Anti-Selective Cyclopropanation of Non-Conjugated Alkenes with Diverse Pronucleophiles via Directed Nucleopalladation

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ABSTRACT: A facile approach to densely functionalized cyclopropanes is described. The reaction proceeds under mild conditions via the directed nucleopalladation of non-conjugated alkenes with readily available pronucleophiles and gives excellent yields and good *anti*-selectivity using I_2 and TBHP as oxidants. Pronucleophiles bearing a diverse collection electron-withdrawing groups, including–CN, $–CO_2R$, –COR, $–SO_2Ph$, -CONHR and $–NO_2$, are well tolerated. Internal alkenes, which are generally challenging substrates in other cyclopropanation methods, provide excellent yields and good diastereoselectivity in this methodology, allowing for controlled access to cyclopropanes substituted at all three C-atoms.

Cyclopropanes are versatile synthetic intermediates and valuable targets in natural products and pharmaceuticals [1,2]. This is due to their unique features, such as conformational rigidity, high ring strain, enhanced π-character of bonding electrons, and unusually strong C–H bonds [3]. Among the most reliable and frequently used synthetic methods to prepare cyclopropanes is the [2+1] addition of various carbenoid equivalents to alkenes (Figure 1A). In the Simmons–Smith reaction, organozinc carbenoids are used to access alkyl-substituted cyclopropanes,[4] whereas ambiphilic substrates are involved in the Michael initiated ring closure (MIRC) where a Michael acceptor and a nucleophile bearing a leaving group are combined. In the latter case, sulfur, phosphorus, arsenium, and telluronium ylides, as well as α-halo carbanions, have all been used as effective coupling partners [5]. More recent methods for constructing cyclopropane units containing electron-withdrawing groups involves alkene cyclopropanations with diazo compounds [6] or iodonium ylides [7]. However, the requirement for hazardous reagents and additional steps to prepare the carbenoid precursor generally limit the applicability of the methodology [8]. An attractive step- and atom-economic strategy to cyclopropanation is the direct coupling of olefins with simple methylene compounds (either via direct engagement or in situ activation). This would obviate the need to prepare and handle carbenoid precursors. However, such methodologies remain generally underdeveloped [10].

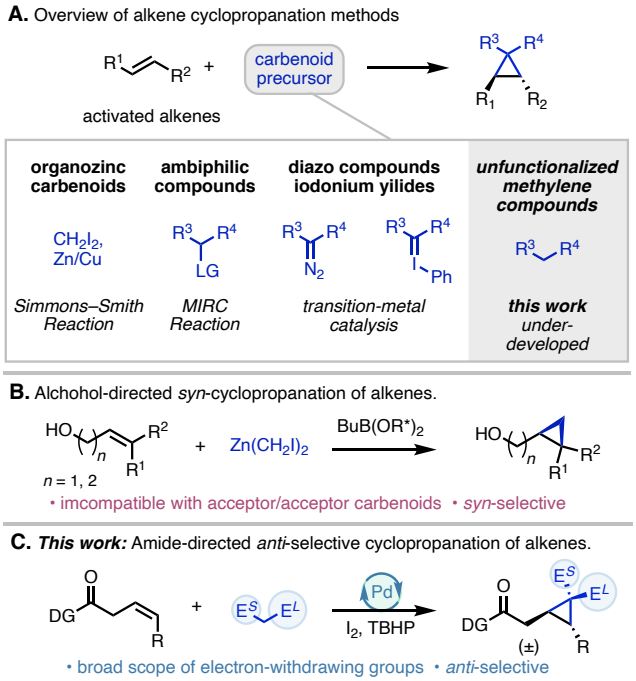


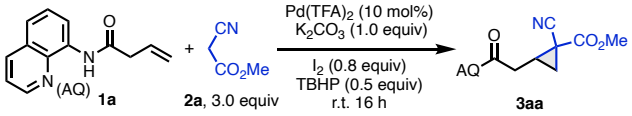
Figure 1. Background and project summary.

Cyclopropanation of internal alkenes is an appealing approach as it generates multiple stereocenters in a single

operation. However, many of the reported cyclopropanation methods are limited in alkene scope, and few methods tolerate non-symmetric, 1,2-dialkyl alkenes [9]. In seminal work, Charette and coworkers demonstrated an enantioselective alcohol-directed Simmons–Smith-type cyclopropanation of non-conjugated alkenes providing high levels of *syn*-selectivity [11] (Figure 1B). Herein, we report an *anti*-selective cyclopropanation method of non-conjugated alkenyl amides with common 1,3-dicarbonyls and other related pronucleophiles (Figure 1C). An 8-aminoquinoline (AQ) auxiliary [12–16] directs carbopalladation, allowing the transformation to proceed under mild reaction conditions with I_2 and TBHP as terminal oxidants. The desired products are obtained in excellent yields with good *anti*-selectivity. Both *(Z)*- and *(E)*-internal alkenes are well tolerated, giving access to cyclopropanes substituted at all three C-atoms in a stereo-controlled fashion.

We began optimization with AQ-containing alkenyl amide **1a** as the model alkene and methyl cyanoacetate (**2a**) as the nucleophilic coupling partner (Table 1). Initial control experiments revealed that the reaction did not proceed under previously reported conditions for metal-free cyclopropanation with malononitrile and non-conjugated alkenes (entry 2, see Supporting Information for details) [9c–e]. Evaluation of key variables led to identification of optimal reaction conditions using catalytic $Pd(TFA)_2$ (10 mol%), K_2CO_3 (1.0 equiv) as the base, and I_2 (0.8 equiv) with TBHP (0.5 equiv) as the co-oxidants. The reaction proceeds at room temperature with excess coupling partner **2a** (3.0 equiv) as the solvent (neat) (entry 1). Under these conditions, the desired cyclopropane **3aa** was formed in 97% yield with 77:23 diastereoselectivity. Using I_2 as the sole oxidant afforded the product in excellent yield, albeit with lower diastereoselectivity (entry 3–4), whereas, TBHP or $PhI(OAc)_2$ as the oxidant was insufficient in the transformation (entry 5–6). TBHP likely serves to regenerate I_2 from iodide, thereby maintaining constant I_2 concentration throughout the course of the reaction. Given that other potential coupling partners of interest are solids at room temperature (see below), we also performed a brief investigation of compatible solvents. With reduced loading of **2a** (1.5 equiv) in 1,2-DCE or HFIP (1.0 M), the desired product was obtained in 92% yield (57:43 *dr*) and 89% yield (66:34 *dr*), respectively (entries 7 and 8). The palladium catalyst and the base are crucial to achieve the desired reactivity, as omitting these from the reaction gave low conversion (entries 9–10). Finally, we attempted a low-temperature experiment, and we were delighted to observe full conversion even at 0 ºC after 3 days; in this case, diastereoselectivity improved to 83:17 *dr* (entry 11).

Table 1. Optimization of reaction conditions.



entry	deviation from above	recovered **1a**	yield of **3aa**[a]
1	**(none)**	**0%**	**97%, 77:23 *dr*[b]**
2	metal-free methods (Refs. 9c–e)	70–100%	<5%
3	I_2 (1.0 equiv) as oxidant	9%	90%, 70:30 *dr*
4	I_2 (1.5 equiv) as oxidant	5%	95%, 58:42 *dr*
5	TBHP (2.0 equiv) as oxidant	92%	<5%
6	$PhI(OAc)_2$ (2.0 equiv) as oxidant	32%	<10%
7	**[Nu] (1.5 equiv) + 1,2-DCE (1.0 M)**	**0%**	**92%, 57:43 *dr***
8	[Nu] (1.5 equiv) + HFIP (1.0 M)	0%	89%, 66:34 *dr*
9	no $Pd(TFA)_2$	>95%	<5%
10	no base	64%	<10%
11	**0 °C, 68 h**	**0%**	**98%, 83:17**

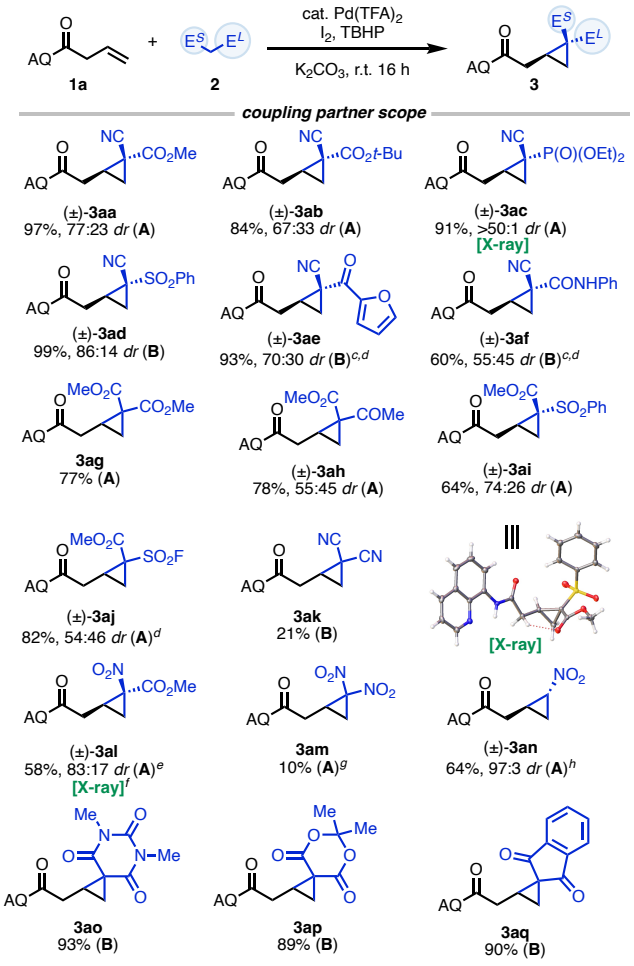
[a] **1a** (0.5 mmol), **2** (3.0 equiv), $Pd(TFA)_2$ (10 mol%), K_2CO_3 (1.0 equiv), I_2 (0.8 equiv), TBHP (70% in water, 0.5 equiv), neat, r.t., 16 h. ^1H NMR yield using $Cl_2CHCHCl_2$ as the internal standard. [b] Isolated yield.

The scope of nucleophilic coupling partners was evaluated using the two conditions, method A (3.0 equiv **2**, neat) for coupling partners that are liquid at room temperature and method B (1.5 equiv **2**, 1,2-DCE (1.0 M)) for coupling partners that are solids at room temperature (Table 2). First, we evaluated the cyano-containing methylene compounds as nucleophiles. Cyanoacetates were well tolerated, giving 97% yield and 77:23 *dr* and 84% yield and 67:33 *dr* for methyl (**3aa**) and *tert*-butyl ester (**3ab**), respectively. The cyanomethyl-phosphonate provided an excellent yield (91%) of the desired product **3ac** as a single diastereomer. An X-ray structure established that the larger $–P(O)(OEt)_2$ group was oriented opposite to the directing group on the cyclopropane ring. Similarly, using the bulky electron-withdrawing group, $–SO_2Ph$, funished the cyclopropane product **3ad** in excellent yield (99%) and high diastereoselectivity (86:14). A furan-containing oxopropanenitrile was compatible with the reaction conditions providing **3ae** in a 93% yield with 70:30 *dr*, while the cyano-phenylacetamide coupling partner furnished product **3af** with lower yield (60%) and *dr* (55:45). Next, ester-bearing methylene nucleophiles were evaluated as coupling partners. Both β-diester (**3ag**) and β-ketoester (**3ah**) coupling partners provided good yields of the corresponding cyclopropane products. Phenylsulfonyl ester nucleophilic coupling partner gave the cyclopropane as a 74:26 *dr* mixture in 64% yield (**3ai**). Separation of the two diastereomers and characterization of the major product by X-ray crystallography revealed that the $–SO_2Ph$ and the directing group are oriented *trans* to one another. A fluorosulfonyl substituted cyclopropane **3aj** was obtained in 82% yield and 54:46 *dr*. Malononitrile gave 21% yield (**3ak**). Methylene nucleophiles with nitro-group were next investigated. Methyl nitroacetate gave the desired product **3al** in a 58% yield, 83:17 *dr*, and a dinitromethane afforded 10 % yield of dinitrocyclopropane **3am**. The monosubstituted coupling partner, nitromethane, gave the desired product **3an** in 64% yield with 97:3 *dr*. We then examined cyclic coupling partners. Meldrum's acid, which is a synthetically useful building block, furnished product **3ao** in 93% yield. Barbituric acid reacted efficiently, furnishing **3ap** in 89% yield, and finally, 1,3-indanedione, which does not undergo keto-enol

tautomerization as readily as other 1,3-diketones [17,18], was well tolerated and gave a 90% yield (**3aq**).

Generally, this transformation can be broadly applied, however, some limitations still persist. First, trifluoromethyl-containing compounds **2r**–**t** were incompatible. Second, $MeNO_2$ was the only singly activated nucleophile that was amenable to the method; similar nucleophiles, such as $MeSO_2F$ (**2u**) and $EtNO_2$ (**2v**), did not lead to the desired products. (For a comprehensive list of unsuccessful examples, see the Supplementary Information). In these unsuccessful trials, unreacted alkene starting material was recovered. Thus, a plausible explanations for the lack of reactivity could be that the pronucleophiles are not within the appropriate pK_a range or are too sterically encumbered.

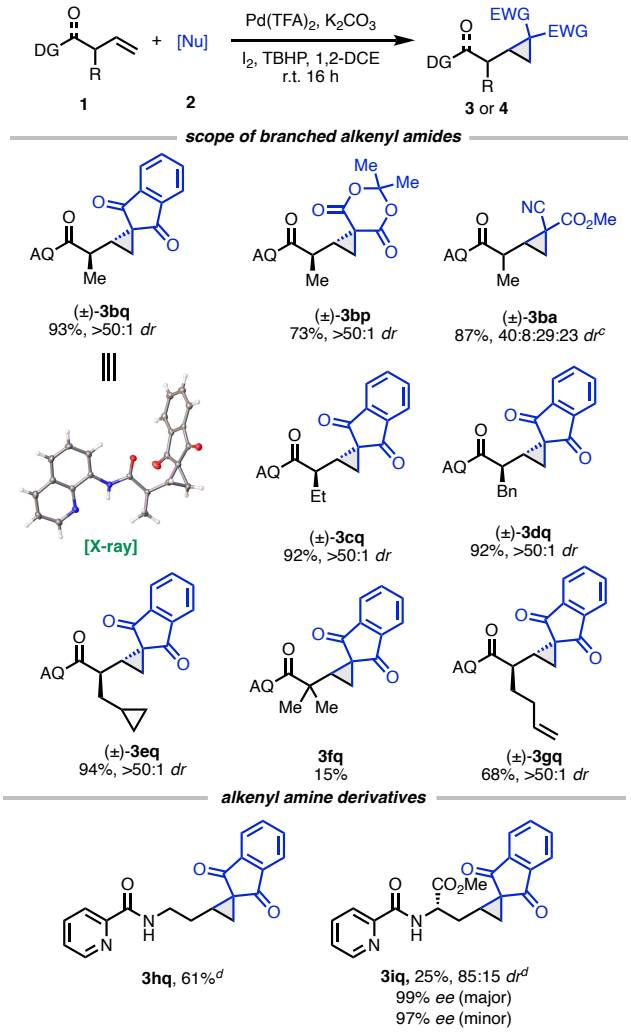
Table 2. Scope of coupling partners.[a,b]



[a] Method **A**: **1a** (0.5 mmol), **2** (3.0 equiv), $Pd(TFA)_2$ (10 mol%), K_2CO_3 (1.0 equiv), I_2 (0.8 equiv), TBHP (70% in water, 0.5 equiv), neat, r.t., 16 h. Method **B**: **1a** (0.5 mmol), **2** (1.5 equiv), $Pd(TFA)_2$ (10 mol%), K_2CO_3 (1.0 equiv), I_2 (0.8 equiv), TBHP (70% in water, 0.5 equiv), 1,2-DCE (1.0 M), r.t., 16 h. [b] Isolated yield. n.r. = no reaction. [c] 0.1 mmol scale. [d] **2** (1.0 equiv). [e] **2** (7.0 equiv). [f] X-ray crystal structure of a derivative. [g] HFIP (3.3 M). [h] HFIP (5.0 M).

Next, the scope of α-substituted β,γ-unsaturated amide substrates was investigated (Table 3). To our delight, an α-methyl-substituent was tolerated, affording the desired cyclopropanes as a single diastereomer in good to excellent yield of **3bq** or **3bp** from 1,3-indanedione or Meldrum's acid, respectively. An X-ray crystal structure confirmed that the cyclopropanation is highly diastereoselective in forming the new β-C–C bond *trans* with respect to the α-methyl. Changing the coupling partner to a cyanoacetate, however, led to a mixture of all four diastereomers (**3ba**) in 87% overall yield. By With 1,3-indanedione as the nucloephile, a series of larger α-substitutes were evaluated, gaving excellent yields of a single diastereomer (**3cq**, **3dq**, and **3eq**). An α,α-*gem*-dimethyl substituted β,γ-unsaturated amide delivered product in 15% yield (**3fq**). To show the chemoselectivity that arises from substrate directivity, a diene substrate was tested and underwent cyclopropanation exclusively at the β,γ-alkene, leaving the δ,ε-alkene untouched (**3gq**).

Table 3. Scope of α-substituted β,γ-unsaturated amides.[a,b]

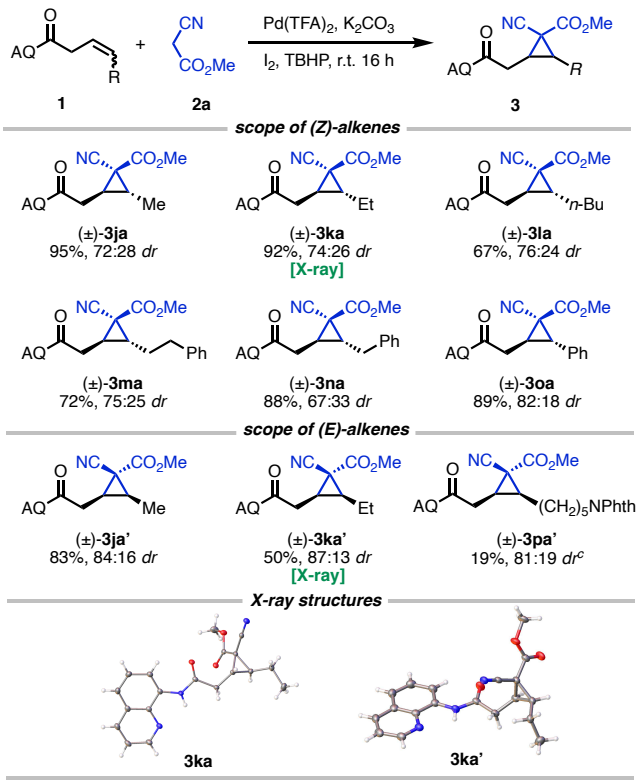


[a] **1a** (0.2 mmol), **2** (1.5 equiv), $Pd(TFA)_2$ (10 mol%), K_2CO_3 (1.0 equiv), I_2 (0.8 equiv), TBHP (70% in water, 0.5 equiv), 1,2-DCE (1.0 M), r.t., 16 h. [b] Isolated yield. [c] **1a** (0.2 mmol), **2** (3.0 equiv), $Pd(TFA)_2$ (10 mol%), K_2CO_3 (1.0 equiv), I_2 (0.8 equiv), TBHP (70% in water, 0.5 equiv), neat, r.t., 16 h. [d] $Pd(TFA)_2$ (20 mol%)

Switching the directing group to a 2-picolinyl amide (PA) allowed access to a structurally distrinct class of cyclopropyl amine products. The combination of 1,3-indanedione and a PA-bearing homoallyl amine derivative yielded **3hq** in 61% yield using 20 mol% $Pd(TFA)_2$. Similarly, an enantioenriched

allylglycine derivative provided **4iq** in a 25% yield with 85:15 *dr* with the preservation of the original stereocenter.

Table 4. Scope of internal alkenes.[a,b]



[a] **1** (0.2 mmol), **2a** (3.0 equiv), $Pd(TFA)_2$ (20 mol%), K_2CO_3 (1.0 equiv), I_2 (0.8 equiv), TBHP (70% in water, 0.5 equiv), neat, r.t., 16 h. [b] Isolated yield. [c] **2** (6.0 equiv)

We then turned our attention to internal alkenes (Table 4). Among various nucleophiles tested, methyl cyanoacetate (**2a**) was found to perform best with internal alkenes. The catalyst loading was increased to 20 mol% $Pd(TFA)_2$ to ensure full conversion (for details, see SI). Under these conditions the cyclopropanation of (*Z*)-alkenes proceeded efficiently with good diastereoselectivity. Notably, only two diastereomers among the four possible were detected. With small groups, such as methyl and ethyl, the corresponding products **3ja** and **3ka**, respectively, were isolated in excellent yields. Substrates containing more sterically demanding groups (**3la**, **3ma**, and **3na**) or styrenyl alkenes (**3oa**), gave slightly diminished yields (67–89%). Stereochemical assignments by X-ray crystallography and NOESY showed that the major product from *Z*-alkenes is in *trans*-configuration arising from net *anti*-addition of the nucleophile, with the larger ester group oriented on the same face as the directing group and opposite to the terminal alkyl/aryl group.

Although (*E*)-alkenes react slower in the nucleopalladation than (*Z*)-alkenes [19], these substrates still underwent cyclopropanation. The product **3ja'** with a methyl group was isolated in an 83% yield with 84:16 *dr*, whereas with an ethyl group, a 1:1 mixture of starting material and product was observed, leading to only 50% yield of **3ka'** with 87:13 *dr*. With an (*E*)-alkene bearing a longer aliphatic chain, in this case $(CH_2)_5NPhth$, the yield drastically decreased to 19% (**3pa'**). In products derived from (*E*)-alkenes, the directing group and the terminal alkyl group are oriented on the same face of the cyclopropane, with *anti*-selectivity confirmed by both X-ray cryallography and NOESY.

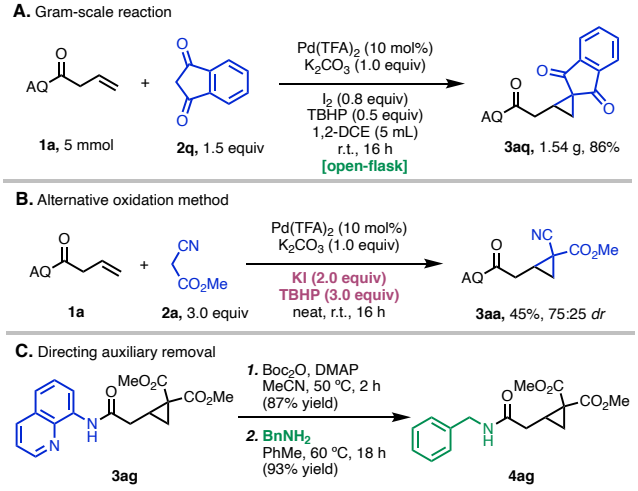


Figure 2. Scale-up, alternative methods, AQ removal

The methodology could conveniently be scaled-up without exclusion of air or moisture, providing gram quantities of cyclopropane **3aq** in 86% yield (Figure 2A). Next, to provide an alternative to I_2, we developed a method that uses KI as the iodine source and demonstrated that preparatively useful yields could still be obtained (Figure 2B). We found that the cyclopropanes prepared from this method are prone to ring opening under many commonly used conditions for AQ deprotection, including the mild Morimoto–Ohshima alcoholysis method [20]. After brief optimization (for details, see SI), we identified mild conditions employing catalytic DMAP to introduce an *N*-Boc-activating group in 87% yield (Figure 2C). From here, the *N*-Boc-AQ group could be cleanly substituted by a representative amine nucleophile in 93% yield [21].

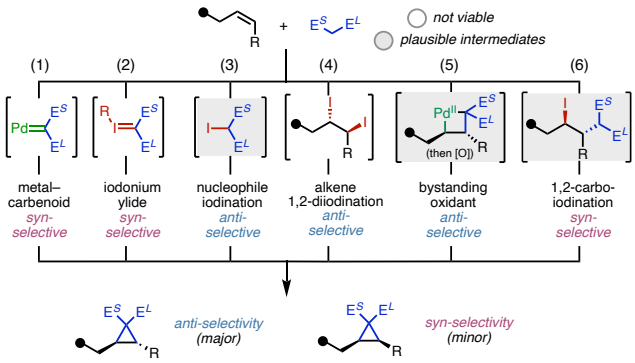


Figure 3. Potential Pathways.

The broad scope, mild conditions, and unusual selectivity of this cyclopropanation method prompted us to investigate the reaction mechanism. At the outset, the observation of both *anti*- and *syn*-addition products with internal alkenes without detectable *E*/*Z* isomerization of the starting material [16] suggested that more than one mechanism may be operative. We

considered six potential pathways for this transformation distinguished by their key intermediates and the expected net stereochemical outcome, namely (1) a palladium–carbenoid mechanism (*syn*), (2) an iodonium ylide mechanism (*syn*), (3) formation of α-iodinated nucleophile capable of engaging in carbopalladation followed by intramolecular Pd(II)/Pd(IV) oxidation addition (*anti*), (4) formation of a 1,2-diiodoalkane via diiodination of the alkene, which can then undergo successive S_N2 additions (*anti*), (5) generation of a alkylpalladium(IV) intermediate formed via carbopalladation followed by I_2-induced Pd(II)/Pd(IV) oxidation and subsequent C–C reductive elimination (*anti*), and (6) Pd(II)/Pd(IV)-catalyzed 1,2-carboiodination followed by intramolecular S_N2 cyclization (*syn*) (Figure 3).

To distinguish among these possibilities, we performed a series of experiments. Treatment of the alkene with a pre-formed iodonium ylide did not lead to cyclopropanation under the standard reaction conditions in the presence or absence of metal, ruling out pathways (1) and (2) (for details, see SI). In situ monitoring of the reaction to form product **3ag** in toluene revealed formation of the α-iodinated nucleophile **2g–I** and 1,2-carboiodinated adduct **5ag** [21], along with expected π-alkene complex **A** (Figure 4A) [22]. Compound **2g-I** was generated rapidly during the first few minutes of the reaction and then was consumed. The fact that the nucleophile is iodinated in preference to the alkene rules out pathway (4). For comparison, the same experiment was performed in the absence of alkene **1a**; in this case **2g-I** is also formed but is further converted to α,α-diiondated compound **2g-I$_2$** (see SI). The rate of consumption of **2g-I** is accelerated in the presence of alkene, consistent with its involvement in formation of cyclopropanated product **3ag**. Independently prepared **2g-I** and **5ag** both converted into product upon subjection to the standard conditions, establishing that they are both competent intermediates (Figures 4B and 4C). While pathway (5) cannot be rigorously excluded at this time, the data in Figure 4 and the stereochemical outcomes can be rationalized by a scenario in which mechanism (3) is the major pathway and mechanism (5) is a minor pathway.

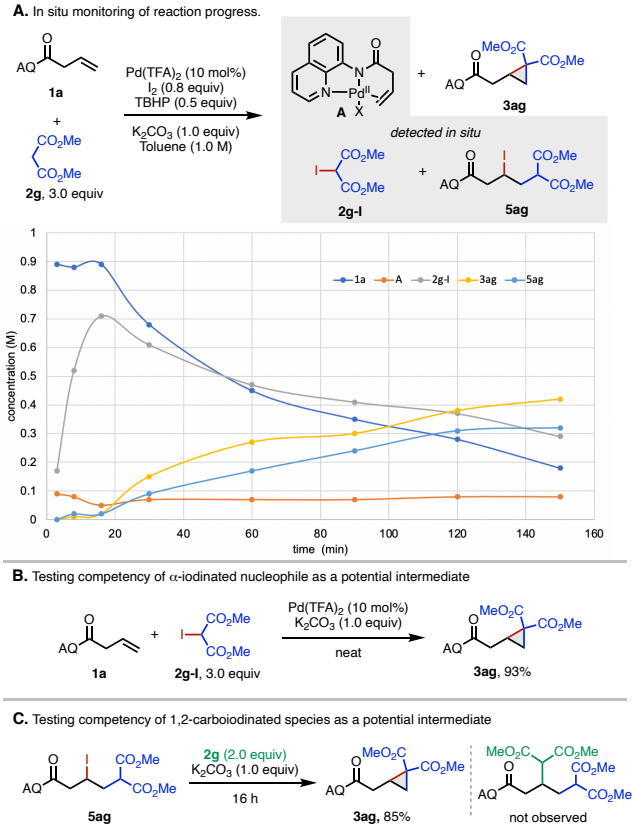


Figure 4. Mechanistic studies.

In conclusion, we have developed a highly selective and versatile Pd(II)/Pd(IV)-catlayzed cyclopropanation of non-conjugated alkenes with C–H pronucleophiles that proceeds via directed nucleopalladation. This method tolerates a diverse collection of readily available pronucleophiles containing different electron-withdrawing groups and is effective with α-substituted alkenyl carbonyl substrates as well as challenging internal alkenes, granting stereocontrolled access to densely functionalized cyclopropane products.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

CCDC 2169362, 2173775, 2167770, 2170564, 2173776, and 2237213 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. /

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ABBREVIATIONS

CCR2, CC chemokine receptor 2; CCL2, CC chemokine ligand 2; CCR5, CC chemokine receptor 5; TLC, thin layer chromatography.

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