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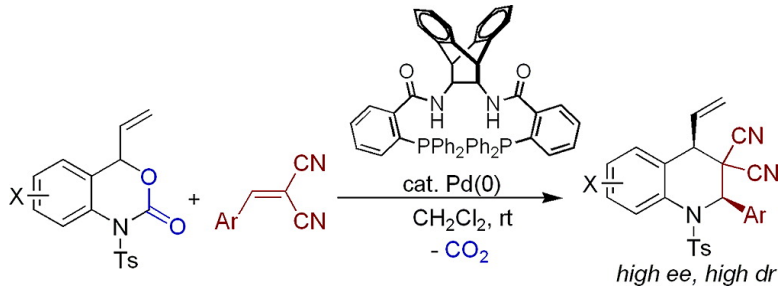

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Asymmetric Cycloadditions of Palladium-Polarized Aza-*o*-xylylenes

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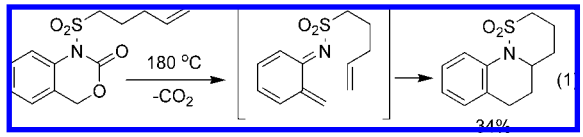
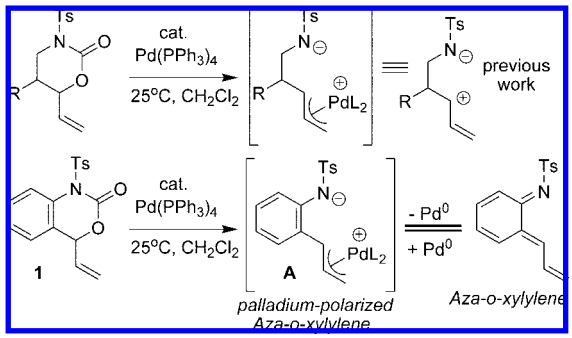
Thermal decarboxylation of benzoxazinanones under conditions of flash vacuum pyrolysis at 180 °C generates aza-*o*-xylylene intermediates that undergo [4 + 2] cycloaddition in moderate to low yield (eq 1).[1]



Recently, we have shown that catalytic decarboxylative cycloadditions of *saturated* analogues occur under mild conditions via zwitterionic π-allyl palladium intermediates (Scheme 1).[2] We reasoned that conjugation of the two charges would allow mild catalytic generation of aza-*o*-xylylene intermediates like those used in the above cycloaddition.[3] Such a scenario creates two possibilities. The zwitterionic intermediate (**A**) can potentially expel Pd(0) to produce a free aza-*o*-xylylene. Alternatively, if Pd remains coordinated, then a polarized aza-*o*-xylylene intermediately will result.[4] Herein we report that such palladium-polarized aza-*o*-xylylenes are likely intermediates in diastereoselective, asymmetric [4 + 2] cycloadditions with electron deficient olefins.

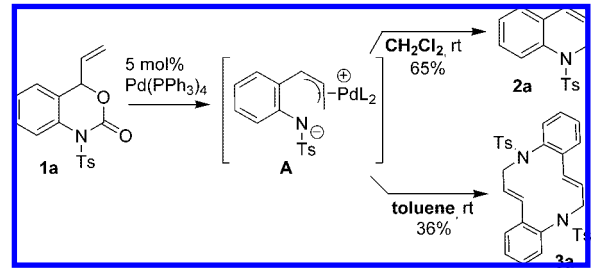
Scheme 1

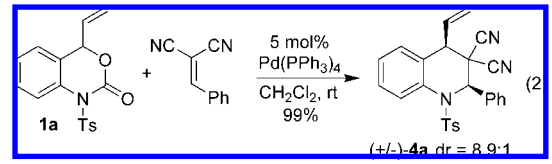


To begin, the parent vinyl benzoxazinanone (**1a**) was prepared and subjected to $Pd(PPh_3)_4$ in CH_2Cl_2. In contrast to the saturated analogues which undergo ring contraction to azetidines,[2] **1a** produces the hydroquinoline **2a** in 65% yield (Scheme 2). This product could arise from either cyclization of the π-allyl intermediate **A** or via electrocyclization of the free aza-*o*-xylenene.[5] Inteterstingly, conducting the same reaction in toluene solvent produces the 12-membered dimer exclusively.[6] Since it is improbable that such a dimer could arise from concerted [6 + 6] cycloaddition, it seems likely that Pd-polarized aza-*o*-xylylene **A** is an intermediate in these reactions.

If zwitterionic Pd-π-allyl intermediates are indeed being formed, then one would also predict that they would undergo [4 + 2] cycloadditions with electron deficient olefins.[7,8] Indeed, upon treatment of the benzoxazinanone **1a** with $Pd(PPh_3)_4$ in the presence of one equivalent of benzylidene malononitrile, cycloaddition occurs to produce the highly substituted dihydroquinoline **4a** with high diastereoselectivity (eq 2).

Scheme 2

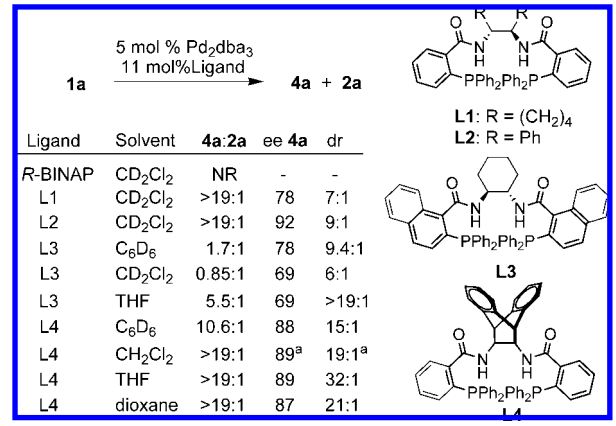




Next, we turned our attention toward the development of an asymmetric version of this cycloaddition. A screen of ligands quickly revealed that the Trost-ligands are superior ligands for the asymmetric cycloaddition (Table 1).[9] While the diphenyldiamine-based ligand (**L2**) provided the highest enantioselectivity, the ligand based on the anthracenyl diamine (**L4**) provided high enantioselectivity as well as superior diastereoselectivity. While THF provided the best combination of ee and dr, the reactions in THF were sluggish, thus CH_2Cl_2 was chosen as the optimal solvent. A single recrystallization of the product provided an 87% yield of highly enantio- and diastereoenriched hydroquinoline (97% ee, 50:1 dr).

Next, we briefly explored the effect of electronics on the reaction. If the benzylidene malononitrile was too electron rich [i.e., *p*-$MeOC_6H_4CHC(CN_2)$] then the intermolecular cycloaddition did not compete with the intramolecular cyclization to form dihydroquinolines.[10] However, if the olefin was sufficiently electron deficient, then

Table 1. Ligand and Solvent Screening Results

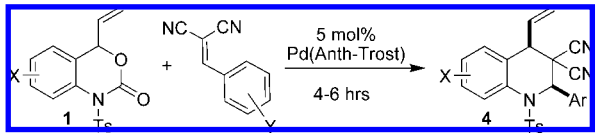


Ligand	Solvent	4a:2a	ee 4a	dr
R-BINAP	CD_2Cl_2	NR	-	-
L1	CD_2Cl_2	>19:1	78	7:1
L2	CD_2Cl_2	>19:1	92	9:1
L3	C_6D_6	1.7:1	78	9.4:1
L3	CD_2Cl_2	0.85:1	69	6:1
L3	THF	5.5:1	69	>19:1
L4	C_6D_6	10.6:1	88	15:1
L4	CH_2Cl_2	>19:1	89[a]	19:1[a]
L4	THF	>19:1	89	32:1
L4	dioxane	>19:1	87	21:1

[a] This reaction produced 97% ee and 50:1 dr after a single recrystallization.

10.1021/ja801742h CCC: $40.75

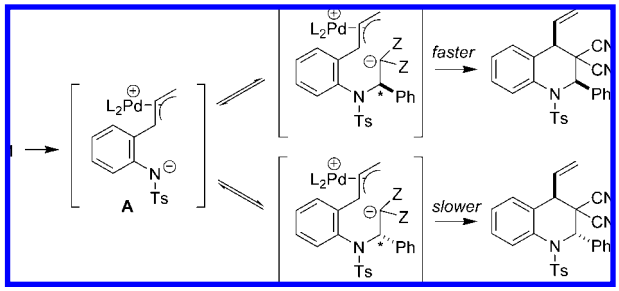
Table 2. Asymmetric Decarboxylative Cycloadditions[a]



product	X	Y	yield	ee	dr
4b[b]	*p*-OMe	*p*-NO_2	91	99	25:1
4c[b]	*p*-Me	*p*-NO_2	90	99	>99:1
4d[c]	H	*p*-NO_2	78	96	>99:1
4e	*p*-OMe	*p*-CO_2Me	99	92	25:1
4f	*p*-Me	*p*-CO_2Me	97	98	37:1
4g	H	*p*-CO_2Me	76	96	25:1
4h	*p*-OMe	*o*-CF_3	97	86	29:1
4i	*p*-Me	*o*-CF_3	85	98	>99:1
4j	H	*o*-CF_3	78	89	36:1
4k	*p*-OMe	*p*-CF_3	93	84	37:1
4l	*p*-Me	*p*-CF_3	88	86	56:1
4m	H	*p*-CF_3	90	91	45:1
4n	*p*-OMe	*p*-OAc	90	80	50:1
4o	*p*-Me	*p*-OAc	73	90	70:1
4p	H	*p*-OAc	52	91	92:1
4q	*p*-F	*p*-OAc	60	87	>99:1
4r	*p*-OMe	H	92	86	54:1
4s	*p*-Me	H	77	92	>99:1
4t	*p*-F	H	75	87	87:1

[a] Run using 1.0 mmol substrate treated with $Pd_2(dba)_3$ (0.05 mmol) and **L4** (0.11 mmol) in CH_2Cl_2 at room temperature for 4−6 h. [b] Run in CH_2Cl_2 at 40 °C for 29 h. [c] Run in toluene at 80 °C for 6 h.

Scheme 3

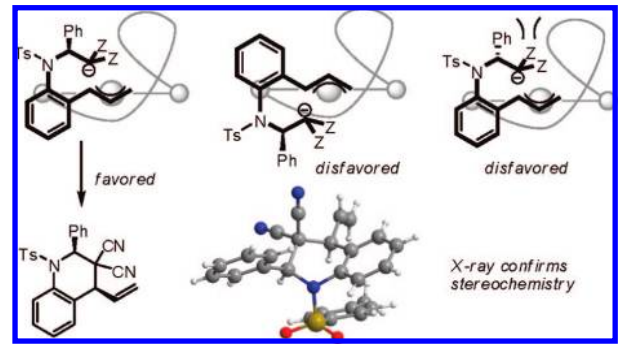


the cycloaddition proceeded with both high enantioselectivity and diastereoselectivity; the ee's and dr's of the product dihydroquinolines before recrystallization are shown in Table 2. Highly electron-deficient olefins slowed the reaction substantially, presumably because of favorable binding to the Pd(0) catalyst.[11] Thus, in contrast to most reactions which were facile at room temperature, the nitro-containing benzylidene malononitrile (entry **4d**, Table 2) required 80 °C for the reaction to proceed. It is noteworthy that the reaction selectivity was largely unaffected by the increased reaction temperature.

The origin of the stereoselectivity in this reaction is not known; however, the reaction likely proceeds through aza-Michael addition of intermediate **A** to the activated olefin (Scheme 3). The resulting stabilized carbanionic intermediate can then undergo intramolecular cyclization. The two potential stereochemistry-determining steps in such a transformation are (1) the aza-Michael addition or (2) the cyclization. Since it is difficult to imagine that the chirality of the ligands could effect a highly enantioselective aza-Michael addition, our working hypothesis is that reversible conjugate addition is followed by stereochemistry-determining cyclization. This hypothesis is consistent with the pK_a values for malononitrile (11.2) and the arylsulfonamide (9−10).[12]

Curtin−Hammett analysis of the resulting kinetic scenario indicates that the major product of the reaction will result from the most favorable

Scheme 4



cyclization.[13] Elegant studies have allowed Lloyd−Jones to develop a model for the binding of Trost ligands to palladium.[14] These studies suggest that the Trost ligand binds to palladium to produce a complex of C1-symmetry where the ligand bulk is concentrated in the upper right-hand and lower left-hand quadrants. Superimposing our intermediate onto Lloyd−Jones' model gives four potential transition states for cyclization; three are shown in Scheme 4. The favored transition state results from placing the benzylidene malononitrile fragment in the least hindered quadrant and the phenyl group is directed away from the bulky ligand in back. Such a prediction is confirmed by an X-ray crystal structure of **4a** that is of sufficient quality to allow determination of the relative and absolute configuration of the product.

In conclusion, we have developed an asymmetric decarboxylative cycloaddition that proceeds through intermediates that may be viewed as palladium-polarized aza-*ortho*-xylylenes. Formal [4 + 2] cycloaddition of these intermediates produces enantioenriched hydroquinolines with high diastereoselectivity. The implied stabilization of aza-*o*-xylylenes by palladium is expected to translate to other reactive intermediates.

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Supporting Information Available: Experimental procedures, the X-ray structure of **4a**, 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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