Communication

Direct Palladium-Catalyzed Arylation of Cyclopropenes

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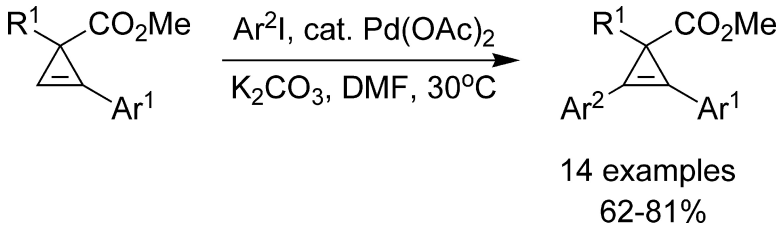

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Direct Palladium-Catalyzed Arylation of Cyclopropenes

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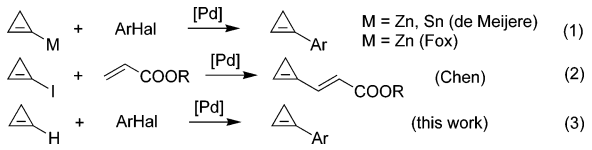
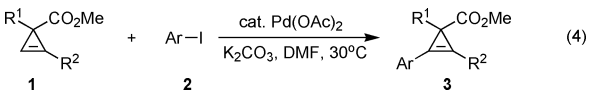
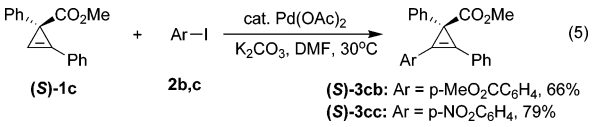
As a result of their enormous ring strain, cyclopropenes display an array of diverse reactivities in both noncatalytic[1] and transition-metal-catalyzed transformations,[2] attracting increasing attention from the synthetic community. Accordingly, a number of methods for construction and further modification of cyclopropenes have been developed. Noncatalytic methods involve trapping of nucleophilic cyclopropenyl metal species with various electrophiles.[3] Introduction of aryl and vinyl substituents can be achieved via Pd-catalyzed Negishi or Stille cross-coupling, reported by de Meijere[4] and Fox[3] (eq 1), or via Heck-type reaction of cyclopropenyl iodides with acrylates, developed by Chen (eq 2).[5] However, to date there are no examples of Heck-type processes involving the double bond of cyclopropene. Moreover, a single report exists on the attempted transformation of this type, which resulted in the ring opening of cyclopropene.[6] Herein, we report the direct and efficient Heck-type arylation of cyclopropenes proceeding with preservation of the ring (eq 3).



Initially, we tested arylation of phenyl-substituted cyclopropene **1b** under various Heck reaction conditions.[7] We have found that the catalyst system $Pd(OAc)_2$ (5 mol %)/K_2CO_3 (2.5 equiv) in DMF efficiently catalyzed arylation of **1a** to give tetrasubstituted cyclopropene **3aa** in 62% isolated yield (eq 4, Table 1, entry 1). Next, the arylation of differently substituted cyclopropenes was examined under these reaction conditions. Cyclopropenedicarboxylates **1a** and **1b** reacted smoothly with aryl iodides **2b,c**, affording highly functionalized tetrasubstituted cyclopropenes in high yields (entries 2−5). 3-Phenyl-containing cyclopropene **1c** also provided good yields in arylation with iodobenzenes **2b**,**c**,**f** (entries 6, 7, and 10), 1-iodonaphthalene (entry 9), and heteroarylation with 2-iodothiophene (entry 8). Likewise, nitroaryl-substituted cyclopropene **1d** underwent smooth arylation under the above reaction conditions (entry 11). *n*-Butyl-substituted cyclopropene **1e**, in contrast to its aryl analog **1a**, reacted much more slowly and provided only a moderate yield in this reaction (entry 12). Notably, 3,3-disubstituted cyclopropene **1f** (R^1 = CO_2Me, R^2 = H) did not undergo the arylation reaction at all.

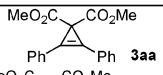
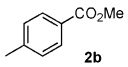
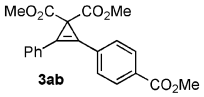
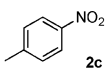
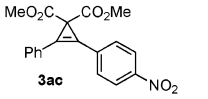
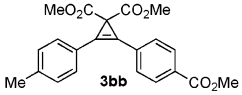
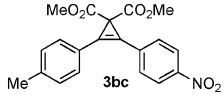
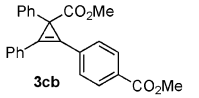
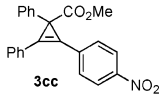
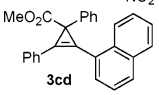
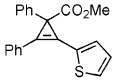
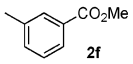
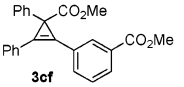
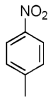
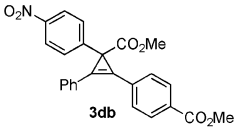
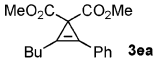


We recognize that this methodology could be especially attractive in application to nonracemic substrates, because it will allow for direct[8] synthesis of optically active tetrasubstituted cyclopropenes, not available via asymmetric cyclopropenation methods.[9,10] Accordingly, optically active cyclopropene (*S*)-**1c**, easily available according to Davies' protocol[10b] was subjected to the arylation under standard conditions. As expected, the reaction proceeded uneventfully to provide (*S*)-**3cb** and (*S*)-**3cc** in excellent yields with complete preservation of stereochemistry (eq 5).



The mechanism of this reaction can be rationalized via several alternative pathways including Heck-type, C−H activation, or cross-

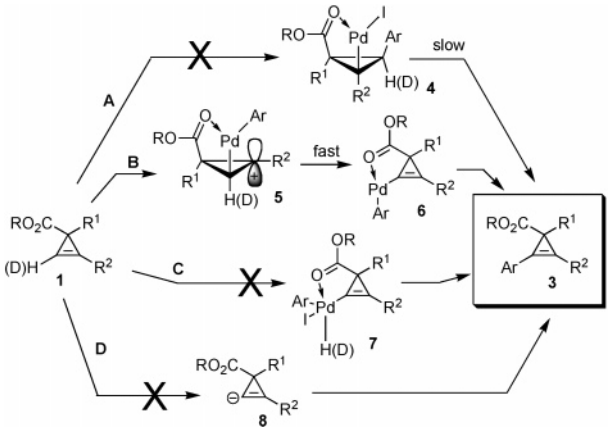
Table 1. Pd-Catalyzed Arylation of Cyclopropenes

#	R^1	R^2	Ar	Product 3	Yield, %[a]
1	CO_2Me	Ph (**1a**)	Ph (**2a**)	 **3aa**	62
2		**1a**	 **2b**	 **3ab**	74
3		**1a**	 **2c**	 **3ac**	78
4	CO_2Me	p-Tol (**1b**)	**2b**	 **3bb**	81
5		**1b**	**2c**	 **3bc**	74
6	Ph	Ph (**1c**)	**2b**	 **3cb**	72
7		**1c**	**2c**	 **3cc**	68
8		**1c**	 **2d**	 **3cd**	68
9		**1c**	 **2e**	 **3ce**	77
10		**1c**	 **2f**	 **3cf**	71
11		Ph (**1d**)	**2b**	 **3db**	69
12	CO_2Me	*n*-Bu (**1e**)	**2a**	 **3ea**	46

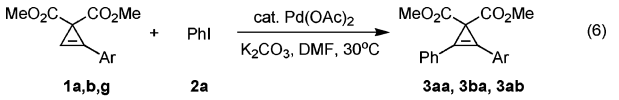
[a] Isolated yields.

10.1021/ja042380k CCC: $30.25

Scheme 1. Alternative Mechanistic Rationales for Pd-Catalyzed Arylation of Cyclopropenes



coupling protocols (Scheme 1). In the event that this arylation proceeds via migratory insertion to form **4**, followed by anti-β-hydride elimination[11] (path **A**), a substantial value of kinetic isotope effect (KIE) should be expected.[12] However, no KIE was observed in this reaction ($k_H/k_D = 1.0$), thus strongly opposing carbopalladation path **A**.[13] Alternatively, arylation of cyclopropenes may proceed through a cationic path **B** (Scheme 1),[14] involving electrophilic addition of $ArPd^+$ species to cyclopropene to form cyclopropyl cation **5**, followed by fast loss of the proton, which is in agreement with the absence of KIE. Benzylic cation **5** (R^2 = Ar) is additionally stabilized by interaction with *d*-orbitals of Pd.[15] If arylation proceeds through path **B**, then the reaction rates should depend on the electronic nature of R^2. Experiments met these expectations: *p*-tolyl-substituted cyclopropene **1b** reacted more quickly than parent **1a**, whereas introduction of a *p*-CO_2Me group (**1g**) suppressed the reaction (eq 6). In addition, less efficient



1b, 3ba: Ar = p-Tol
1a, 3aa: Ar = Ph
1g, 3ab: Ar = p-$MeO_2CC_6H_4$

$k_{3ba} : k_{3aa} : k_{3ab}$ = 2.70 : 1.00 : 0.83

stabilization of nonbenzylic cations **5**, derived from **1e** (R^2 = Alk) and **1f** (R^2 = H), is in good agreement with the observed decrease in their reactivity (vide supra).

Two other possible mechanisms, involving C−H activation (path **C**) and Sonogashira-like cross-coupling (path **D**, Scheme 1), were essentially ruled out, as the former should experience a substantial H/D KIE,[16] whereas the latter is in conflict with our observations of the lack of H/D scrambling in the starting material through the course of the reaction.[17] Furthermore, addition of Cu(I) or Ag(I) salts, which are known to facilitate Sonogashira reaction,[18] totally inhibited the described process.

In summary, we have shown the first examples of direct Pd-catalyzed arylation and heteroarylation of cyclopropenes. Mechanistic data acquired to date strongly support electrophilic character of this transformation. Further studies to set the scope and the precise mechanism of this reaction are currently underway in our laboratories.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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