

Palladium–Catalyzed Direct Cyclopropylation of Heterocycles

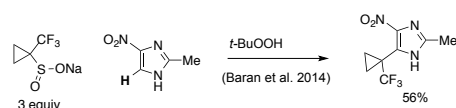
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Cyclopropane rings are present in many bioactive natural products and synthetic compounds.^[1] They also exist in medicines including an antibacterial agent Ciprofloxacin, an antidepressant Milnacipran and Lumacaftor, a drug for the treatment of cystic fibrosis. As useful pharmacophores, cyclopropyl rings have several unique properties. The rings are small and rigid while ring substituents have very specific orientations in space. They have high built-in strains, which can induce ring opening under proper conditions. In the past decades, many stereoselective reactions have been invented to access substituted cyclopropanes.^[2] Among them, [2+1] cycloadditions of olefins and stabilized diazo compounds, which used various metal catalysts such as Rh,^[3] Cu,^[4] and Co,^[5] are the most extensively studied and developed. In recent years, zinc carbenoids^[6] and sulfur ylides^[7] were also successfully utilized as carbene precursors in these cycloadditions. However, in [2+1] cycloadditions and other stereoselective reactions,^[8] heteroaryl rings were rarely incorporated onto cyclopropyl rings through C–C bond connection.

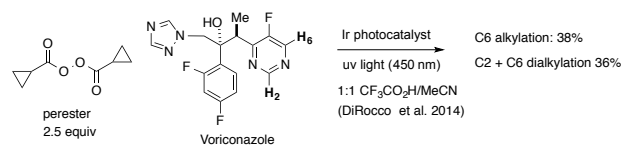
alkylation in the types of heterocycles and preferred sites of alkylation. So far, 1,3-azoles^[10] and those carrying directing groups^[11] are commonly utilized. Alkylations of other types of heterocycles are rather limited.^[12] Recently, we disclosed a general method for alkylation of many families of heteroarenes.^[13] In these cases, palladium catalysts reacted with common alkyl halides to give alkyl radicals, which added directly to heteroarenes. Good selectivity was observed favoring conjugate sites to electron-withdrawing groups on the rings. However, few examples of metal-catalyzed cyclopropylation of heterocycles have been reported.^[14]

Recently, two examples of radical alkylation of heteroarenes^[15] were disclosed. Baran *et al.* used cyclopropylsulfinate salts, which carried an α -trifluoromethyl group, to produce cyclopropyl radicals (Scheme 1a).^[16] In another example, DiRocco *et al.*^[17] employed dicyclopropyl perester for alkylation of electron-poor azacycles under photocatalytic conditions,^[18] but the regioselectivity was an issue (Scheme 1b).

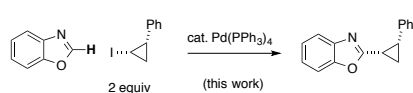
a) Baran's method using cyclopropylsulfonates



b) photocatalytic cyclopropylation



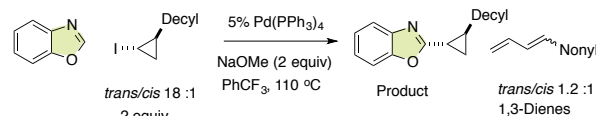
c) Pd-catalyzed stereoretentive cyclopropylation



Scheme 1. Recent examples of cyclopropylation of heterocycles.

In recent years, metal-catalyzed alkylation of heteroarenes have emerged as useful methods,^[9] which are distinct from Friedel–Crafts

Table 1. Change from the optimized condition in a model coupling (Calibrated GC yield of the product from 0.1 mmol of benzoxazole. GC conversion of cyclopropyl iodide and GC yield of its diene byproducts are based on maximal 200%).



Entry	Change of conditions	Conv of RI (%)	Product yield (%)	Trans/cis ratio of product	Dienes Yield (%)
1	No change	200	96	26:1	52
2	Dppf	200	75	24:1	74
3	dppp	164	94	24:1	32
4	Xantphos	163	72	19:1	61
5	BINAP	190	87	25:1	70
6	NaOH	200	45	22:1	65
7	KOH	200	9	20:1	106
8	KOMe	188	82	22:1	50
9	K ₃ PO ₄	127	0	--	98
10	Cs ₂ CO ₃	200	8	20:1	146
11	LiOt-Bu	184	62	27:1	8
12	Et ₃ N	20	0	--	12

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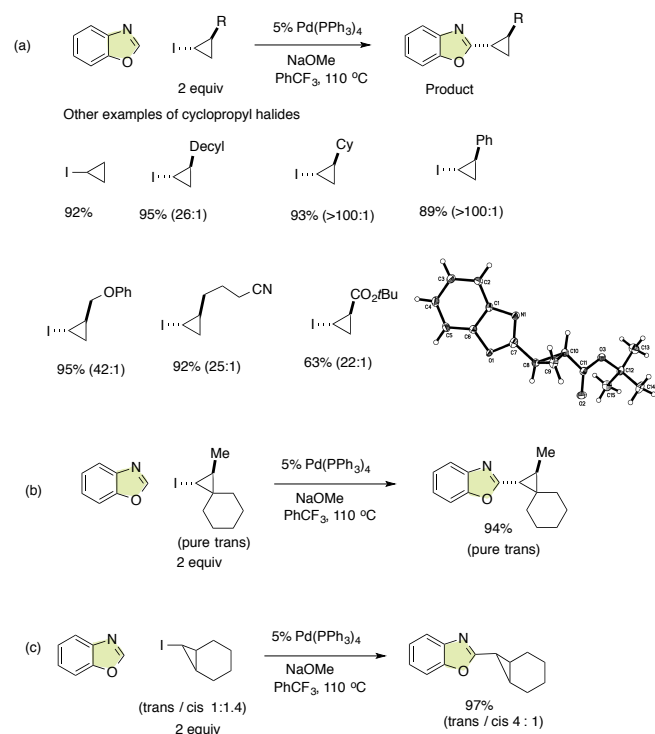
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13	Toluene	193	96	19:1	72
14	Dioxane	200	84	19:1	84

Initially, we attempted a model reaction between *trans*-2-decylcyclopropyl iodide and 1,3-benzoxazole.^[19] The *trans*-cyclopropyl iodide was easily prepared from 1-dodecene, iodoform and CrCl₂ using Takai's procedure.^[20] We found that a simple catalyst Pd(PPh₃)₄ promoted the desired reaction in good yield and high *trans*-selectivity (Table 1, entry 1). When 7 mol% of bisphosphines were added, e.g., dppp, dppf, BINAP and XantPhos, only negative impact was seen except that dppp gave 94% yield (entries 2–5). The choice of bases was also important (entries 6–12). 2 equiv of NaOMe was the optimal base for the model reaction. When it was replaced with KOH and Cs₂CO₃, for example, a significant amount of diene byproducts (entry 7 and 10). Et₃N inhibited the coupling process (entry 12). The desired coupling proceeded efficiently in other solvents, e.g., toluene and dioxane (entries 13–14).

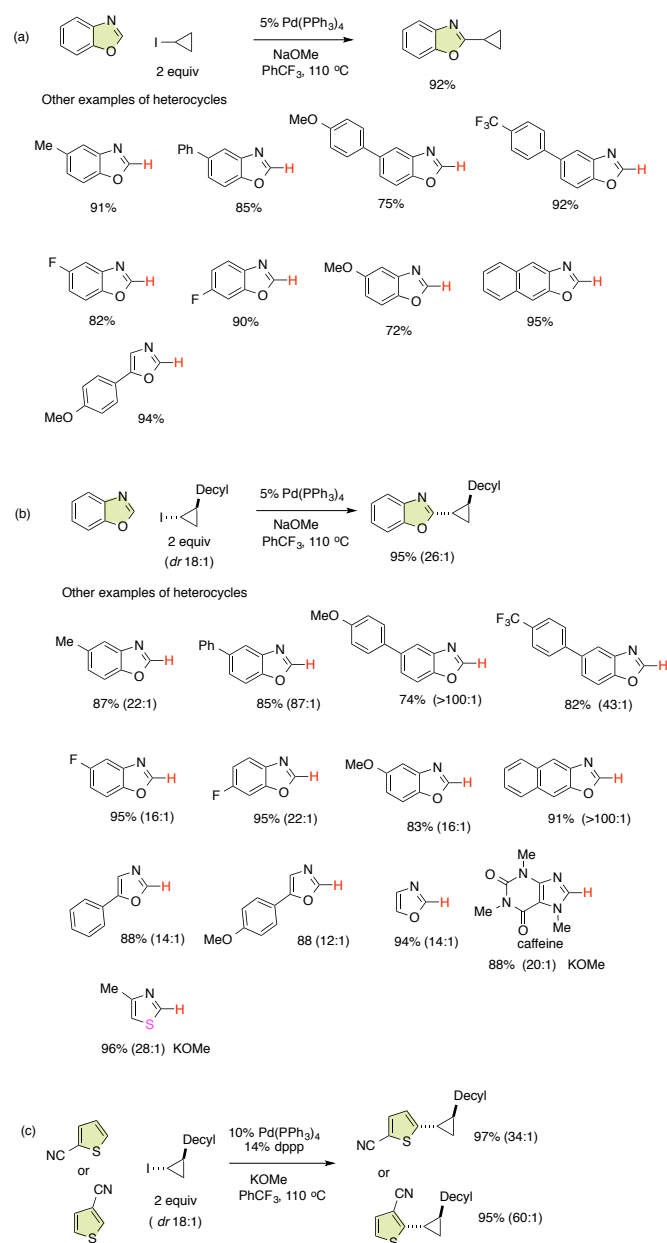
Notably, we identified a previously unknown side reaction from cyclopropyl halides. It underwent an HI-elimination/ring opening to give a mixture of *trans*- and *cis*-1,3-dienes (Table 1). In a control experiment, NaOMe alone did not cause this elimination. Thus, both the base and palladium catalyst were needed to effect this side reaction.

In terms of the scope of cyclopropyl iodides, various aryl and alkyl groups can be present on the ring (Scheme 2a). We noticed that a bulky *t*-butyl group on cyclopropane inhibited the coupling process. Polar functional groups such as ethers, nitriles and esters were well tolerated. A product containing a *t*-butyl ester group was crystalline and it allowed us to unambiguously assign the *trans* configuration in the product. A hindered spiro-cyclopropyl halide reacted efficiently and its *trans* configuration was retained in the product (Scheme 2b). When a 1.4:1 mixture of *cis*- and *trans*-isomers of bicyclo[4.1.0]hept-2-yl iodide was subjected to the coupling conditions, the *trans* product was the major product (Scheme 2c). Cyclopropyl bromides gave very low yields under similar conditions.



Scheme 2. Examples of cyclopropyl iodides in couplings with 1,3-benzoxazole (isolated yields from 0.3 mmol of benzoxazole). The ratio in parentheses refers to *trans/cis* selectivity of products. ORTEP of a product in *trans* configuration is shown with 50% thermal ellipsoid probability.^[32]

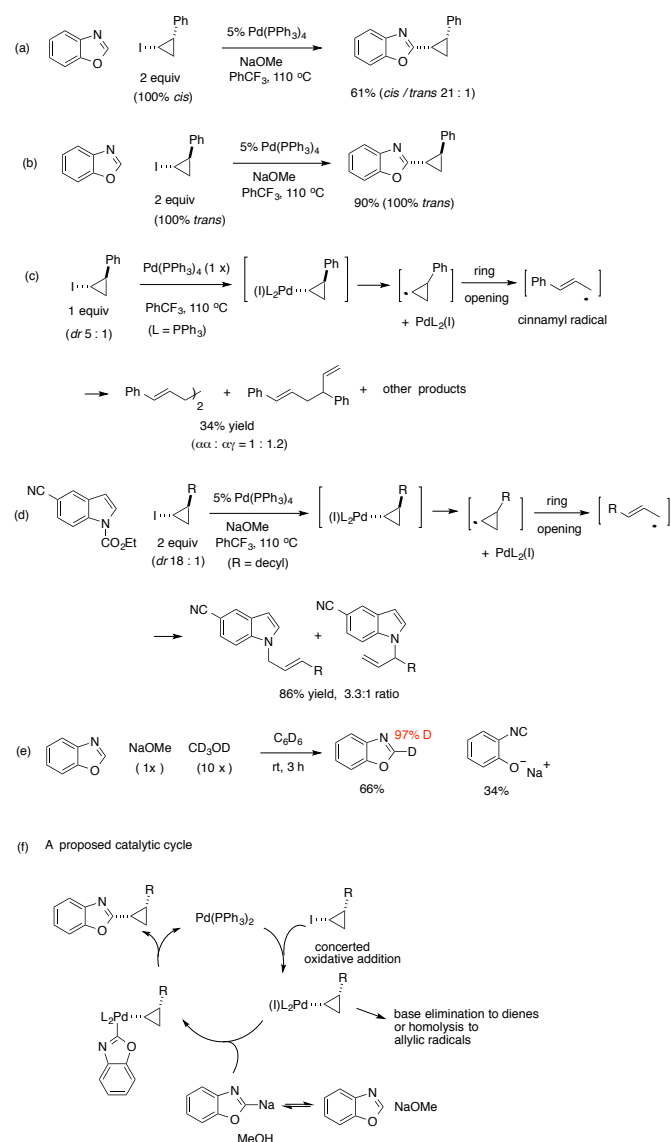
Next, we used the parent cyclopropyl iodide and an *n*-decyl derivative to evaluate the scope of heterocycles. Many 1,3-benzoxazoles and 1,3-oxazoles coupled smoothly, as well as caffeine and a thiazole (Scheme 3a and 3b). Furthermore, two thiophenes carrying electron-withdrawing groups also gave desired products in satisfactory yields (Scheme 3c). It should be pointed out that both 1,3-azoles and thiophenes have relatively acidic CH bonds. Their pK_a values are below 30 in DMSO, which have mechanistic implications.^[21]



Scheme 3. Examples of unsaturated heterocycles in cyclopropylation (isolated yields from 0.3 mmol of a heterocycle). The ratio in parentheses refers to the *trans/cis* ratio of products.

With regard to reaction mechanism, we initially suspected that the Pd(0) catalyst reacted with cyclopropyl iodides via single electron transfer to generate a cyclopropyl radical, which then added

onto heteroarenes directly, in a similar way as alkylation of common alkyl halides.^[13] However, cyclopropyl radicals are special σ -radicals.^[22] They are known to be much less nucleophilic than cyclohexyl radical in addition to electron-poor heteroarenes.^[23]



Scheme 4. Mechanistic studies and a catalytic cycle of cyclopropylation

Surprisingly, when we tested geometrically pure *cis*-2-phenylcyclopropyl iodide in a coupling with benzoxazole, the *cis* product was detected as the major product (Scheme 4a). In comparison, the *trans* organic halide led to a pure *trans* product (Scheme 4b). This argues strongly against the radical pathway. Substituted cyclopropyl radicals are known to undergo rapid inversion with a very low barrier of 3–4 kcal/mol.^[24]

Next, we attempted to isolate an oxidative adduct of *trans*-2-phenylcyclopropyl iodide and Pd(PPh₃)₄ (Scheme 4c). No reaction occurred at 50 °C. At 110 °C, a complex mixture resulted without a major signal on a ³¹P NMR spectrum. In the resulting reaction mixture, cinnamyl dimers were formed in 34% yield (with a maximal value of 100%). In addition, the 1:1.2 ratio of $\alpha\alpha$ and $\alpha\gamma$ cinnamyl dimers is characteristic of dimerization of cinnamyl radicals.^[25] Other conceivable organic products such as phenylcyclopropane, phenylcyclopropene, allylbenzene and

β -methylstyrene were not detected. When TEMPO was added in the reaction at 110 °C, no trapped byproduct was identified.^[26]

When we tried to couple another heterocycle, an *N*-carbamoyl indole, no cyclopropylation was seen at C-3 or C-2 position of the indole. Instead, two isomers of *N*-allylation were isolated in good yields (Scheme 4d). The nitrile group on the indole was unimportant, since a similar result was obtained if it was changed to a methoxy group. We propose that after oxidative addition, the C–Pd bond undergoes homolysis to give a cyclopropyl radical, which then ring-opens to yield an allylic radical.^[27] The indole loses its carbamoyl group by the action of NaOMe and then it traps the allylic radical to afford *N*-allylation. An alternative pathway involving external attack of an indole on π -allylpalladium complexes is less likely. It would have led to C3-allylation at more nucleophilic site of indole.^[28]

We wondered how a CH bond of benzoxazole was cleaved under the reaction condition. When benzoxazole was stirred with NaOMe and 10 equivalents of *d*₄-methanol, it underwent facile H/D exchange at room temperature via reversible deprotonation.^[29] The H/D exchange process was accompanied by partial ring opening of benzoxazole. The ring-opened form existed as an isonitrile in a [D₆] benzene solution (34% NMR yield) (Scheme 4e).^[30] It was this mechanistic insight that led us to try similar couplings with thiophenes, which have CH bonds of pK_a values below 30 in DMSO. Indeed they reacted well in the presence of KOMe (Scheme 3c).

All of the data put together, we propose a catalytic cycle that involves concerted oxidative addition of a cyclopropyl iodide, transmetalation of an in situ formed heteroaryl anion and final C–C reductive elimination. For heterocycles that are less acidic, e.g., indole, furan and benzimidazole, the deprotonation is unfavorable and transmetalation to palladium cannot take place. The oxidative adduct will be sidetracked to elimination to form dienes or ring opening to allylic radicals.

In conclusion, we report a cyclopropylation reaction of benzoxazoles and other heteroarenes using cyclopropyl halides and a simple palladium catalyst. The coupling process is stereo-retentive on the three-membered rings. This confirms that oxidative addition of cyclopropyl C–X bonds on Pd(0) is a concerted process. Subsequent transmetalation of an anionic heterocycle and C–C reductive elimination leads to the coupling products. Thus, the pathway is different from our recent work on alkylation of common alkyl halides, which relied on direct addition of alkyl radicals to the unsaturated rings.^[13] If heterocycles are not acidic enough to undergo facile deprotonation, however, the cyclopropylpalladium intermediate will be sidetracked to form dienes and allylic radicals. This underscores the complexity and challenge of this cyclopropylation. Notably, most of the products herein are new entities, despite structural simplicity.

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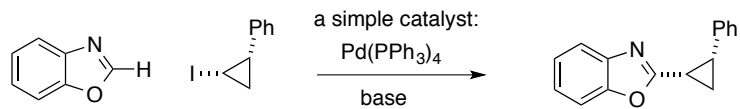
Keywords: palladium · cyclopropane · oxidative addition · heterocycle · synthetic method

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Heterocycles

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no alkyl radicals are involved

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Palladium-Catalyzed Direct
Cyclopropylation of Heterocycles

Retention of configuration on cyclopropane rings. The cyclopropylation reaction proceed via concerted oxidative addition of C–I bonds on palladium instead of direct radical addition to heteroarenes.