Heterocycle Synthesis

Deutsche Ausgabe: DOI: 10.1002/ange.201504735
Internationale Ausgabe: DOI: 10.1002/anie.201504735

Palladium-Catalyzed Direct Cyclopropylation of Heterocycles**

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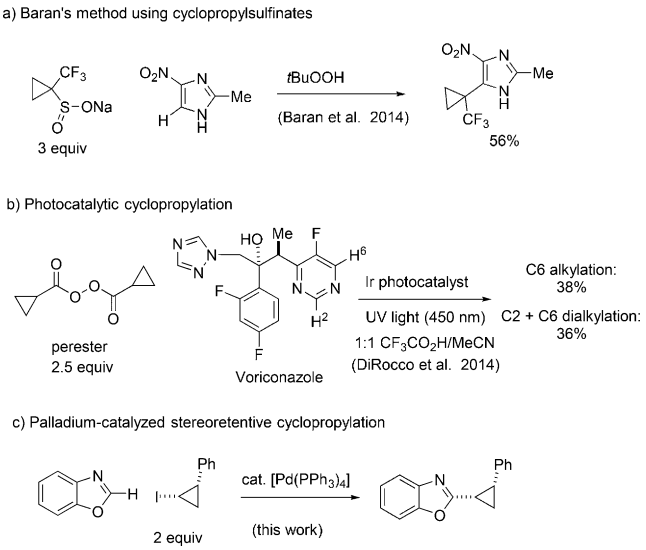
Abstract: *Many 1,3-azoles and thiophenes are directly cyclopropylated in the presence of a simple palladium catalyst. The relative configuration on the three-membered rings is retained in the products. Thus, the cyclopropyl–halide bond undergoes concerted oxidative addition to palladium(0) and cyclopropyl radicals are not involved in the productive pathway.*

Cyclopropane rings are present in many bioactive natural products and synthetic compounds.[1] They also exist in medicines including the antibacterial agent Ciprofloxacin, the 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 strain, which can induce ring opening under proper reaction 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, including 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, for the [2+1] cycloadditions and other stereoselective reactions,[8] heteroaryl rings were rarely incorporated into cyclopropyl rings through C–C bond formation.

In recent years, metal-catalyzed alkylation of hetreoarenes has emerged as a useful method,[9] which is distinct from Friedel–Crafts alkylation with respect to the types of heterocycles and prefered 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 the alkylation of many families of heteroarenes.[13] In those cases, palladium catalysts reacted with common alkyl halides to give alkyl radicals, which added directly to the heteroarenes. Good selectivity was observed, thus 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 the radical alkylation of heteroarenes[15] were disclosed. Baran et al. used cyclopropylsulfinate salts, which carried an α-trifluoromethyl group, to produce cyclopropyl radicals (Scheme 1 a).[16] In another example, DiRocco et al.[17] employed a dicyclopropyl perester for alkylation of electron-poor azacycles under photocatalytic conditions,[18] but the regioselectivity was an issue (Scheme 1 b).



Scheme 1. Recent examples for the cyclopropylation of heterocycles.

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 $CrCl_2$ by using the procedure reported by Takai et al.[20] We found that a simple catalyst, $[Pd(PPh_3)_4]$, promoted the desired reaction in good yield and high *trans* selectivity (Table 1, entry 1). When 7 mol% of a bis(phosphine) was added (e.g., dppp, dppf, BINAP and XantPhos), only a negative impact was observed, except for the case of dppp, which gave 94% yield (entries 2–5). The choice of base was also important (entries 6–12), and 2 equivalents of NaOMe were optimal for the model reaction. When NaOMe was replaced with either KOH or Cs_2CO_3, a significant amount of diene byproducts was observed (entries 7 and 10). Et_3N inhibited the coupling process (entry 12). The desired coupling proceeded efficiently in other solvents, such as toluene and 1,4-dioxane (entries 13 and 14). Notably, we identified a previously unknown side reaction, wherein the cyclopropyl undergoes an HI elimination/ring opening

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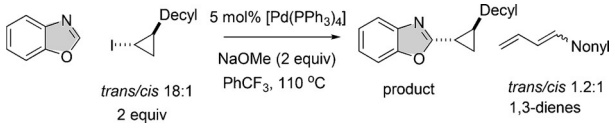
[**] We thank the Singapore Ministry of Education Academic Research Fund (MOE2013-T2-2-057 and MOE2014-T1-001-021) and the Chinese Scholarship Counsel for financial support for G.Y.

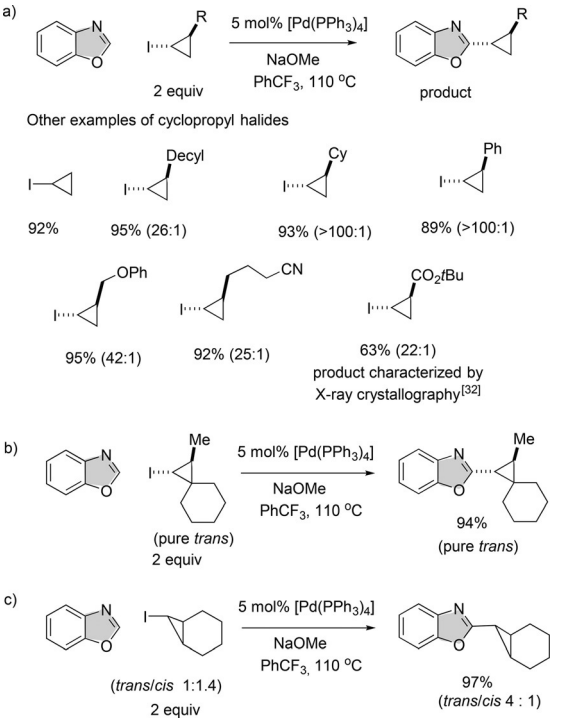
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504735.

Table 1: Changes from the optimized reaction conditions in the model reaction.



Entry	Change in reaction conditions	Cyclopropyl iodide Conv. [%][b]	Product Yield [%][a]	Product *trans*/*cis*	Dienes Yield [%][b]
1	–	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_3PO_4	127	0	–	98
10	Cs_2CO_3	200	8	20:1	146
11	LiO*t*Bu	184	62	27:1	8
12	Et_3N	20	0	–	12
13	toluene	193	96	19:1	72
14	1,4-dioxane	200	84	19:1	84

[a] Determined by GC for reactions using 0.1 mmol of benzoxazole. [b] Conversion of cyclopropyl iodide and yield of its diene byproducts were determeind by GC and are based on maximal 200%. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene, dppp = 1,3-bis(diphenylphosphino)propane, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.



Scheme 2. Examples of cyclopropyl iodides in couplings with 1,3-benzoxazole. Yields are those of the isolated product when using 0.3 mmol of benzoxazole. The ratio within parentheses refers to the *trans*/*cis* selectivity of the products.

sequence to give a mixture of *trans*- and *cis*-1,3-dienes. In a control experiment, NaOMe alone did not cause this elimination. Thus, both the base and palladium catalyst are needed to effect this side reaction.

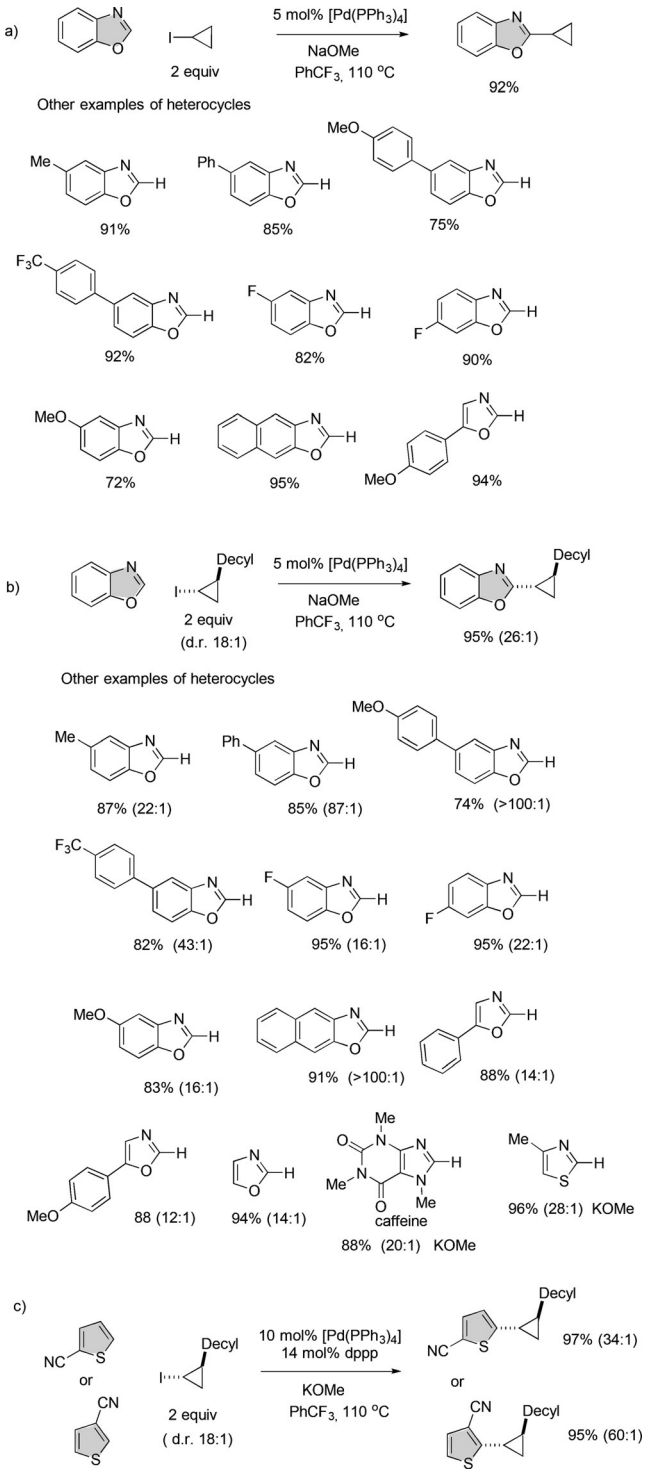
In terms of the scope with respect to cyclopropyl iodides, various aryl and alkyl groups can be present on the ring (Scheme 2a). We noticed that a bulky *tert*-butyl group on cyclopropane inhibited the coupling process. Polar functional groups such as ethers, nitriles, and esters were well tolerated. A product containing a *tert*-butyl ester group was crystalline and it allowed unambiguous assignment of the *trans* configuration in the product.[32] 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 reaction conditions.

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

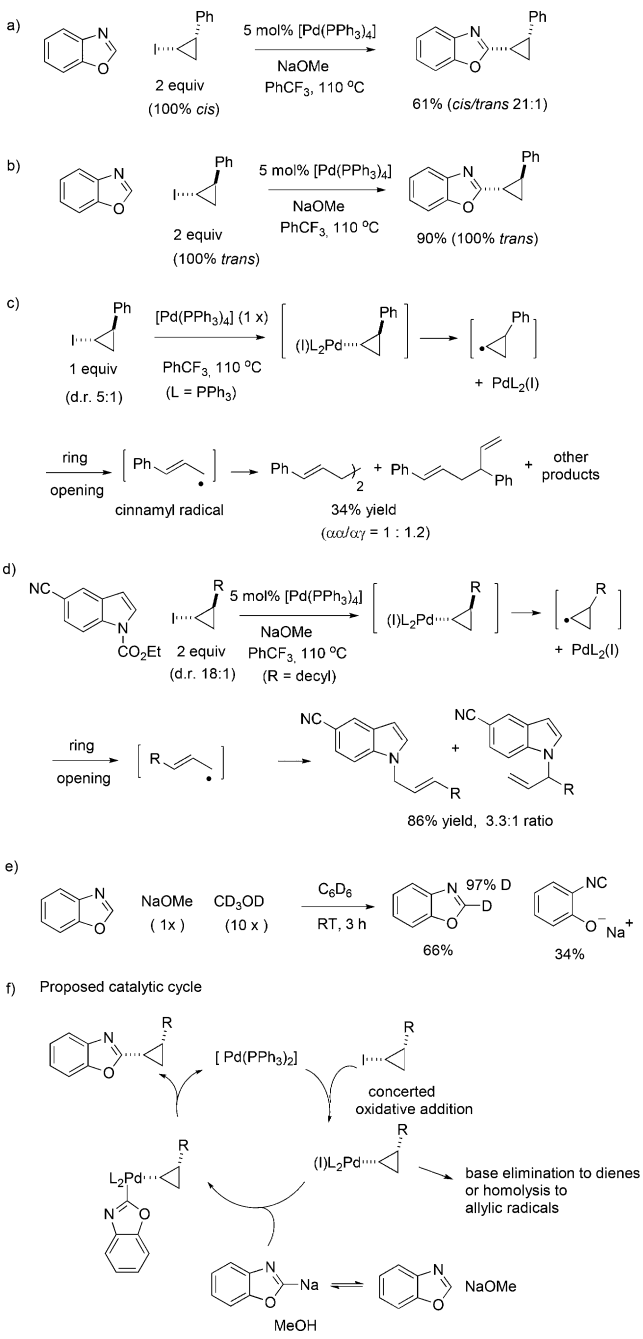
With regard to reaction mechanism, we initially suspected that the palladium(0) catalyst reacted with cyclopropyl iodides through a single-electron transfer to generate a cyclopropyl radical, which then added to the heteroarenes directly, similar to the alkylation of common alkyl halides.[13] However, cyclopropyl radicals are special σ-radicals,[22] and are known to be much less nucleophilic than cyclohexyl radicals in the addition to electron-poor heteroarenes.[23]

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*-2-phenylcyclopropyl iodide led to a pure *trans* product (Scheme 4b). This observation 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^{-1}.[24] Next, we attempted to isolate an oxidative adduct of *trans*-2-phenylcyclopropyl iodide and [Pd(PPh$_3$)$_4$] (Scheme 4c). No reaction occurred at 50 °C. At 110 °C, a complex mixture resulted and a major signal in the ^{31}P NMR spectrum was not observed. In the resulting reaction mixture, cinnamyl dimers were formed in 34% yield (with a maximum value of 100%). In addition, the 1:1.2 ratio of αα and αγ 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 either C3 or C2 of the indole (Scheme 4d). Instead, two isomers of the



Scheme 3. Examples of unsaturated heterocycles in cyclopropylation. Yields are those of the isolated product when using 0.3 mmol of the heterocycle. The ratio within parentheses refers to the *trans*/*cis* ratio of products.



Scheme 4. Mechanistic studies and a catalytic cycle of cyclopropylation.

N-allylation product were isolated in good yields. 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 the N-allylation product. An alternative pathway involving external attack of an indole on π-allylpalladium complexes is less likely. It would have led to allylation at C3, more nucleophilic site of indole.[28]

We wondered how a C–H bond of benzoxazole could be cleaved under the reaction conditions. When benzoxazole was stirred with NaOMe and 10 equivalents of [D_4]methanol, it underwent facile H–D exchange at room temperature by reversible deprotonation (Scheme 4e).[29] The H–D exchange process was accompanied by partial ring opening of benzox-

azole. The ring-opened form existed as an isonitrile (34% yield; NMR) in a [D_6]benzene solution.[30] It was this mechanistic insight that led us to try similar couplings with thiophenes, which have C–H bonds with pK_a values below 30 in DMSO. Indeed they reacted well in the presence of KOMe (see Scheme 3c).

All the data taken together led us to propose a catalytic cycle which 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, for example, 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 stereoretentive for the three-membered rings, and confirms that oxidative addition of cyclopropyl C–X bonds to palladium(0) is a concerted process.[31] Subsequent transmetalation of an anionic heterocycle and C–C reductive elimination leads to the coupling products. Thus, the pathway is different from that of our recent work on alkylation of common alkyl halides, a reaction 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 form dienes and allylic radicals. This observation underscores the complexity and challenge of this cyclopropylation. Notably, most of the products herein are new entities, despite structural simplicity.

Keywords: alkyl halides · heterocycles · palladium · cyclopropane · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9601–9605
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[32] CCDC 1048525 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: May 26, 2015
Published online: July 14, 2015

