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Arylation of Aldehyde Homoenolates with Aryl Bromides

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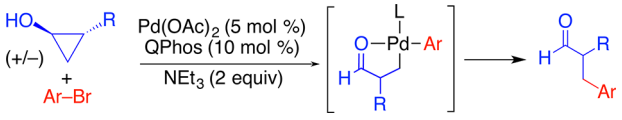
ABSTRACT



A mild palladium catalyzed coupling of reactive aldehyde homoenolates with aryl bromides is described. Aldehyde homoenolates are generated by ring opening of cyclopropanols via a C–C cleavage step. The coupling generates aldehyde products at room temperature in 59–93% yield.

The α-arylation of carbonyl compounds with aryl halides has become a powerful synthetic method since its introduction by Buchwald,[1−5] Hartwig,[6−10] and Miura.[11−13] An analogous method for β-arylation would likewise be useful but has lagged because it is more difficult to access metalated homoenolate intermediates.[14−21] Although homoenolates of ketones and esters[22−28] have been arylated, only one aldehyde homoenolate has succumbed to arylation (Scheme 1). In pioneering work, Nakamura, Kuwajima, and co-workers[22] demonstrated that a silylated cyclopropanol generated an aldehyde homoenolate with catalytic palladium and underwent coupling with two aryl triflates (58–65% yield).

Although the scope of this transformation has not been expanded beyond Scheme 1, some limitations are evident. The reaction was successful only with aryl triflates and the polar solvent HMPA. The requirement of triflates and polar solvent were rationalized to favor the formation of a cationic palladium intermediate necessary to promote siloxy cyclopropane ring opening. Given the well-known utility of aldehydes in synthesis, we set out to develop a

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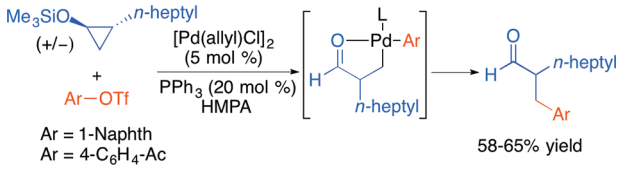
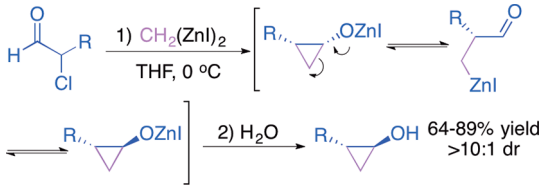
practical method for the β-arylation of aldehyde homoenolates with aryl bromides.

Scheme 1. β-Arylation of Aldehyde Homoenolate Generated from Silylated Cyclopropanol



We recently reported a straightforward synthesis of *trans*-cyclopropanols from α-chloro aldehydes and $CH_2(ZnI)_2$ (Scheme 2).[29,30] The high *trans* selectivity is the result of equilibration of the diastereomeric cyclopropoxy intermediates. Inspired by observations by Cha and co-workers,[31,32] who demonstrated that tertiary cyclopropanols underwent palladium mediated ring opening to form α,β-unsaturated ketones more rapidly than their silylated analogues, we applied our cyclopropanols to the generation and arylation of aldehyde homoenolates.

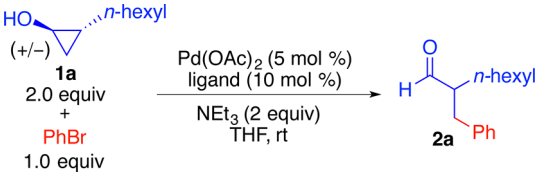
Scheme 2. Diastereoselective Synthesis of Cyclopropanols



We envisioned a key intermediate in the generation of the palladium homoenolate would be the palladium cyclopropoxide. Although a variety of bases can be used to form palladium alkoxides, we were attracted to the use of mild amine bases, as demonstrated by the work of Stoltz,[33] Uemura,[34,35] and Sigman.[36,37] Thus using triethylamine, a handful of the most successful mono- and bidentate ligands in cross-coupling chemistry were screened in the presence of $Pd(OAc)_2$ (5 mol %), bromobenzene (limiting reagent), and 2 equiv of triethylamine at rt (Table 1).[38]

Triphenylphosphine, which gave moderate yields with the aryl triflates employed by Nakamura, Kuwajima, and co-workers,[22] resulted in a low yield (entry 1). Buchwald's monodentate phosphines JohnPhos, DavePhos, and *t*-BuXPhos also gave very low yields under our conditions (entries 2–4). In contrast, Hartwig's QPhos resulted in near-quantitative formation of the aldehyde homoenolate coupling product (entry 5). The ferrocene-based bis(phosphine) ligands performed poorly under these reaction conditions (entries 6–7). The reaction with QPhos and $Pd(OAc)_2$ led to an isolated yield of 86% on laboratory scale.

Table 1. Identification of Ligands for the Aldehyde Homoenolate Arylation with Bromobenzene



entry	ligand =	assay yield (%)[a]
1	PPh_3	14
2	JohnPhos	<5
3	DavePhos	8
4	*t*-BuXPhos	<5
5	QPhos	98[b]
6	Dppf	12
7	Dtbpf	7

[a] Yields determined by integration of ^1H NMR spectra of the crude reaction mixtures against an internal standard. [b] 86% isolated yield.

With suitable conditions in hand, we examined the scope of racemic cyclopropanols (Table 2). In addition to the *n*-hexyl (entry 1), *n*-butyl and cyclohexyl substituted cyclopropanols (entries 2–3) furnished aldehydes in 93% and 88% yield, respectively. Aldehyde homoenolates with silyl or trityl protected β- or δ-hydroxy groups (entries 4–8) were arylated in 59–83% yield. Substrates **1e** and **1f**, however, required an increase in loading to 10 mol % $Pd(OAc)_2$. The indole substrate (entry 9) gave the desired aldehyde in 61% yield at 50 °C.

We then examined the scope of aryl bromides in homoenolate cross-coupling with (±)-*trans*-2-*n*-hexylcyclopropanol (Table 3). Electron-rich aryl bromides are very good substrates (73–81% yield, entries 1–4). 2-Bromotoluene resulted in a diminished yield (59%, entry 5), most likely due to the increased steric hindrance. The electron-poor aryl bromides furnished products in 79–83% yields (entries 6–8). Our coupling exhibited interesting chemoselectivity: both unprotected 4-bromobenzyl alcohol and 4-bromophenol generated the corresponding β-arylated aldehydes in 84% and 66% isolated yields, respectively (entries 9 and 10). The result in entry 10 indicates that phenol arylation is slower than homoenolate arylation.[23]

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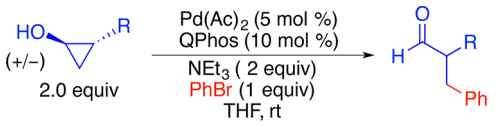
(38) Using less than 2.0 equiv of cyclopropanol resulted in slightly diminished yields; however, excess cyclopropanol can be recovered quantitatively after column chromotography.

Table 2. Scope of Cyclopropanols



SM	product	yield (%)
1) HO, *n*-hexyl, **1a**	H, O, Ph, **2a**	86
2) HO, *n*-butyl, **1b**	H, O, Ph, **2b**	93
3) HO, **1c**	H, O, Ph, **2c**	88
4) HO, OTBS, **1d**	H, O, OTBS, Ph, **2d**	83
5) HO, OTIPS, **1e**	H, O, OTIPS, Ph, **2e**	59[a]
6) HO, OTBDPS, **1f**	H, O, OTBDPS, Ph, **2f**	73[a]
7) HO, O, Ph, Ph, Ph, **1g**	H, O, Ph, Ph, Ph, Ph, **2g**	71
8) HO, O, Ph, Ph, Ph, **1h**	H, O, Ph, Ph, Ph, Ph, **2h**	73
9) HO, NTIPS, **1i**	H, O, Ph, NTIPS, **2i**	61[b]

[a] 10 mol % $Pd(OAc)_2$, 20 mol % QPhos. [b] Reaction run at 50 °C.

Finally, replacing *trans*-2-*n*-hexylcyclopropanol with *trans*-2-benzylcyclopropanol (entries 11 and 12) and reaction with 4-bromoanisole and 4-bromo-*N*,*N*-dimethylaniline provided the desired aldehydes in 89% and 73% yield, respectively. It is noteworthy that no α-arylation of the aldehyde products was detected, presumably because the mild conditions do not result in the generation of enolate intermediates.[39]

To determine the scalability of the reaction, we conducted the arylation of *trans*-2-hexylcyclopropanol with bromobenzene on 6.3 mmol scale. As shown in Scheme 3,

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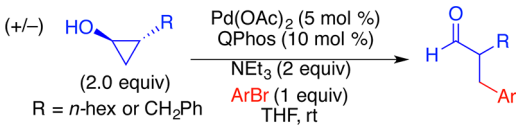
Table 3. Scope of Aryl Bromides

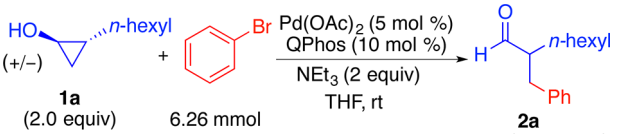


product	yield (%)	product	yield (%)
1) H, O, OMe, **3a**	80	7) H, O, NO_2, **3g**	79
2) H, O, OMe, **3b**	81	8) H, O, Cl, **3h**	83
3) H, O, NMe_2, **3c**	73	9) H, O, OH, **3i**	84
4) H, O, **3d**	77	10) H, O, OH, **3j**	66[a]
5) H, O, Me, **3e**	59	11) H, O, Ph, OMe, **3k**	89[b]
6) H, O, CO_2Me, **3f**	79	12) H, O, Ph, NMe_2, **3l**	73[b]

[a] Yield based on isolation of reduced aldehyde. [b] 2-*trans*-Benzylcyclopropanol.

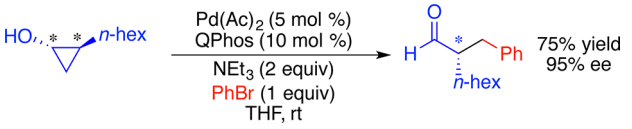
the desired arylated product was isolated in 98% yield (1.34 g).

Scheme 3. Scale-up Cross-Coupling between **1a** and Bromobenzene



Given the observed regioselectivity of the cyclopropane ring opening, we hypothesized that enantioenriched

Scheme 4. Enantioselective Synthesis of β-Arylated Aldehyde



cyclopropanols should allow ring opening and cross-coupling without loss of stereochemistry (Scheme 4). Enantioenriched 2-*trans*-chlorooctanal was synthesized according to MacMillan's method (96% ee)[40] and subjected to our cyclopropanation reaction with $CH_2(ZnI)_2$ to yield the corresponding cyclopropanol (**1a**, 60% yield, Scheme 2). Use of **1a** in the homoenolate arylation afforded the desired β-arylated aldehyde (**2a**) in 75% yield with 95% ee. Thus, little or no erosion of ee occurs during the cyclopropanation or the arylation steps.

A possible catalytic cycle is pictured in Scheme 5 based on Uemura[41−43] and Martín's[44,45] work on the ring opening of cyclobutanols to provide γ-arylated ketones. After oxidative addition of the aryl bromide to palladium(0), the aryl palladium intermediate is proposed to bind the alcohol. Deprotonation by triethylamine is expected to generate the palladium alkoxide. β-Carbon elimination then gives the palladium homoenolate intermediate. Because QPhos is a monodentate ligand, it is likely that the aldehyde carbonyl binds to the palladium. Such an interaction would stabilize the intermediate with respect

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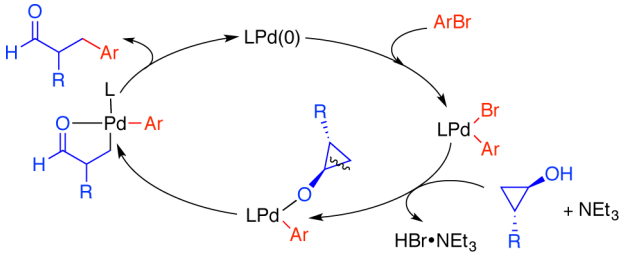
Scheme 5. Plausible Reaction Pathway



to β-hydride elimination, which we have not observed in this system. Reductive elimination then occurs to give the β-arylated aldehyde and regenerates Pd(0).

In conclusion, we have developed a mild method for the C−C bond cleavage of cyclopropanols to form intermediate aldehyde homoenolates that undergo arylations catalyzed by a QPhos-based palladium catalyst. The reaction was determined to be easily scalable. Unlike prior methods, which required more expensive aryl triflates and very high boiling, polar, and toxic HMPA, our method gives good results with more readily available aryl bromides in THF. Additionally, we have demonstrated that the arylation proceeds without loss of stereochemistry with enantiomerically enriched cyclopropanols.

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Supporting Information Available. Procedures and full characterization are available. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.