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Access to Cyclopropyl-Fused Azacycles via a Palladium-Catalyzed Direct Alkenylation Strategy

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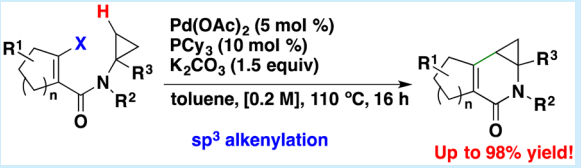
Supporting Information

ABSTRACT: Palladium-catalyzed direct alkenylation of cyclopropyl C−H bonds proceeds in high efficiency. This transformation provides access to novel cyclopropyl-fused azacycles. Ligand studies suggest that bisphosphine monoxide analogues of dppf and *rac*-BINAP are the active ligand species. Preliminary results support that both BozPhos and IPrMonophos ligands can achieve high enantioinduction for this novel direct alkenylation reaction. To date, this represents the first example of enantioselective C−H functionalization employing a bisphosphine monoxide ligand.

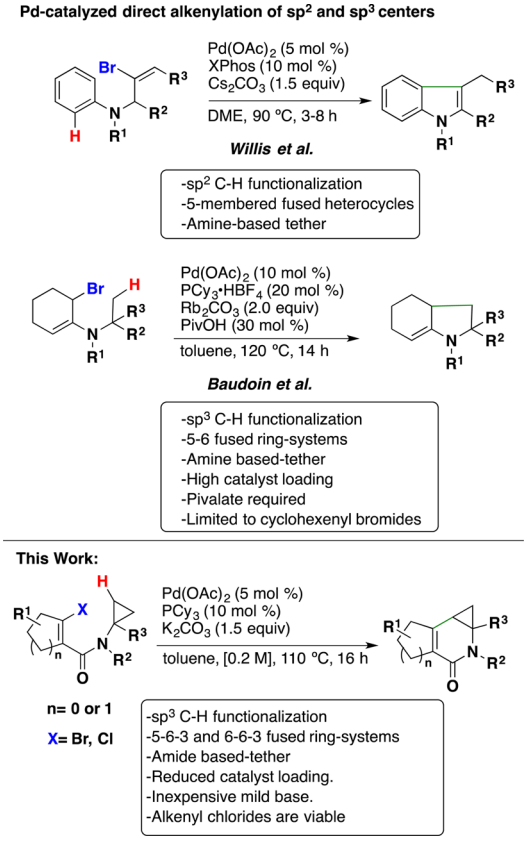


As a promising synthetic tool, direct functionalization offers an alternative to traditional cross-coupling and other environmentally hazardous classical methods.[1] In spite of significant advances within this field, research interests have been concentrated on developing direct arylation strategies to access unsaturated systems.[2] Increasing the number of sp^3 centers within drug candidates can improve metabolic stability, allow access to a more diverse chemical space, and reduce target promiscuity.[3] Despite industrial motivations to build more complex three-dimensional architectures, the synthetic tools required for efficient parallel synthesis of nonaromatic ring systems remain limited. More recently, there has been a push toward addressing this knowledge deficiency. For example, based on the pioneering contributions by Fujii and Ohno, Baudoin and Willis developed Pd-catalyzed direct alkenylation protocols employing amine-based tethers (Scheme 1).[4]

Cyclopropane incorporation has contributed to accessing a portfolio of pharmacologically diverse compounds, including eight of the top 200 FDA-approved best-selling drugs.[5] Such successful applications of the cyclopropyl ring-system continue to drive efforts toward designing more efficient and novel synthetic pathways. Previously, we and others have shown that both inter- and intramolecular direct arylation can generate highly functionalized cyclopropyl scaffolds.[6,7] Building on this foundation, we postulated that a direct alkenylation strategy could provide access to a novel class of cyclopropyl-fused azacycles possessing an internal alkene motif (Scheme 1).

Herein, we disclose a novel palladium-catalyzed, intramolecular cyclopropyl direct alkenylation that proceeds under mild conditions employing an inexpensive base, providing access to both 5−6−3 and 6−6−3 fused heterocyclic ring systems. Additionally, we disclose a rare example of asymmetric intramolecular C−H alkenylation employing IPrMonophos. Finally, we provide preliminary evidence that bisphosphine monoxide ligands, such as BozPhos, can be employed in asymmetric C−H functionalization reactions.

Scheme 1. Pd-Catalyzed Direct Alkenylation of sp^2 and sp^3 Centers Employing *N*-Based Tether Systems



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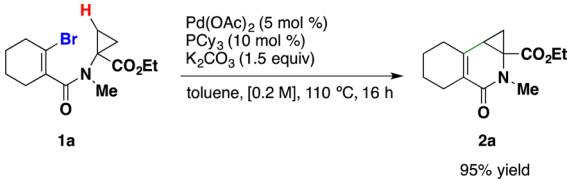
Based on our previous successes involving an amide tether, we chose 2-bromocyclohexenyl amide **1a** as our starting substrate. Cyclization produced saturated cyclopropyl-fused azacycle **2a** in excellent yield using reduced amounts of catalyst, ligand, and base (Scheme 2).

Scheme 2. Initial Discovery of Cyclopropyl Direct Alkenylation



To further understand this transformation, we performed a full optimization (see Supporting Information). The addition of pivalic acid did not significantly improve yields, and silver additives inhibited reactivity. Various Pd(II) and Pd(0) sources could also be employed; however, $Pd(OAc)_2$ provided the best conversion, indicative of the important role of acetate in promoting reactivity.[8] Bases that varied in strength and in metal cation were also screened. For example, weak bases, such as K_3PO_4 and KOAc, were ineffective as were organic bases, such as DIPEA and DBU. Strong bases, such as KO*t*Bu, caused protodebromination and decomposition of starting material. In terms of metal carbonates, K_2CO_3 was superior compared to its Cs and Rb analogues, while Na_2CO_3 was ineffective. A range of solvents were also well tolerated. During the ligand screen, some interesting observations were revealed. Steric limitations were observed as $PtBu_3{\cdot}HBF_4$ was ineffective. In particular, bidentate phosphines, such as dppf and *rac*-BINAP, were viable ligands.[9]

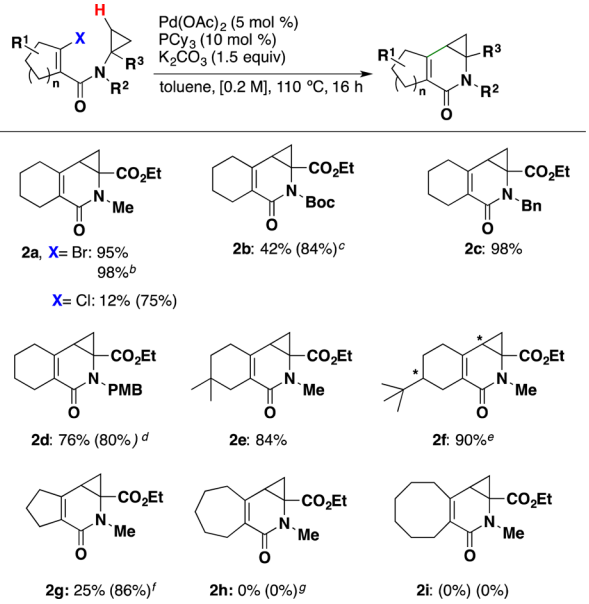
We then explored the reaction scope (Scheme 3). For yields <80%, we also ran the reaction with pivalate for comparison. The chloro analogue **1ab** was also viable, albeit pivalate was required. Other *N*-protecting groups were also employed. Despite previous difficulties, Boc-protected product **2b** formed efficiently with pivalate. Both benzyl and PMB also exhibited excellent reactivity (**2c**–**2d**). *gem*-Dimethyl and *tert*-butyl substituton afforded cyclized products in good yield (**2e**–**2f**). We also tested different ring sizes. Much to our delight, the cyclopentyl derivative **2g** gave excellent conversion with pivalate. Notably, cycloheptyl and cyclooctyl derivatives **2h**–**2i** failed to cyclize.[10] Additionally, substrates **2a**, **2b**, **2d**, and **2g** could also be scaled.

We also explored the effect of α-substitution (Scheme 4). The cyano group (**2k**) impeded reactivity, and free carboxylic acid **2l** also failed to cyclize.[11] Similar to previous reports,[12] without α-substitution, ring opening occurred, providing access to **2m**.[13] Additionally, we observed no reaction with other related sp^3 systems indicative of the orthogonal reactivity of the cyclopropyl moiety under the optimized reaction conditions (see Supporting Information). We are currently developing complementary conditions to target these noncyclopropyl sp^3 systems.

It was also possible to cleave Boc and PMB groups to access free NH-product **3** (Scheme 5).

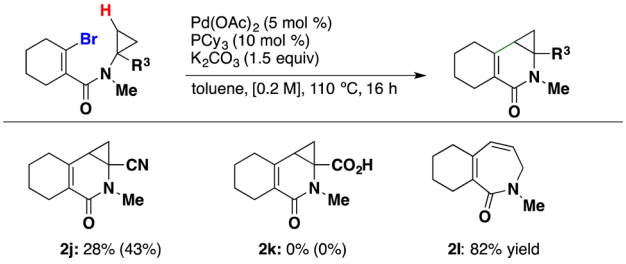
Cognizant of recent studies by Blackmond and the Merck Process Group on Pd[14] and previous work by our group involving Cu,[15] we were curious to discover if dppf and *rac*-BINAP[16] were being oxidized *in situ* to their monophosphine oxide analogues and if these ligands were in actuality the active component for our reaction. Notably, in the presence of Pd(0) sources, no reactivity was observed, even with the addition of dba and pivalic acid additives (Table 1).[17] These preliminary experiments suggest that dppf(O) and BINAP(O) can function as active ligands for this reaction.

Scheme 3. Reaction Scope for Intramolecular Cyclopropyl Direct Alkenylation[a]



[a]Unless otherwise stated, X = Br. Reactions were performed on 0.2 mmol scale. Yields with 30 mol % PivOH given in parentheses. [b]1.0 mmol scale. [c]0.72 mmol scale. [d]1.9 mmol scale. [e]Isolated as a mixture of inseparable diastereomers. [f]1.2 mmol scale. [g]88% starting material recovered.

Scheme 4. Effect of α-Substitution[a]



[a]Reactions were performed on 0.2 mmol scale. Yields with 30 mol % PivOH given in parentheses.

Scheme 5. Deprotection of Boc and PMB Groups

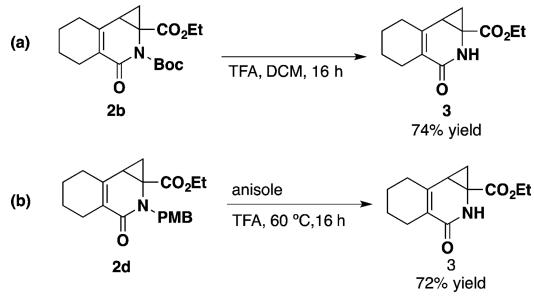


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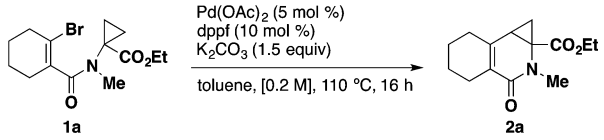
Table 1. Ligand Studies with dppf



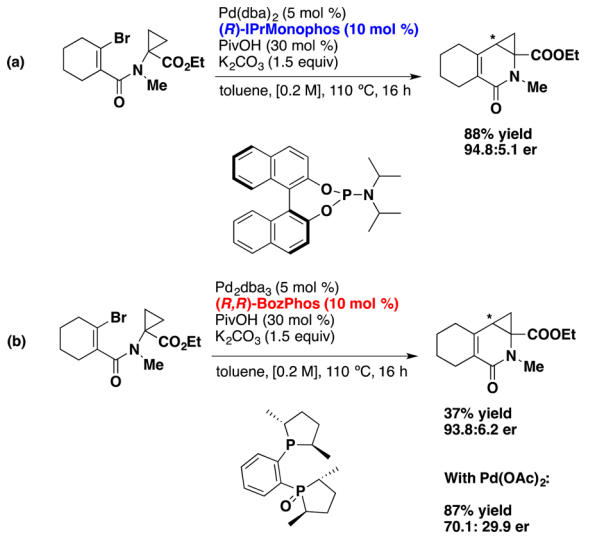
entry	variation from standard conditions[a]	yield (%)[b]
1	none	85
2	with 10 mol % dba	73
3	$Pd(dba)_2$ instead of $Pd(OAc)_2$	<20
4	$Pd(dba)_2$ instead of $Pd(OAc)_2$, with 30 mol % PivOH	<20

[a]Reactions were performed on 0.2 mmol scale. [b]Determined via ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Within the field of asymmetric catalysis, several classes of privileged ligands have been applied to direct functionalization processes. Some of these ligands include amino acid derivatives,[18] TADDOL-phosphoramidates,[19] NHC-based ligands,[20] and BINEPINE-based ligands.[21] In light of our ligand screen, we hypothesized that hemilabile chiral bisphosphine monoxide ligands might be suitable in our system to induce enantioselectivity, thus adding to the toolbox of chiral ligands for C−H functionalization.[22]

The Cramer group has previously shown success in applying Feringa-based TADDOL-phosphoramidites toward enantioselective arylation and alkylation of cyclopropyl and related sp^3 centers.[23] In parallel with these observations, we also discovered that Feringa-based BINOL phosphoramidite (IPrMonophos)[24] could provide excellent enantioselectivity (Scheme 6). Notably, this is a rare example of asymmetric

Scheme 6. Preliminary Conditions for Enantioselective Direct Alkenylation Employing (a) IPrMonophos, (b) BozPhos



direct alkenylation with high enantioinduction. We were equally delighted to discover that BozPhos, a ligand discovered in our group, could access **2a** with excellent enantioselectivity, albeit only modest reactivity. Notably, when $Pd(OAc)_2$ was employed, reactivity was improved, but with diminished enantioselectivity.[25]

Both IPrMonophos and BozPhos have yet to be explored in asymmetric C−H functionalization processes. We are currently investigating and optimizing both of these asymmetric reactions and will provide a full report in due course.

In conclusion, we have developed a rare example of Pd-catalyzed, intramolecular cyclopropyl direct alkenylation, providing access to novel saturated azacycles. Ligand studies revealed that bisphosphine monoxide ligands could function as active ligands. Cognizant of this observation, we reported examples of enantioselective direct alkenylation employing both IPrMonophos and BozPhos. Notably, this is the first example of enantioselective C−H functionalization employing a chiral bisphosphine monoxide ligand and demonstrates the potential for other ligands of this nature to be exploited in related C−H functionalization processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02982.

Optimization tables, experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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