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Regio- and Diastereoselective Decarboxylative Coupling of Heteroaromatic Alkanes

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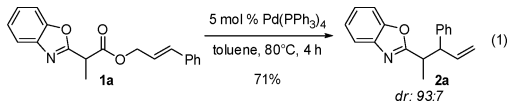
Heterocycles represent a large class of pharmaceutical targets. Currently, greater than 65% of drugs in late development stages or on the market are heterocycles,[1] and seven of the top ten selling pharmaceutical drugs contain nitrogen heterocycles.[2] Therefore, a great demand for efficient derivatization of heterocycles exists. While the development of sp^2-sp^2 coupling of heteroaromatics has significantly impacted this area,[3] the catalytic coupling of alkyl heteroaromatics is still an area that lacks breadth.[4]

Recently, we and others have been developing coupling reactions that proceed by decarboxylative metalation.[5,6] So-called decarboxylative couplings have potential advantages over standard methods of cross-coupling since decarboxylative metalation avoids highly basic conditions and stoichiometric amounts of toxic reagents which are often necessary to effect transmetalation. With these advantages in mind, it became apparent that the ability to incorporate heteroaromatic groups into the repertoire of decarboxylative coupling may create opportunities for the synthesis of a variety of pharmaceutical targets.

To begin, **1a** was synthesized and treated with 5 mol % $Pd(PPh_3)_4$ in toluene at 80 °C. The reaction proceeded smoothly to the product of decarboxylative coupling (**2a)** in 71% yield (eq 1).

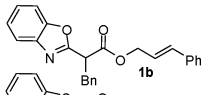
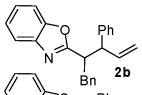
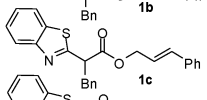
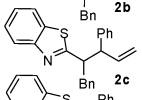
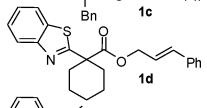
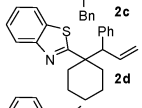
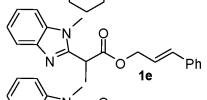
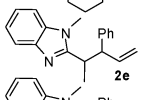
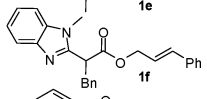
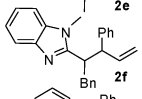
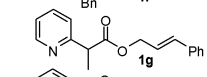
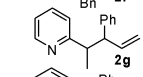
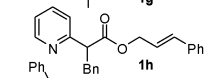
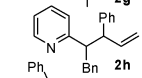
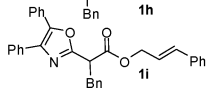
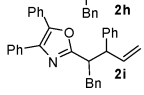


Surprisingly, the product apparently originated from attack at the more hindered allylic terminus and occurred with high diastereoselectivity (93:7). Generally, Pd-catalyzed allylations afford products from attack at the least substituted allylic terminus, although there are exceptions.[7] Moreover, standard palladium-catalyzed allylations rarely exhibit such high diastereoselectivities with acyclic nucleophiles.

Next, a range of heteroaromatic amines were tested which all provided the same regioselectivity as **1a** (Table 1).[8] Furthermore, the diastereoselectivity of the couplings is generally high. The exception is the coupling of *N*-methyl benzimidazole (dr = 2.2−2.9:1). The products could nonetheless be obtained with high dr, albeit in somewhat reduced yield, after separation. Finally, the relative rates of the reactions appear to be dependent on the choice of heteroaromatic ring, and track loosely with the rates of decarboxylation of related heterocycles.[9]

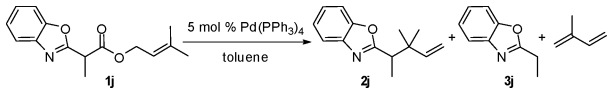
Cinnamyl esters are among the most effective substrates for allylation because the lack of β-hydrogens obviates elimination. To test whether alkyl-substituted allyls could be utilized, substrate **1j** was subjected to a variety of reaction conditions (Table 2). Although the elimination pathway could not be avoided altogether, the amount of elimination is dramatically reduced at elevated reaction temperature, whereas substrate concentration had a less pronounced impact. A combination of the optimal concentration and temperature afforded a significant amount of desired product (Table 2, entry 7). Changes in catalyst concentration were not beneficial.

Table 1. Decarboxylative Coupling of Heterocyclic Cinnamyl Esters[a]

	Substrate	Product	Time (h)	Yield (dr)
entry 1	 **1b**	 **2b**	4	66 (>95:5)
entry 2	 **1c**	 **2c**	2	75 (>95:5)
entry 3	 **1d**	 **2d**	2	95
entry 4	 **1e**	 **2e**	16	43 (>95:5)[b]
entry 5	 **1f**	 **2f**	16	52 (>95:5)[c]
entry 6	 **1g**	 **2g**	20	43 (>95:5)
entry 7	 **1h**	 **2h**	20	53 (>95:5)
entry 8	 **1i**	 **2i**	2	47 (>95:5)

[a] 0.25 mmol substrate was treated with 0.013 mmol $Pd(PPh_3)_4$ in toluene at 80 °C. [b] Crude dr = 2.2:1. [c] Crude dr = 2.9:1.

Table 2. Effects of Concentration and Temperature on Elimination



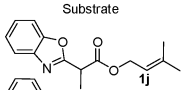
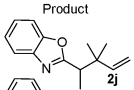
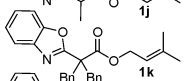
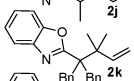
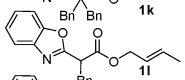
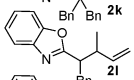
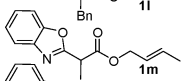
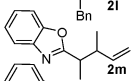
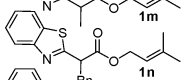
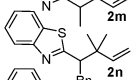
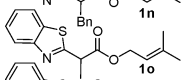
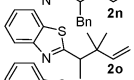
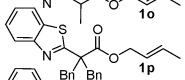
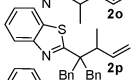
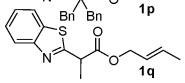
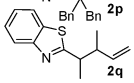
	[1j]	temp (°C)	2j	3j
1	0.025	80	66	34
2	0.05	80	58	42
3	0.10	80	53	47
4	0.05	25	0	100
5	0.05	60	40	60
6	0.05	100	59	41
7	0.025	100	75	25

Once it was determined that alkyl-substituted allylic esters would be tolerated by the less basic heterocycles, benzoxazole and benzothiazole, a variety of prenyl and crotyl esters were subjected to the reaction conditions (Table 3). In general, the less basic benzothiazole substrates gave higher yields and higher diastereoselectivities than benzoxazoles. Furthermore, the ability to form C−C bonds between tertiary and quaternary carbon centers without extensive elimination is remarkable.

The unusual regio- and diastereoselectivity prompted us to further examine the mechanism and scope of the reaction. To verify the reaction was catalytic in Pd, **1j** was heated to 80 °C for 4 h in the absence of $Pd(PPh_3)_4$ and gave no product or degradation. It seemed possible that trace amounts of Pd(II) present could catalyze a Lewis acid-promoted Carroll-like rearrangement. However, a catalytic

10.1021/ja070116w CCC: $37.00

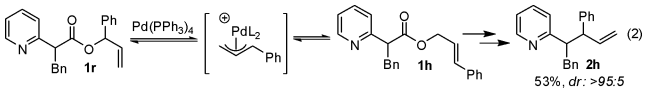
Table 3. Decarboxylative Coupling of Heterocyclic Alkyl-Allyl Esters[a]

Substrate	Product	Time (h)	Yield (dr)[b]
 **1j**	 **2j**	2	57
 **1k**	 **2k**	2	30[c]
 **1l**	 **2l**	2	64 (2.5:1)[c,d]
 **1m**	 **2m**	2	61 (2.8:1)[e]
 **1n**	 **2n**	1	74
 **1o**	 **2o**	1	50
 **1p**	 **2p**	1	74[c]
 **1q**	 **2q**	1	72 (10:1)[f]

[a] 0.25 mmol substrate was treated with 0.013 mmol $Pd(PPh_3)_4$ in toluene at 100 °C. [b] Isolated yields. [c] Reaction run at 80 °C. [d] *branched:linear (b:l)* = 93:7. [e] *b:l* = 94:6. [f] *b:l* = 95:5.

amount of several Lewis acids [$Sc(OTf)_3$, $PdCl_2(CH_3CN)_2$, $Cu(OAc)_2$] failed to effect any reaction of **1g** at 80 °C in tol-d_8 after 16 h.

Also, both **1r** and **1h** produce **2h** as the major product which is suggestive of a common Pd-π-allyl intermediate (eq 2).



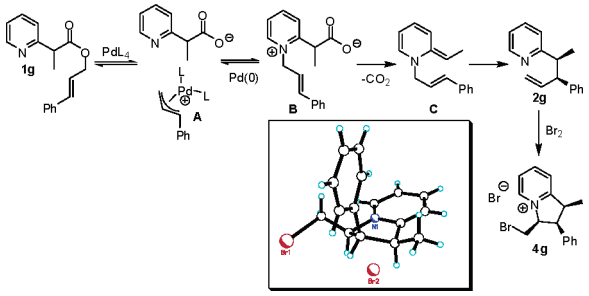
In fact, observation of this reaction by ^{1}H NMR spectroscopy revealed complete isomerization of the substrate (**1r**) to the linear substrate (**1h**) prior to decarboxylative coupling. Therefore, we believe that a mechanism involving Pd-π-allyl intermediates is probable and π-allyl formation is much faster than the formation of product.

To better understand the role of nitrogen, a cinnamyl *4-pyridyl* ester was treated under the standard conditions of catalysis. The reaction produced an intractable mixture of products that was devoid of terminal olefinic products akin to **2h** (by ^{1}H NMR). Thus, the presence of the nitrogen at the 2-position of the heteroaromatic is essential for the reaction to proceed efficiently.[10]

Following these preliminary mechanistic investigations, we propose the mechanism shown in Scheme 1. The reaction is initiated by nucleophilic attack of Pd(0) on the allyl ester to give Pd-π-allyl complex **A**. At this point, two competing reactions are possible. If the heteroarene acts as a base, unproductive elimination occurs. However, the heteroaromatic can also undergo nucleophilic attack on the π-allyl complex to produce **B**. It is important to note that this allylation occurs with the "standard" preference for attack at the less substituted allylic carbon. Formation of the pyridinium intermediate will facilitate decarboxylative dearomatization to give intermediate **C**.[9] A subsequent [3,3]-sigmatropic rearrangement affords the observed product and accounts for the unusual regioselectivity. Furthermore, since the aza-Cope is driven by rearomatization of the pyridine ring, it takes place under much milder conditions than standard 3-aza-Cope rearrangements which can require ~200 °C.[11,12] Such a mechanism also accounts for the observed diastereoselectivity. Related tandem allylation/Cope-rearrangement[5c] and allylation/Thio−Claisen[13] rearrangement likewise proceed with high diastereoselectivity.

In order to determine the relative configuration of the product, compound **2g** was treated under conditions for bromocyclization.[14]

Scheme 1



Crystallization and analysis via single-crystal X-ray diffraction revealed a *cis*-configuration of the C-2 and C-3 centers (**4g**, Scheme 1). This stereochemistry suggests a boat-like transition state involving the *E*,*E*-geometry of **C**. It has been suggested that certain cyclic substrates are more apt to undergo [3,3]-sigmatropic rearrangements via a boat transition state in an effort to relieve steric strain imposed by the chair conformation.[15]

In conclusion, we have demonstrated a tandem allylation/aza-Cope rearrangement strategy for the diastereoselective sp^3-sp^3 coupling of allyl electrophiles and heteroaromatic alkanes. To the best of our knowledge, this is the first report of a tandem allylation/aza-Cope reaction that is driven by decarboxylative dearomatization/rearomatization.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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