b] Diastereomeric ratios determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC.

are more reactive for steric (**6b**) or electronic reasons (**4g**), gave reduced diastereo- and enantioselectivities, while those with increased steric bulk (**6c**) or with electron donating (**6a**) substituents appeared gave good selectivity but reduced (or no) yield.

To rationalize the observed stereoselectivity, we propose a modification of our previously reported "wall and flap" model (Scheme 3).[10b,13] Both the matched and mismatched ionization of the starting vinyl cyclopropane ((***R***)**-1b**, (***S***)**-1b**)) occur to give complexes **8** and **9**. By π–σ–π equilibration, **8** and **9** can interconvert to the thermodynamically favored **8**, where the malonate resides under the "flap" in order to avoid the steric bulk of the "wall" in **9**. The malonate anion attacks the alkylidene azlactone, when the aryl group on the alkylidene is oriented away from the back "wall" of the ligand (**10**). Finally, attack of the azlactone anion onto the π-

Table 3: Cycloaddition of vinyl cyclopropanes with non-aryl alkylidene azlactones.

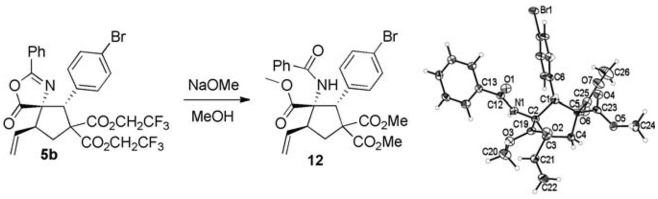


Entry	Substrate	Product	Yield [%][a]	d.r.[b]	*ee* [%][c]
1			51	>19:1	94
2			63	8:1	74
3			0	n.d.	n.d.
4			64	3:1[d]	77[e]
5			73	10:1	63

[a] Yields of isolated product. [b] Diastereomeric ratios determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC. [d] A 3:1 mixture of the *E*/*Z* isomers of **6d** was used. [e] Determined on a derivative of this compound.

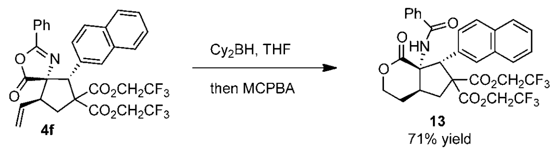
allyl-palladium (**11**) provides the observed major diastereomer **5a**.

In order to determine the configuration of **5b**, it was treated with sodium methoxide in methanol (Scheme 4) to afford trimethyl ester **12** in quantitative yield as a crystalline solid. Single-crystal X-ray diffraction analysis secured the relative and absolute configuration of **12**.[14] Interestingly, our method provides a *trans* relationship between the vinyl and aryl groups, rather than the thermodynamically more favored *cis* diastereomer.[15]



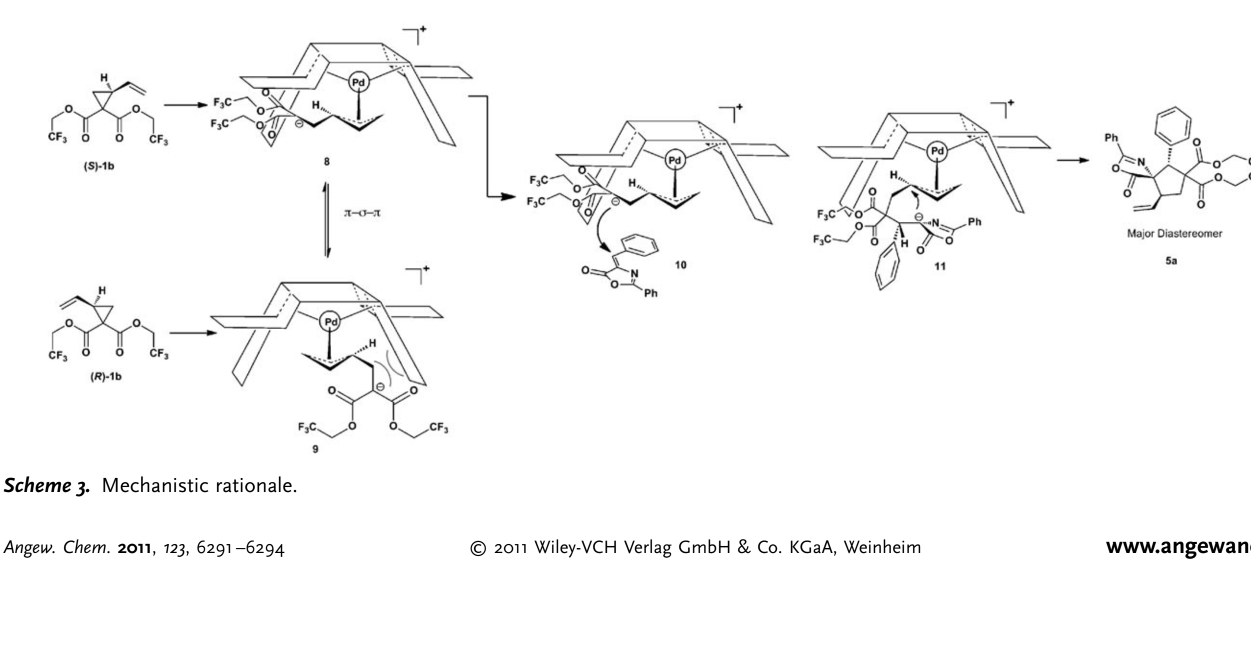
Scheme 4. Functionalization of cycloadduct for crystallographic analysis.[16]

The juxtaposition of functionality allows for ready structural modification (Scheme 5). For example, treatment of **5f** with dicyclohexyl borane in THF, followed by *m*-CPBA (*meta*-chloroperbenzoic acid) oxidation of the trialkylborane gives the primary alcohol in situ, which cyclizes onto the azlactone to give lactone **13**.



Scheme 5. One-step functionalization to bicyclic system.

In conclusion, we have developed a new palladium-catalyzed enantioselective formal [3+2] cycloaddition between vinyl cyclopropanes and prochiral Michael acceptors. The use of the bis(2,2,2-trifluoroethyl)malonate vinylcyclopropanes allows much higher yields and selectivities. Using alkylidene azalactones as the acceptor for this reaction provides access to highly functionalized chiral amino acid derivatives, a method which simultaneously sets three stereogenic centers in excellent enantio- and diastereoselectivies.



Scheme 3. Mechanistic rationale.

This represents the first time this class of chiral ligands has been used to induce asymmetry in conjugate addition reactions, as well as the first time racemic vinyl cyclopropanes have been utilized in a formal [3+2] cycloaddition to form carbocycles in an asymmetric fashion. Work continues in our laboratory towards expanding the scope of this reaction towards a range of other acceptors.

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[14] The relative and absolute configurations of the other products are assigned by analogy to **5b**.

[15] The heats of formation of **5b** and epi-**5b** were calculated using SPARTAN 06 Essential 1.0.1. Epi-**5b** was found to be 11.6 kJ$\,$mol^{-1} more stable. For details, see Supporting Information.

[16] CCDC 825686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

