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Enantioselective Inverse Electron Demand (3 + 2) Cycloaddition of Palladium-Oxyallyl Enabled by a Hydrogen-Bond-Donating Ligand

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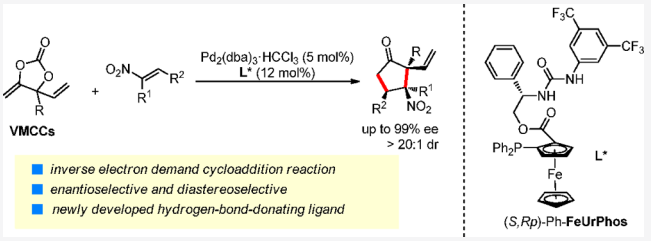
ABSTRACT: Cycloaddition reactions between oxyallyl cations and alkenes are important transformations for the construction of ring systems. Although (4 + 3) cycloaddition reactions of oxyallyl cations are well-developed, (3 + 2) cycloadditions remain rare, and an asymmetric version has not yet been developed. Moreover, because oxyallyl cations are highly electrophilic, only electron-rich olefins can be used as cycloaddition partners. We herein report a method for enantioselective (3 + 2) cycloaddition reactions between palladium-oxyallyl species and electron-deficient nitroalkenes. This transformation was enabled by a rationally designed hydrogen-bond-donating ligand (FeUrPhos) and proceeded via an inverse electron demand pathway. Using this method, we could assemble cyclopentanones with up to three contiguous stereocenters with high enantioselectivity and good to excellent diastereoselectivity.



1. INTRODUCTION

Cycloadditions are among the most powerful bond-forming reactions in organic synthesis, not only because they offer efficient access to cyclic compounds in a single step but also because they can simultaneously generate multiple stereocenters with controllable stereoselectivity.[1] In the past several decades, oxyallyl cations related cycloaddition reactions have attracted considerable attention.[2] These highly electrophilic species react with electron-rich 1,3-dienes (or their equivalents) exclusively via a (4 + 3) cycloaddition pathway to give seven-membered ring products.[3] Because the concerted (3 + 2) pathway is thermally forbidden, there are few reports of cycloaddition reactions of oxyallyl cations with 2π alkene acceptors (Figure 1a). Rare examples include Wu's work on cycloaddition reactions of cyclic oxyallyl cations with indole derivatives[4a] and Kuwajima's work on (3 + 2) cycloaddition reactions of α-sulfur oxyallyl cations with enol ethers.[4b] On the other hand, due to the lack of general means for discriminating between the two faces of the planar oxyallyl cation, asymmetric variants of these cycloaddition reactions are inherently challenging. So far only a few strategies have met with success, and furan is the only successful cycloaddition partner in these works.[5]

Conventionally, oxyallyl cations are generated from α-halo- or sulfonyl-substituted ketones or enol ethers by the action of stoichiometric acids,[3d,g,j,4b] bases,[3c,4a] or reductants.[3a,b] Oxidation of allenamide with excess amount of strong oxidant is another useful alternative method.[3e,f,h] Catalytic generation and cycloaddition of oxyallyl cations eluded synthetic chemists until a recent breakthrough by Trost et al. (Figure 1b).[6] In this elegant work, they combined a protected ester-substituted enol ether with a Pd(0) catalyst to generate a Pd-oxyallyl, which cyclizes with 1,3-dienes to produce (3 + 2) cycloaddition products. Density functional theory (DFT) calculations by Chen and Houk revealed that the electron-withdrawing ester substituent is crucial because it decreases the energy of the LUMO of the Pd-oxyallyl species, leading to a more favorable energy match with the HOMO of the diene.[7] Trost's pioneering work paved the way for the discovery of new catalytic Pd-oxyallyl cycloaddition reactions.[8] However, challenges remain, such as widening the substrate scope to include electron-deficient olefins and achieving an enantioselective version.

The oxyallyl cation is a structurally zwitterionic species that contains a nucleophilic enolate moiety and an electrophilic allyl carbocation moiety. Based on its resonance structures, the negative charge could be delocalized from the oxygen atom to the carbon atom, rendering this carbon reaction site amphoteric (Figure 1c). However, the nucleophilic reactivity of oxyallyl cation has largely been underdeveloped. The underlying challenges became quickly apparent from the fact that a rare inverse electron demand cycloaddition reaction has been reported to date (Figure 1d). In 2013, Krenske, Houk, and Hsung have reported an intramolecular cycloaddition reaction of a nitrogen-substituted oxyallyl cation with a carbonyl compound. This transformation featured a formal

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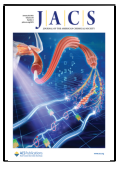

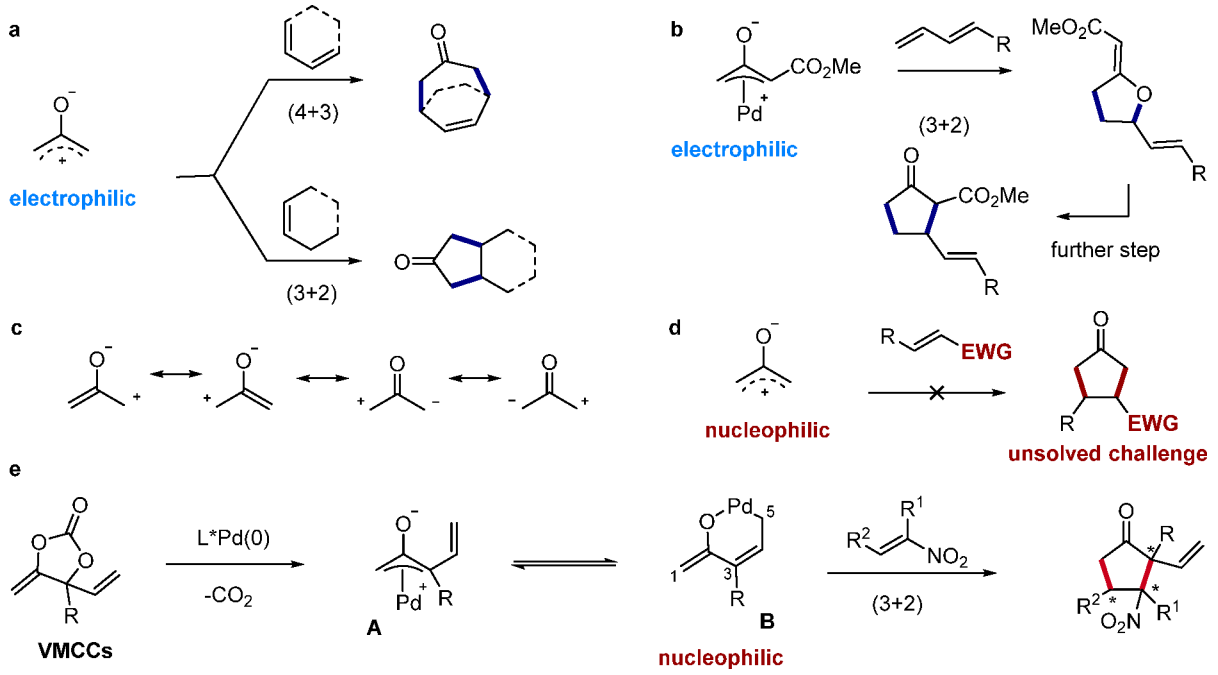

Figure 1. Cycloaddition reactions of oxyallyl cations and Pd-oxyallyl species. (a) (4 + 3) and (3 + 2) Cycloaddition of oxyallyl cation with alkenes featuring an electrophilic pathway. (b) Trost's catalytic Pd-oxyallyl (3 + 2) cycloaddition reaction featuring electrophilic pathway and the thereafter [3,3]-sigmatropic rearrangement to prepare cyclopentanone. (c) Resonance structures of oxyallyl cation. (d) Nucleophilic oxyallyl cation and the challenging inverse electron demand cycloaddition. (e) Our strategy to pursue a nucleophilic Pd-oxyallyl and its asymmetric inverse electron demand (3 + 2) cycloaddition with nitroalkene.

inverse electron demand cycloaddition. Calculation studies revealed that it involves a highly asynchronous process, from which the C−O bond formation is much more advanced at the transition state than C−C bond formation.[9] This elegant work first revealed that a nitrogen substituent makes the oxyallyl cation possess a quite different reactivity. In our efforts to develop new Pd-catalyzed cycloaddition reactions,[10,11] we recognized that merging an oxyallyl cation with a palladium catalyst might effectively tune the reactivity of the oxyallyl cation. Furthermore, by using a chiral ligand on Pd, enantioselective cycloaddition reaction might be achieved. To this end, we designed a series of vinyl methylene cyclic carbonates (VMCCs) to act as reactive precursors to Pd-oxyallyl species. We envisioned that the VMCCs could react with Pd(0) to form a vinyl-substituted Pd-oxyallyl species **A** after extrusion of one molecular CO_2 (Figure 1e). Because the charge delocalization that results from the equilibrium between **A** and Pd-oxypentadienyl species **B**, we reasoned that the electron density at C1 would be enhanced and that **B** might display some nucleophilicity at C1 position, allowing us to achieve inverse electron demand cycloaddition.

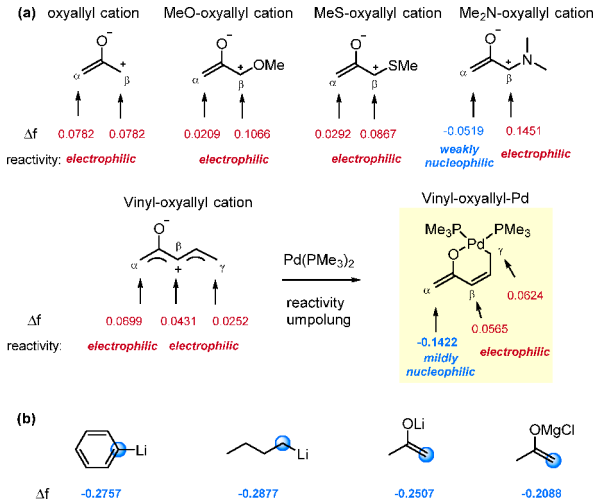

Figure 2. DFT calculations of the condensed dual descriptor. (a) The Δf and reactivity for oxyallyl cation species. (b) The Δf of typical carbon nuclephiles.

2. RESULTS AND DISCUSSION

The initial investigation was focused on understanding the reactivity of the Pd-oxyallyl. We began our studies by performing DFT calculations with Fukui function[12] to predict the reactivity of various oxyallyl cation related species (Figure 2a). The condensed dual descriptor (Δf)[13] derived by Hirshfeld charge[14] was adopted to evaluate the electrophilicity and nucleophilicity.[15] Generally, a positive Δf value implies an electrophilic site, while a negative Δf value corresponds to a nucleophilic site. The oxyallyl cation had a Δf of 0.0782 for C_α, which is consistent with the electrophilic nature of this species. However, the Δf values for the α-carbons of the MeO-oxyallyl and the MeS-oxyallyl cation were lower (0.0209 and 0.0292, respectively), which implies that the presence of carbocation-stabilizing groups weakened the electrophilicity of the α-carbon. In an extreme example, we found that an amino-oxyallyl cation had a negative Δf (−0.0519), that is, the α-carbon went from being strongly electrophilic to weakly nucleophilic. This result is consistent with Krenske, Houk, and Hsung's work that nitrogen-substituted oxyallyl would undergo inverse electron demand cycloaddition with carbonyl.[9] A vinyl group might also stabilize cations via p−π conjugation, but we found that the α-carbon of a vinyl-oxyallyl cation had a Δf of 0.0699, just a little lower than that of oxyallyl cation. However,

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when a Pd atom was incorporated into the vinyl-oxyallyl cation, the Δf of the α-carbon dropped dramatically to −0.1422, which suggested a reversed reactivity. As a comparison, the Δf values of some typical carbon nucleophiles were also calculated under the same calculation method. For example, lithium enolate and magnesium enolate have a Δf of −0.2507 and −0.2088, respectively (Figure 2b). Based on these data, we reasoned that the vinyl-oxyallyl-Pd might exhibit a mild nucleophilic property.

To better understand the reactivities of those species, the dual descriptor isosurface of the oxyallyl cation, Me_2N-oxyallyl cation, and vinyl-oxyallyl-Pd were illustrated (Figure 3).[16,17]

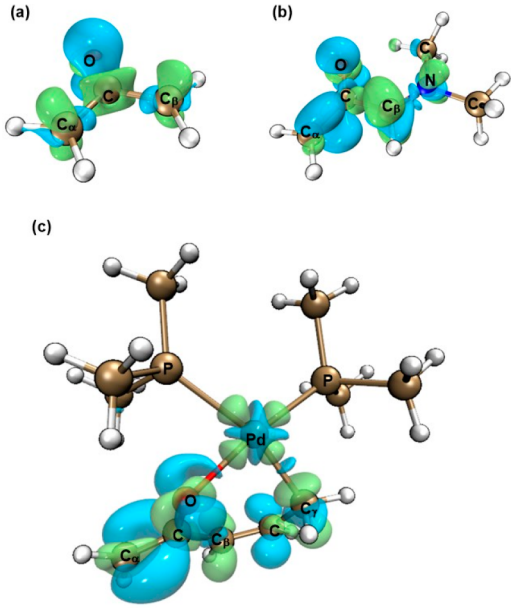
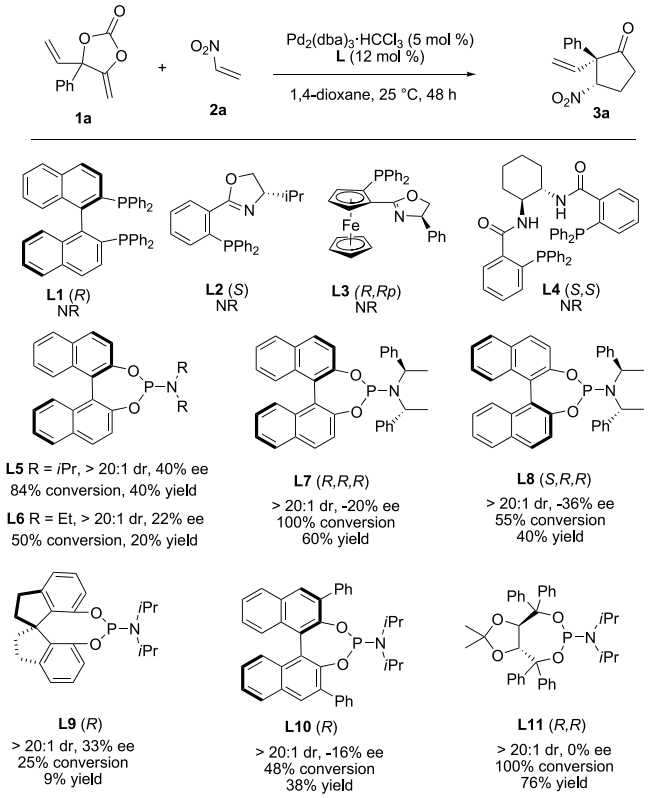


Figure 3. Topology of dual descriptor isosurfaces. (a) oxyallyl cation. (b) Me_2N-oxyallyl cation. (c) Vinyl-oxyallyl-Pd. All isosurfaces are depicted at 5×10^{-3} au. Green lobes represent electrophilicity, and blue lobes represent nucleophilicity.

Herein, in these topological structures, green lobes represent electrophilic reactivity and blue lobes represent nucleophilic reactivity. For the oxyallyl cation, the C_α is equivalent to C_β, and both of them show a strong electrophilic reactivity, as indicated by the outsphere green lobes around them. For the Me_2N-oxyallyl cation, the substitution group disproportioned the two carbons, and while the C_β still maintains its electrophilicity, the C_α becomes a nucleophilic carbon center. Similarly, the local reactivity behavior of C_α in vinyl-oxyallyl-Pd is also determined to be nucleophilic, because this site is surrounded by blue lobes.

Encouraged by the DFT results, we moved on to proof-of-concept studies aimed at achieving an inverse electron demand cycloaddition reaction of Pd-oxyallyl by carrying out reactions of phenyl-substituted VMCC **1a** with nitroethylene (**2a**) at 25 °C in the presence of $Pd_2(dba)_3{\cdot}HCCl_3$ and various ligands (Table 1). Although most of the tested ligands, including Binap (**L1**), *i*Pr-PhOX (**L2**), Phosferrox (**L3**), and DACH-Ph-Trost ligand, failed to mediate the desired (3 + 2) cycloaddition, we were pleased to find that the phosphoramidite-type ligand **L5** afforded cycloaddition product **3a** in 40% yield with >20:1 dr and 40% ee. Further experiments indicated that the use of **L11** could increase the yield to 76%,

Table 1. Initial Investigation of Ligands[a]



[a]Reaction conditions: **1a** (0.05 mmol), **2a** (2.0 equiv), $Pd_2(dba)_3{\cdot}HCCl_3$ (5 mol %), ligand (12 mol %), 1,4-dioxane (1.0 mL), 25 °C under argon. Yields and diastereomeric ratios (dr) were determined by ^{1}H NMR analysis of the crude product. The enantiomeric excess (ee) was determined by chiral HPLC on commercial columns. NR, no reaction.

but all efforts to improve the enantioselectivity met with failure, which prompted us to consider an alternative strategy for designing ligands for this reaction.[18]

MacMillan and co-workers developed an elegant, creative strategy for enantioselective nucleophilic substitution reactions of oxyallyl cations.[19] These investigators used an amino alcohol organocatalyst to form an enantiodiscriminant hydrogen-bonded oxyallyl cation (Figure 4a). Jacobsen et al. reported a hydrogen-bond-donating organocatalyst that mediates highly enantioselective (4 + 3) cycloaddition reactions of oxyallyl cations with furans (Figure 4b).[5d] Inspired by these studies as well as recent achievements in the application of noncovalent interactions in asymmetric transition-metal catalysis,[20,21] we conceived a strategy involving the introduction of an organocatalyst moiety into the ligand to improve the enantiocontrol. Specifically, we designed a new type of hydrogen-bond-donating phosphine ligand, designated FeUrPhos, as shown in Figure 4c. These ligands contain a tethered urea moiety that can engage in hydrogen bonding with the electron-rich oxygen of Pd-oxyallyl, an interaction that has the potential to enhance chiral induction.

Starting from commercially available (*S,Sp*)-Phosferrox ligands, after semi-hydrolysis of the oxazoline ring and following by condensation with 3,5-bis(trifluoromethyl)phenyl isocyanate, a series of (*S,Sp*)-FeUrPhos ligands with various R groups were prepared (Figure 4d). On the other hand, the diastereoisomeric (*S,Rp*)-FeUrPhos ligands could be as-

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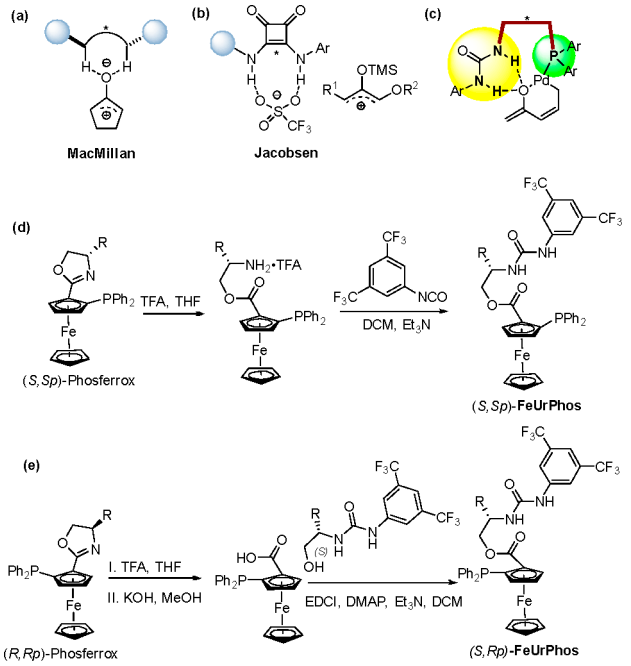
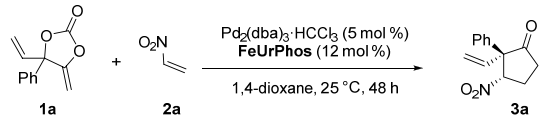


Figure 4. Development of hydrogen-bond-donating ligand FeUrPhos. (a) MacMillan's model of using a hydrogen bond to control the enantioselectivity in the oxyallyl cation substitution reaction. (b) Jacobsen's model of hydrogen-bond-donor catalyst for enantioselective (4 + 3) cycloaddition of an oxyallyl cation. (c) Our model of incorporation of hydrogen-bond-donating ligand for enantioselective cycloaddition of vinyl-oxyallyl-Pd. (d) Synthetic route to (*S*,*Sp*)-FeUrPhos. (e) Synthetic route to (*S*,*Rp*)-FeUrPhos.

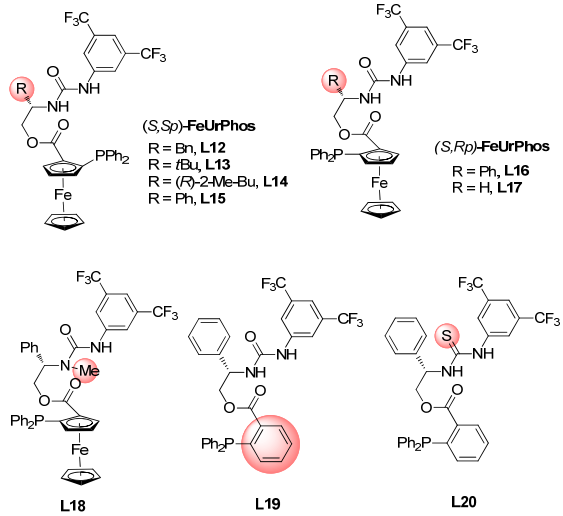
sembled by sequential oxazoline ring hydrolysis/condensation with a (*S*)-configuration aminol urea derivative (Figure 4e) (for more details see the Supporting Information).

With these FeUrPhos ligands in hand, we started to evaluate the performance of these ligands for the model reaction (Table 2). For (*S*,*Sp*)-FeUrPhos with alkyl R groups (**L12**−**L14**, entries 1−3), good to excellent enantioselectivity was obtained, although the yield was moderate. Among them, (*S*,*Sp*)-**L13**, which has a *t*Bu group, showed the best results, giving the desired cycloaddition product **3a** in 70% yield with 94% ee. When the R of the ligand was a phenyl group (**L15**), both the yield and ee of the product dropped (entry 4). However, the corresponding diastereoisomeric ligand **L16** displayed excellent reactivity, giving **3a** in 90% yield with 95% ee (entry 5). These results indicated that matching the planar chirality with the central chirality was crucial for the performance of the catalyst system. A ligand without the central chirality (**L17**, R = H) was also tested and found to afford **3a** in only 40% yield with 25% ee (entry 6). In a control experiment, we tested ligand **L18**, which has a methylated urea moiety; this ligand afforded none of the desired product (entry 7). We speculated that the hydrogen bonding not only improved chiral induction but also contributed to the catalyst's activity. A reaction involving (*S*)-UrPhos (**L19**), which does not have a ferrocene moiety, could catalyze the transformation, albeit with a lower yield and enantioselectivity (compare entries 5 and 8). However, replacement of the urea group in **L19** with a thiourea group (**L20**) resulted in no occurrence of cycloaddition reaction. This is probably because the strong coordination of sulfur atom to the Pd destroyed the hydrogen-bonding model.

Table 2. Investigation of FeUrPhos[a]



entry	Ligand	conversion (%)	yield (%)	dr	ee (%)
1	**L12**	100	67	>20:1	85
2	**L13**	100	70	>20:1	94
3	**L14**	90	46	>20:1	94
4	**L15**	50	19	>20:1	85
5	**L16**	100	90	>20:1	95
6	**L17**	60	40	>20:1	25
7	**L18**	<5	<5	n.d.	n.d.
8	**L19**	100	86	>20:1	90
9	**L20**	<5	<5	n.d.	n.d.



[a]For reaction conditions: **1a** (0.05 mmol), **2a** (2.0 equiv), $Pd_2(dba)_3 \cdot HCCl_3$ (5 mol %), chiral ligand (12 mol %), 1,4-dioxane (1.0 mL), 25 °C under argon. Yields and diastereomeric ratios (dr) were determined by ^1H NMR analysis of the crude product. The enantiomeric excess (ee) was determined by chiral HPLC on commercial columns. n.d., not determined.

Having identified the optimal ligand, we next explored the substrate scope of the (3 + 2) cycloaddition, beginning with reactions of VMCCs **1** bearing various R^1 groups (Table 3). A variety of aryl-substituted VMCCs underwent the cycloaddition reaction with **2a** to provide the corresponding products (**3a**−**3l**) in good yields (58−84%) with excellent stereoselectivities (90−96% ee ≥16:1 dr).[22] Electron-donating (Me, *t*Bu, Ph, MeO) and electron-withdrawing (F, Cl) substituents on the aryl ring were well tolerated. For a substrate with a Br substituted phenyl ring, the reaction was compatible, and the desired cycloaddition product **3g** was obtained 60% yield with 94% ee. No debromination was observed in this catalytic system. A naphthyl-substituted VMCC was a competent reaction partner, giving cyclopentanone product **3l** in 75% yield with 95% ee.

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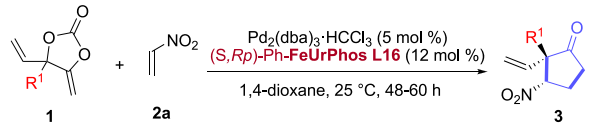
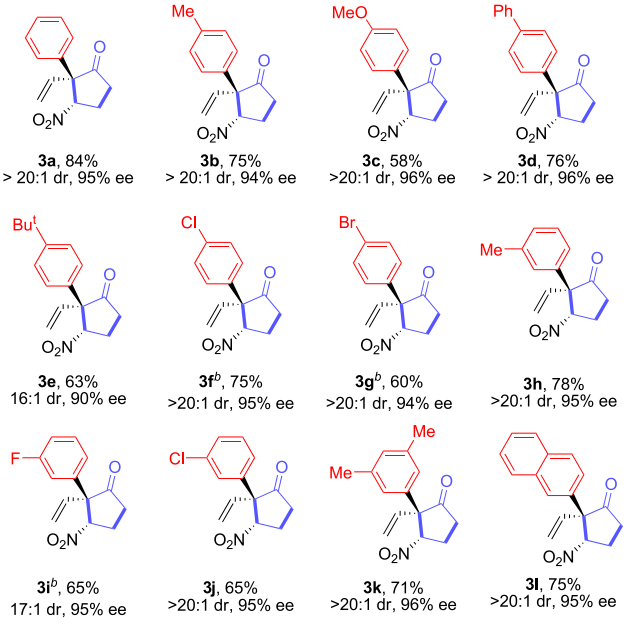
Table 3. Substrate Scope with Respect to the VMCCs[a]

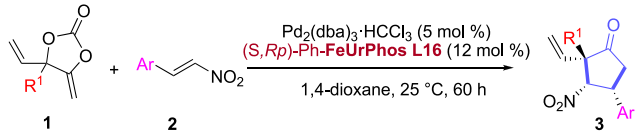


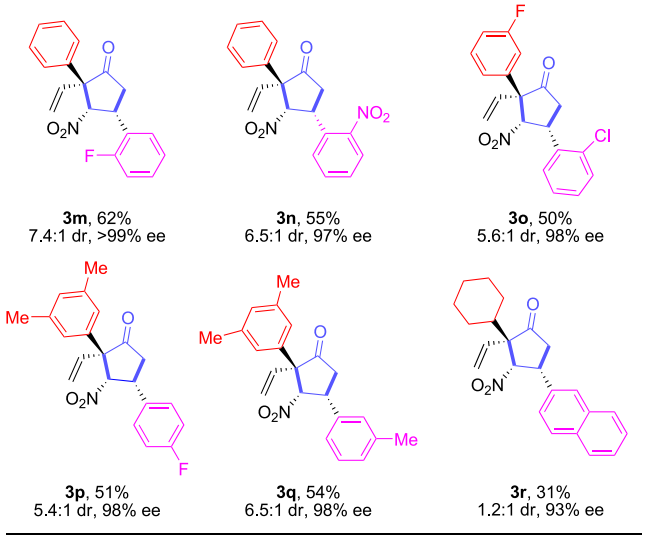


[a]See the SI for experimental details. [b]**L13** was used instead of **L16**.

We next investigated the scope of the reaction with respect to the nitroethylenes (Table 4). Various β-aryl nitroethylenes **2**

Table 4. (3 + 2) Cycloadditions with β-Substituted Nitroethylenes[a]



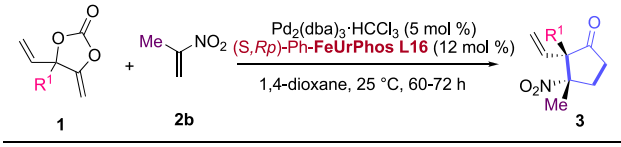


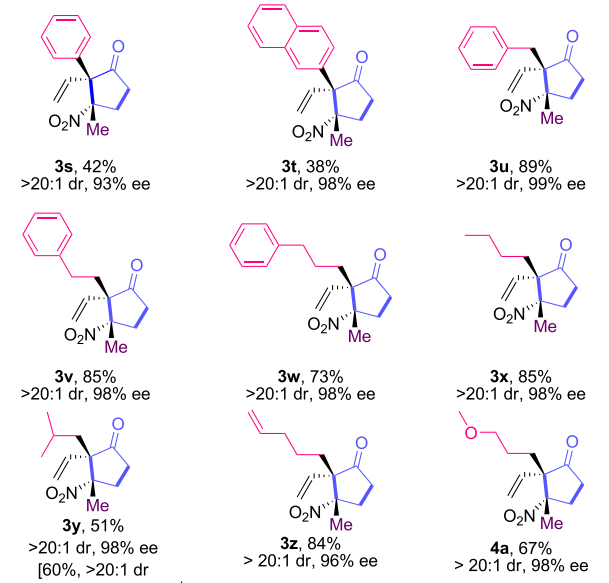
[a]See the SI for experimental details.

underwent the cycloaddition reaction under the standard conditions to afford cyclopentanones **3m**−**3r**, which have three contiguous stereocenters. Due to the possible epimerization of the nitro group, the diastereoselectivities for these products were only moderate, but the enantioselectivities were generally excellent (97−99% ee), except in the case of cyclohexyl substituted cyclopentanone **3r**.

Finally, we explored the use of this method for the stereoselective preparation of cyclopentanones with tertiary nitro group (Table 5). We found that (3 + 2) cycloaddition

Table 5. (3 + 2) Cycloadditions with α-Methyl Nitroethylene[a]





[a]See the SI for experimental details. [b]With $Pd_2(dba)_3CHCl_3$ (2.5 mol %), **L16** (6 mol %), and 1,4-dioxane (10 mL).

reactions of VMCCs with α-methyl nitroethylene smoothly gave $\alpha,\alpha,\beta,\beta$-tetrasubstituted cyclopentanones in moderate to good yields with excellent enantio- and diastereoselectivities. VMCCs containing phenyl (**3s**, **3t**), benzyl (**3u**), alkyl (**3v**−**3y**), terminal alkene (**3z**), and MeO ether moieties (**4a**) were well tolerated. Scaling the reaction up to 1 mmol scale with decreased 2.5 mol % catalyst loading did not affect the yield or stereoselectivity (**3y**). However, the reaction was highly sensitive to the steric bulk of the α-substituent of the nitroethylene. When α-ethyl nitroethylene was employed instead α-methyl nitroethylene, the reaction became sluggish, and only a trace of the desired product was observed under the standard conditions.

A proposed mechanism is given in Figure 5. Using the reaction of **1a** with **2a** as a model, the first step involves a Michael addition of intermediate **Int A** to nitroethene **2a**, which occurs via the transition state **TS B**. Given that the urea subunit usually forms a strong hydrogen bond with the nitro group, as noted in Jacobsen type catalytic process,[23] the

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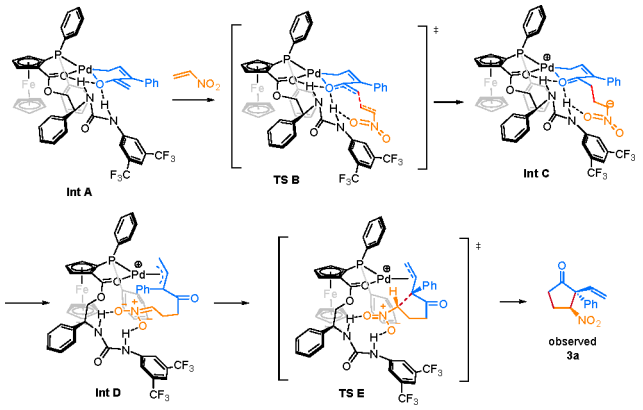

Figure 5. Proposed mechanism.

resulting **Int C** would be transformed to more a stable intermediate **Int D**, which contains urea-nitro hydrogen bonds and a η^3-allyl Pd. **Int D** undergoes rapid inner-sphere allylic substitution via **TS E** to furnish the final cycloaddition product **3a**. We speculated that the hydrogen bond in such a model might play a key role in controlling the stereochemistry.[24] A detailed mechanism study is currently ongoing in our lab.

3. CONCLUSION

In summary, we carried out proof-of-concept studies demonstrating that inverse electron demand cycloaddition reactions of Pd-oxyallyl can be achieved by employing VMCCs as precursors for vinyl-oxyallyl-Pd species. These reactions were accomplished with rationally designed hydrogen-bond-donating ligands, designated FeUrPhos. This method was used to realize the first enantioselective (3 + 2) cycloaddition reactions of Pd-oxyallyl with nitroalkenes. Cyclopentanones with up to three contiguous stereocenters were prepared with high enantioselectivity and good to excellent diastereoselectivity by means of this cycloaddition reaction. We envision that this methodology will not only open up new avenues to discover novel oxyallyl cation-related cycloaddition reactions but also inspire the utility of noncovalent interactions in asymmetric transition-metal catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11504.

X-ray crystallographic data for (2*R*,3*S*)-**3a** (CIF)
X-ray crystallographic data for (2*R*,3*S*,4*R*)-**3m** (CIF)
X-ray crystallographic data for (2*R*,3*S*)-**3s** (CIF)
X-ray crystallographic data for (2*S*,3*S*)-**3v** (CIF)
Experimental procedures for all reactions and characterization data for all products, including ^{1}H and ^{13}C NMR spectra, HPLC spectra, and crystal data (PDF)

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Notes

The authors declare no competing financial interest.

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