

Palladium-Catalyzed [3 + 2 + 2] Cycloaddition Between Carbonyl-Tethered Alkylidenecyclopropanes and Isocyanates

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Dedicated to Prof. Erick M. Carreira

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Carbonyl-tethered alkylidenecyclopropanes can react with aryl isocyanates in presence of Pd(0)-phosphoramidite catalysts to give seven-membered heterobicyclic products in a formal [3 + 2 + 2] cycloaddition process. The reaction involves the formation of a palladium π -allyl complex intermediate (**A**), which behaves as a formal 1,5-dipole, and can be trapped by externally added isocyanates. This report also includes preliminary assays of asymmetric variants, as well as DFT computational studies that shed some light on the nature of the catalytic cycle.

Keywords: alkylidenecyclopropane, palladium, cycloaddition, dipole, zwitterionic, phosphoramidite.

Introduction

Dipolar cycloadditions between 1,*n*-dipoles and unsaturated acceptors (dipolarophiles) have played an essential role in both classical and contemporaneous organic synthesis, enabling access to a wide variety of structurally diverse carbo- and heterocyclic scaffolds.^[1–3] These reactions originally employed canonical 1,3-dipoles such as azides, nitrones, carbonyl ylides or nitrile oxides, but have evolved to include newly designed 1,*n*-dipolar species. Especially attractive are those intermediates that are generated *in situ* from stable neutral precursors using transition metal catalysts.^[4–6]

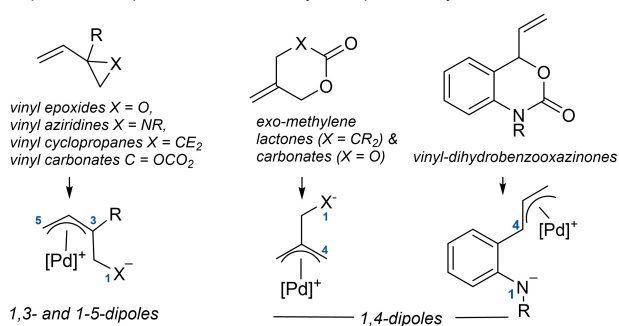
This is the case for zwitterionic species featuring π -allyl palladium complexes, which can behave as 1,*n*-dipoles in intermolecular cycloadditions with different unsaturated partners.^[7–9] This type of palladium intermediates can be generated from vinylcyclopro-

panes, epoxides, aziridines or carbonates, as well as from alkylidene lactones, among others (*Scheme 1a*); and can participate as 1,3- or 1,4-dipoles in formal [3 + *n*] and [4 + *n*] cycloadditions. The development of methods wherein this type of intermediate participates as 1,5-dipoles has clearly lagged behind, with some exceptions involving vinyl carbonate precursors.^[10–16]

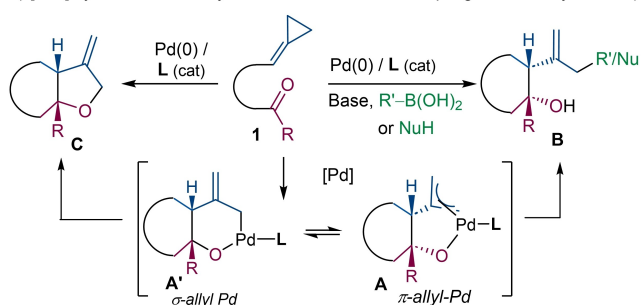
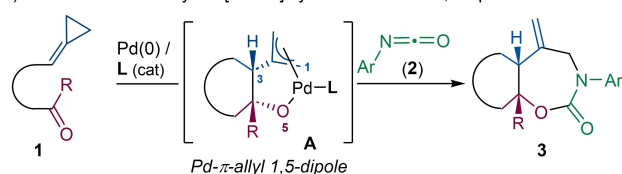
As part of our ongoing work on transition metal-catalyzed annulations of alkylidenecyclopropanes (ACPs),^[17–22] we have recently uncovered a palladium-catalyzed tandem cycloisomerization/cross-coupling reaction between carbonyl-tethered ACPs and external nucleophiles, such as boronic acids (*Scheme 1b*).^[23] Mechanistically, this process is proposed to proceed via a π -allyl oxapalladacyclic species of type **A**, which in the presence of a nucleophile, such as an organic boron reagent, undergoes a transmetalation/reductive elimination process to give the coupling product **B**.

In this context, we questioned whether these oxapalladacyclic species of type **A** could behave as Pd π -allyl 1,5-dipoles, and react with appropriate unsatu-

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a) Representative precursors of 1,*n*- π -allyl Pd dipoles for cycloaddition reactions


b) [3+2] cycloaddition and cycloisomerization/cross-couplings of carbonyl-ACPs (1)


 c) This work: Pd-catalyzed [3+2+2] cycloadditions via 1,5-dipoles **A**


Scheme 1. Pd- π -allyl dipoles (a), previous Pd-catalyzed reactions of carbonyl-tethered ACPs via species **A/A'** (b), and current work (c).

rated partners to give seven-membered cycles. The whole process could be formally considered as a [3+2+2] cycloaddition. However, implementing this cycloaddition concept is challenging because unlike most of the previously developed Pd- π -allyl dipoles, which are irreversibly generated by exclusion of CO₂ or by the opening of a strained ring, dipole species **A** as well as their σ -allyl isomeric counterpart **A'** might irreversibly cyclize to adducts of type **C** by reductive elimination.^[24] Moreover, these species could also potentially be trapped by external nucleophiles (Nu-H, e.g. alcohols) to give products like **B**.

Herein, we demonstrate the successful development of such formal [3+2+2] heterocycloadditions. Specifically, we show that a Pd catalyst, generated in situ from Pd₂(dba)₃ and a simple phosphoramidite ligand, is able to promote this type of annulation between ACP-tethered carbonyls of type **1** and aryl isocyanates (**2**), to provide 5,7 and 6,7 heterobicyclic

systems **3**, exhibiting a seven-membered cyclic carbamate moiety (Scheme 1c). Additionally, we provide DFT studies that support the participation of species **A**, and its preferred evolution via a migratory insertion of the isocyanate partner leading to the experimentally observed cycloadducts of type **3**.

Results and Discussion

We initiated our studies by analyzing the reactivity of the keto-ACP precursor **1a** with different partners, using Pd catalysts that had been shown effective in our previous cycloisomerization/cross-coupling tandem processes, made of Pd₂(dba)₃ and the electron-poor phosphine **L1**.^[23] Among all the partners tested (i.e. carbonyls, imines, carbonyl ylides, ketenes or isocyanates, among others; Table S1),^[25] the reaction with isocyanate **2a** was the only one affording the desired seven-membered cycloadduct, **3aa**, in a modest 14% yield, while acyclic diene **5a**, resulting from a non-productive ring opening of the ACP was also observed in 21% yield (Table 1, entry 1). The use of Ph₃P instead of **L1** provided similar results (entry 2), whereas Buchwald biaryl-phosphine ligands like ^tBuXPhos, which had been shown effective for the intramolecular [3+2] cycloadditions of carbonyl-tethered ACPs like **1a**,^[24] led to the five-membered adduct **4a** as major product, in a moderate 35% yield, with a 12% of the seven-membered ring (**3aa**, entry 3).

Further analysis of alternative electron deficient ligands led us to find that a simple phosphoramidite like **L3** allows to increase the efficiency and selectivity of the desired multicomponent annulation, which enabled the [3+2+2] adduct **3aa** to be exclusively obtained after just 3h at 100 °C (76% yield, entry 5). Remarkably, the product was obtained with complete *cis*-selectivity at the ring fusion. Under these conditions, performing the reaction in the absence of isocyanate **2a**, led to the intramolecular oxacycloadduct **4a**, in 67% yield. Finally, we also explored alternative solvents to 1,4-dioxane, finding out that using 1,2-dichloroethane, toluene or hexane, the reaction gives **3aa** in similar yields (entries 7–9).^[25]

With these optimal conditions in hand, we explored the scope of the reaction (Scheme 2). First, we evaluated different carbonyl tethered ACPs of type **1**, using isocyanate **2a** as model partner. The use of a precursor bearing a NTs group at the linker, instead of the diester moiety, led to the desired product **3ba** in a modest 36% yield. On the other hand, precursors with shorter linkers between the ACP and the methyl

Table 1. Optimization of a [3 + 2 + 2] cycloaddition between **1a** and **2a**.

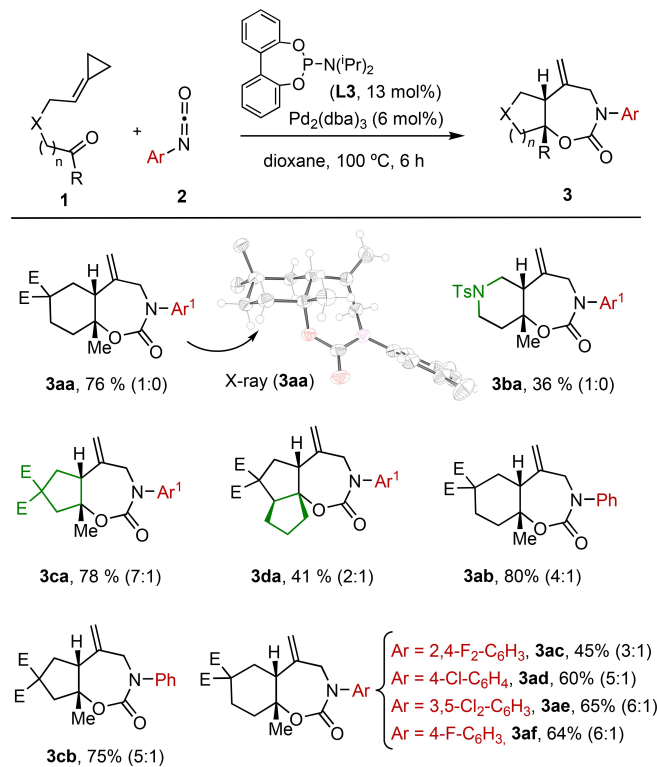
X = C(CO₂Me)₂
Ar = 3,5-(CF₃)₂C₆H₃

entry ^[a]	L	3aa (% yield) ^[b]	4a (% yield) ^[b]	5a (% yield) ^[b]
1	L1	14	–	21
2 ^[c]	PPh ₃	12	–	28
3	^t BuXPhos	12	35	–
4 ^[d]	L2	–	–	11
5	L3	76	–	–
6 ^[e]	L3	–	67	–
7 ^[f]	L3	75	–	–
8 ^[g]	L3	72	–	–
9 ^[h]	L3	80	–	–

[a] Conditions: **1a**, isocyanate (**2a**, 2 equiv), Pd₂(dba)₃ (6 mol%), ligand (**L**, 13 mol%), dry 1,4-dioxane (0.05 M) under Ar atmosphere at 100 °C. Full conversion unless otherwise noted. [b] Yields determined by NMR with an internal standard. [c] Conversion = 46%. [d] Conversion = 38%. [e] Carried out without isocyanate **2a**. [f] Carried out in 1,2-DCE. [g] Carried out in toluene. [h] Carried out in hexane.

ketone also reacted efficiently, so that the 5,7 bicyclic adduct **3ca** was obtained in a good 78% yield, in this case as a 7:1 mixture of *cis* : *trans* isomers at the ring fusion. We also tested the cycloaddition of a substrate bearing the ACP tethered to a cyclopentanone moiety through its α -carbonyl position (**1d**). Despite this precursor already holds a stereocenter, the reaction proceeded moderately well, delivering the tricyclic carbamate **3da** in 41% yield, as a 2:1 mixture of diastereoisomers.

Gratifyingly, the reaction is not limited to the use of 3,5-bistrifluoromethyl phenyl isocyanate (**2a**). The cycloaddition of phenyl isocyanate with ACP precursors **1a** and **1c** provided the corresponding bicyclic products (**3ab** and **3cb**) in 80 and 75% yields, respectively. Moreover, other aryl isocyanates bearing electron withdrawing substituents at the aromatic ring also participated in the process, affording the desired cycloadducts in good yields (**3ac–3af**, 45–65% yield).

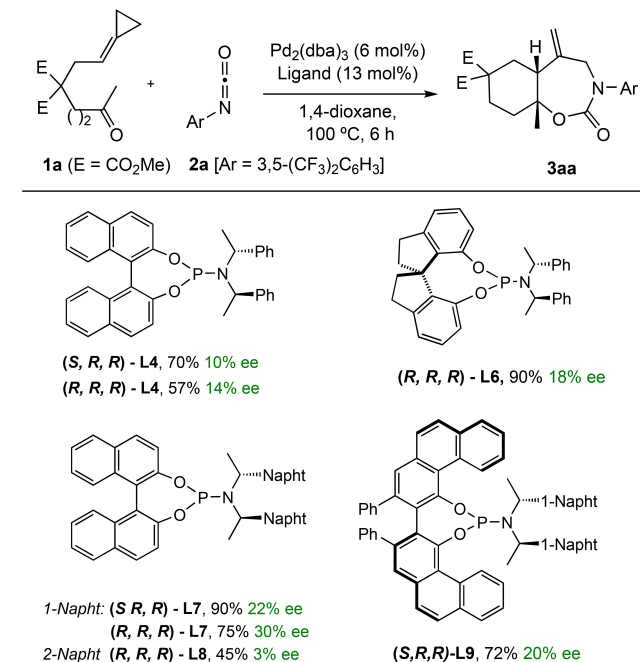


Scheme 2. Scope of the Pd-catalyzed cycloaddition. Ar¹ = 3,5-(CF₃)₂C₆H₃. Diastereoselectivities at the ring fusion are given in parenthesis.

Considering the effectiveness of phosphoramidites as ancillary ligands and their widespread use in enantioselective metal-catalyzed reactions, we conducted a preliminary assay of chiral phosphoramidites to assess their ability to induce asymmetry in the model reaction between **1a** and **2a** (Scheme 3). Notably, most of the ligands tested led to the desired reactivity, affording the formal [3 + 2 + 2] adduct **3aa** with moderate to good yields.^[25] Among them, the binol-derived phosphoramidite (*R,R,R*)-**L7** afforded the highest asymmetric induction, with a moderate ee of 30%. Although modest, this value preliminarily confirms the viability of the processes.

To shed a light on the mechanism of these cycloaddition processes, we performed a DFT computational study using ACP **1e** and isocyanate **2a** as model substrates, and a Pd(0) complex equipped with the phosphoramidite ligand **L3** as model reagent (Figure 1).^[25]

As previously calculated in the context of ACP cycloadditions and cycloisomerization reactions,^[23,24] an oxidative addition of the distal C–C bond of the ACP to the Pd(0) complex is the most accessible initial step, leading to the palladacyclobutane species **11**



Scheme 3. Preliminary tests of an asymmetric variant

through an energy barrier of 17 kcal/mol (Figure S7).^[25] Then, species **I1** might evolve via a

migratory insertion of the carbonyl unit, with an energy barrier of 20.8 kcal/mol (**TS1-2**), to afford the π -allyl oxapalladacycle **I2**. This type of intermediate species was previously located in the context of intramolecular [3 + 2] cycloadditions of carbonyl-tethered ACPs like **1e**.^[24] Although it might evolve via a reductive elimination toward the tetrahydrofuran cycloadduct **4e**, with an energy barrier of 12.6 kcal/mol (**T2-4e**), we found more accessible pathways from its more stable σ -allyl intermediate **I3**.^[26] This σ -allyl species might also yield the formal [3 + 2] cycloadduct, but through a substantial energy barrier of 23.1 kcal/mol (via **TS3-4e**). However, its interaction with the isocyanate moiety, leads to a more stable regioisomeric intermediate (**I3'**),^[27] from which two new favorable pathways were eventually located.

Thus, intermediate **I3'** easily evolves to a new species, **I3''**, which holds the nitrogen atom of the isocyanate close to the Pd center [d(N–Pd) = 2.7 Å]. Then, an oxygen attack to the central carbon of the isocyanate unit (**TS3''-4**) leads to the oxazapalladacyclic intermediate **I4**, with an overall energy barrier of 6.5 kcal/mol from **I3'**. All attempts to find a C–N reductive elimination from **I4** were unsuccessful; however, this step became feasible from the isomeric

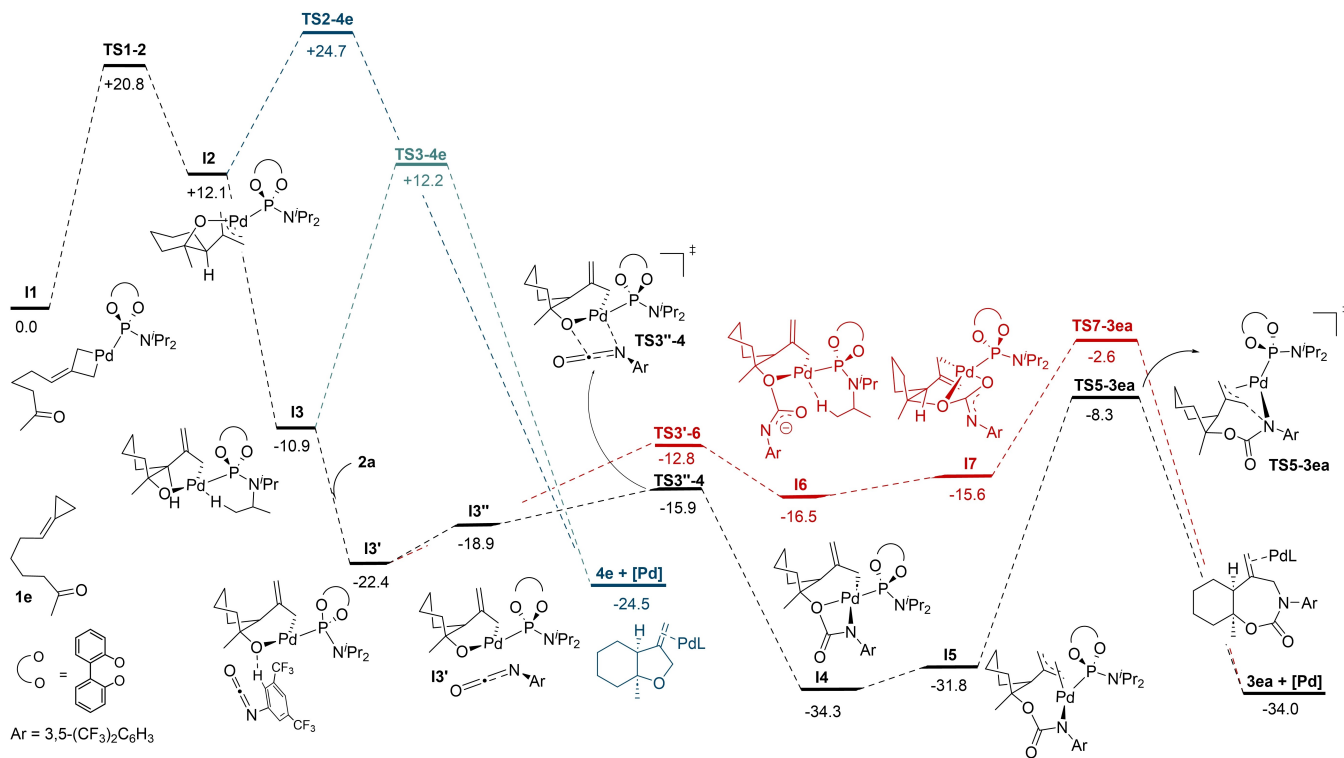


Figure 1. DFT-calculated energy profile ΔG_{solv} (kcal/mol) for the [3 + 2 + 2] cycloaddition of **1e** and **2a** using Pd(0)-**L3** as catalyst in 1,4-dioxane, with [B3LYP/6-31G(d) (LANL2DZ for Pd)//B3LYP-GD3/6-311 + + g(d,p) (SDD for Pd)].

π -allyl azapalladacycle **15**, which lies 2.5 kcal/mol above **14**. This reductive elimination, which occurs via an energy barrier of 23.5 kcal/mol, releases the experimentally observed bicyclic carbamate (**3ea**), which keeps the Pd(0)-phosphoramidite complex coordinated to the exocyclic C–C double bond. This energy gap is in accordance with the heating requirements of the reaction, and suggests that this is the turnover limiting step of the overall process.

We also found an alternative migratory insertion of the isocyanate moiety on intermediate **13'**, to yield the σ -allyl oxapalladacyclic intermediate **16**. However, this insertion, via **TS3'-6**, entails a significantly higher energy barrier ($\Delta\Delta G=3.1$ kcal/mol), and the resulting intermediate, **16**, is substantially less stable than **14** ($\Delta\Delta G=17.8$ kcal/mol). Moreover, its evolution toward the final product, although feasible, also occurs via a more energetic path (via **TS7-3ea**). Therefore, the pathway via **TS5-3ea** is generally favored.

The absence of the [3+2] cycloadduct **4e** under the reaction conditions can be explained by the easier evolution of intermediate **12** to the σ -allyl complexes of type **13**, and the favored migratory insertions of isocyanate, compared to the C–O reductive eliminations (**TS3-4e**).^[28] Notably, prior calculations using biaryl Buchwald ligands (e.g. ^tBuXPhos) showed that this type of ligands favor the formation of five-membered cycloadduct **4** due to subtle hemilabile interactions between the Pd center and specific atoms of the ligand.^[24] Our new results confirm that with **L3** this pathway is less favored, enabling the new route towards the desired seven-membered adduct.

Conclusions

We have uncovered a formal Pd-catalyzed [3+2+2] intermolecular cycloaddition between carbonyl-tethered alkylidenecyclopropanes of type **1** and aryl isocyanates, to give a variety of interesting bicyclic heterocycles featuring seven-membered rings. The process, which is promoted by a Pd(0) catalyst featuring a phosphoramidite ligand, involves the generation of a palladium π -allyl species (**A**) that behaves as a formal 1,5-dipole. Key for the success of the tandem reaction over competitive intramolecular [3+2] annulations is the use of phosphoramidite ancillary ligands. Preliminary results suggest the viability of performing enantioselective variants. These results open new avenues for building relatively complex polyheterocycles from simple precursors.

Experimental Section

General Procedure for the Pd(0)-Catalyzed [3+2+2] Cycloaddition Reaction

In a dry sealed tube, Pd₂(dba)₃ (5.5 mg, 6.0 μ mol, 6 mol%), phosphoramidite **L3** (4.1 mg, 13 μ mol, 13 mol%) and carbonyl-ACP **1a** (26.8 mg, 100 μ mol, 1.0 equiv) were dissolved in dry 1,4-dioxane (2 mL). Then, the aryl isocyanate **2a** (34.6 μ L, 200 μ mol, 2.0 equiv) was added with a micropipette, and the resulting mixture was stirred and heated at 100 °C for 6 h. Upon completion, the milieu was cooled down to room temperature, filtered over Florisil[®], concentrated and purified by flash chromatography (25–40% Et₂O/Hexane) to afford (5*aR*,9*aR*)-3-(3,5-bis(trifluoromethyl)phenyl)-9*a*-methyl-5-methylene-2-oxooctahydrobenzo[*f*][1,3]oxazepine-7,7(6*H*)-dicarboxylate (**3aa**) as a colourless solid (39.8 mg, 76 μ mol, 76% yield).

Supporting Information

Full experimental procedures, optimization of the catalyst and characterization of all new compounds, including ¹H-, ¹³C-NMR spectra. The authors have cited additional references within the Supporting Information.^[29–43]

Author Contribution Statement

F. L., J. L. M. and R. R. conceived and designed the experiments, wrote the manuscript and revised the data. R.R performed the experiments, and analyzed the data.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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- [26] This isomerization between **12** and **13** has been simplified in Figure 1, as it is almost barrierless ($\Delta G = 2.3$ kcal/mol). See the Supporting Information, Figure S8, for the complete energy profile.
- [27] Intermediates **13'** and **13''** mainly differ on the orientation of the isocyanate with respect to the O–Pd bond.
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