Decarboxylative Coupling

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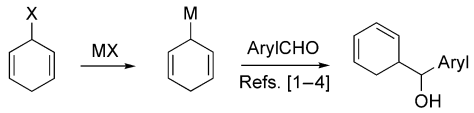
Stereospecific Palladium-Catalyzed Decarboxylative C(sp^3)–C(sp^2) Coupling of 2,5-Cyclohexadiene-1-carboxylic Acid Derivatives with Aryl Iodides**

*Chih-Ming Chou, Indranil Chatterjee, and Armido Studer**

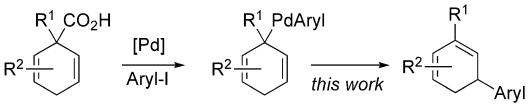
During the past few years we have shown that metalated cyclohexadienes are useful intermediates in asymmetric synthesis. Chiral cyclohexadienyl titanium derivatives, readily obtained by transmetalation of the corresponding lithiated species, react with various aldehydes with excellent stereoselectivities [Eq. (1)].[1] We later found that such desymmetrizations[2] can be run with Ag and Cu catalysts in combination with silylated and stannylated cyclohexadienes as precursors.[3,4] However, all these methods are currently restricted to the metalation of the parent 1,4-cyclohexadiene; the generation of substituted cyclohexadienyl metal intermediates has not been achieved. Moreover, as electrophiles only aldehydes and sulfinyl imines[5] have shown acceptable reactivities. We therefore decided to investigate cyclohexadienyl palladium complexes, which should make it possible to apply aryl halides electrophiles.



(1)

X = Li, Si(O*i*Pr)$_3$, SnBu$_3$ M = TiR$_3$, AgL$_n$, CuL$_n$

Along this line, we planned to use cyclohexadienyl carboxylic acids as precursors which are readily available by Birch reduction [Eq. (2)].[6] We note that substituted cyclohexadienyl compounds are easily accessible by the Birch approach, and generation of organometallic compounds through decarboxylation of the corresponding metal carboxylates has been intensively investigated.[7–9] Substituents R^1 and R^2 should strongly influence C–C bond formation for steric reasons, and this should make it possible to control the regioselectivity of the C–C bond formation. Herein, we present highly stereospecific Pd-catalyzed arylations of cyclohexadienyl carboxylic acids. Whereas stereoselective allylation through metal-catalyzed decarboxylative metalation has been reported,[8] to our knowledge stereoselective C(sp^3)–C(sp^2) bond formation through metal-catalyzed decarboxylative arylation is unknown.

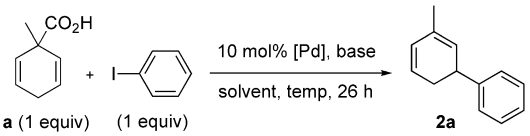


(2)

To evaluate our new concept, we first investigated the decarboxylative coupling of readily prepared 1-methyl-2,5-cyclohexadiene-1-carboxylic acid (**1a**; see the Supporting Information) with iodobenzene in the presence of 10 mol% of Pd(OAc)$_2$, 20 mol% of P(*o*-tol)$_3$, and various bases. Reactions were conducted in toluene at 110°C for 26 h.

With *t*BuOK, *t*BuOLi, and K$_2$CO$_3$ little or no formation of the targeted phenylated cyclohexadiene **2a** was observed (Table 1, entries 1–3). The yield was improved to 30% by switching to Cs$_2$CO$_3$ (Table 1, entry 4). We then studied the

Table 1: Decarboxylative coupling of **1a** with iodobenzene to give **2a**.



1a (1 equiv) (1 equiv) **2a**

Entry[a]	Pd cat.	Base[b]	Solv.	*T* [°C]	Lig.[c]	Yield [%][d]
1	Pd(OAc)$_2$	*t*BuOK	toluene	110	P(*o*-tol)$_3$	8
2	Pd(OAc)$_2$	*t*BuOLi	toluene	110	P(*o*-tol)$_3$	0
3	Pd(OAc)$_2$	K$_2$CO$_3$	toluene	110	P(*o*-tol)$_3$	<2
4	Pd(OAc)$_2$	Cs$_2$CO$_3$	toluene	110	P(*o*-tol)$_3$	30
5	Pd(OAc)$_2$	Cs$_2$CO$_3$	toluene	110	–	15
6	Pd(OAc)$_2$	Cs$_2$CO$_3$	toluene	110	PPh$_3$	12
7	Pd(OAc)$_2$	Cs$_2$CO$_3$	toluene	110	PCy$_3$	27
8	Pd(OAc)$_2$	Cs$_2$CO$_3$	toluene	110	P*t*Bu$_3$	47
9	Pd(OAc)$_2$	Cs$_2$CO$_3$	toluene	110	dppb	<2
10	Pd(OAc)$_2$	Cs$_2$CO$_3$	toluene	110	binap	<2
11	**[Pd(dba)$_2$]**	**Cs$_2$CO$_3$**	**toluene**	**110**	**–**	**63**
12	[Pd$_2$(dba)$_3$]	Cs$_2$CO$_3$	toluene	110	–	59
13	[Pd(dba)$_2$]	Cs$_2$CO$_3$	toluene	110	P*t*Bu$_3$	57
14	[Pd(dba)$_2$]	Cs$_2$CO$_3$	NMP	90	–	<2
15	[Pd(dba)$_2$]	Cs$_2$CO$_3$	THF	60	–	41
16	[Pd(dba)$_2$]	Cs$_2$CO$_3$	DCE	80	–	36
17[e]	[Pd(dba)$_2$]	Cs$_2$CO$_3$	toluene	110	–	55
18[f]	[Pd(dba)$_2$]	Cs$_2$CO$_3$	toluene	110	–	41

[a] Test experiments conducted at 0.3 M. [b] With 1.1 equiv of base. [c] With 20 mol% of additive. [d] Yield of isolated product. [e] With 5 mol% of Pd. [f] With 1.5 equiv of Cs$_2$CO$_3$.

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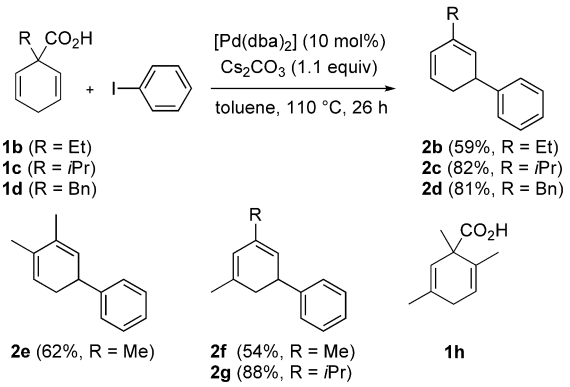
effect of the P ligand, keeping Cs_2CO_3 as base. The reaction in the absence of any ligand under otherwise identical conditions was low yielding (Table 1, entry 5). The yield improved when electron-rich monodentate phosphines were used (Table 1, entries 6–8), and with bidentate phosphines as ligands no product was identified (Table 1, entries 9 and 10). Pleasingly, yields increased significantly when $[Pd(dba)_2]$ and $[Pd_2(dba)_3]$ were used as precatalysts in the absence of ligands (Table 1, entries 11 and 12). Addition of P*t*Bu_3 led to a slightly lower yield (Table 1, entry 13), therefore the following optimizations were conducted without P ligand. Solvent screening revealed that toluene is best suited for this reaction (Table 1, entries 14–16). Reducing the $[Pd(dba)_2]$ loading or increasing the amount of Cs_2CO_3 provided worse results (Table 1,entries 17 and 18). Based on these initial studies, all following experiments were conducted with 10 mol% of $[Pd(dba)_2]$, 1.1 equiv of Cs_2CO_3, and 1.1 equiv of aryl iodide in toluene at 110 °C for 26 h.

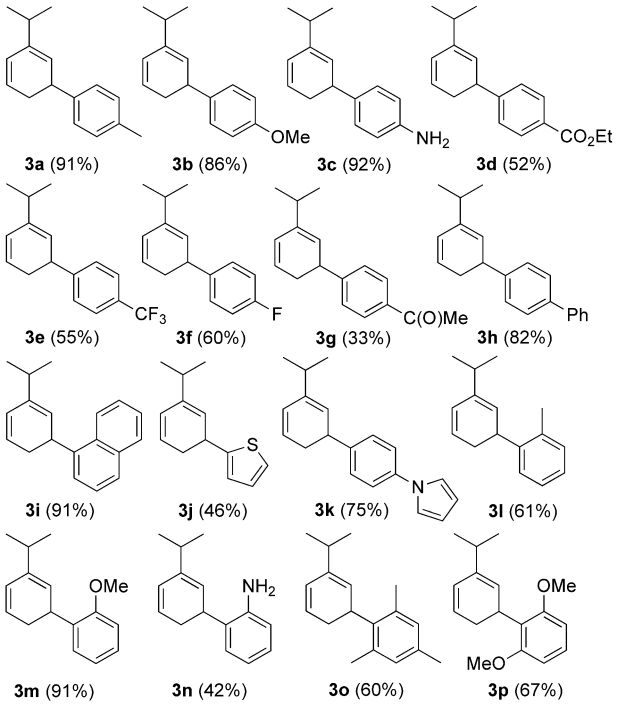
In order to evaluate the substrate scope, cyclohexadienyl carboxylic acids **1b–g** were prepared and reacted under optimized conditions with iodobenzene to give **2b–g** (see Scheme 1 and the Supporting Information). The size of the



Scheme 1. Decarboxylative coupling of substituted 2,5-cyclohexadiene-1-carboxylates with iodobenzene. dba = *trans*,*trans*-dibenzylideneacetone.

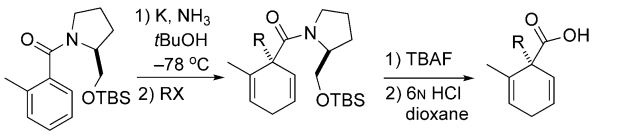
α substituent influenced the reaction outcome, and the highest yields were achieved with isopropyl- and benzyl-substituted acids **1c**,**d**. Substrates without an α substituent gave low yields. Thanks to the reliable Birch reduction, the substitution pattern at the cyclohexadiene core was readily varied. An additional methyl group either at the 2- or 3-position of the 2,5-cyclohexadiene-1-carboxylate was tolerated, and reactions occurred with excellent regioselectivity to give **2e** and **2f**, respectively. Again with the larger *i*Pr group at the 1-position a higher yield was achieved (see **2g**). However, the 2,5-dimethyl derivative **1h** did not deliver the corresponding coupling product, likely for steric reasons.

We then varied the iodoarene component in the Pd-catalyzed decarboxylative coupling with **1c**, and products **3a–p** were obtained in moderate to excellent yields. Aryl iodides with methoxy, methyl, aminyl, ethoxycarbonyl, trifluoromethyl, fluoro, and acyl substituents in the *para* position were tolerated. However, electronic effects strongly influenced the reaction outcome. Whereas the decarboxylative coupling of aryl iodides bearing electron-donating substituents provided the corresponding products in high yields, iodobenzene derivatives with electron-deficient groups were significantly less reactive. 4-Iodobiphenyl, 1-iodonaphthalene, and also *N*-phenylpyrrole were good substrates for the decarboxylative coupling (**3h**, **3i**, **3k**). Reductive elimination, which is in competition with aromatization, is known to be faster for electron-rich aryl groups and this is reflected by the yields obtained.



Also a heteroarene, 2-iodothiophene, was successfully reacted to give the corresponding coupling product **3j**. We were pleased to find that *ortho*-substituted aryl iodides were also transformed into the corresponding decarboxylation/coupling products (**3l–n**). Even sterically hindered 2,6-disubstituted aryl iodides underwent smooth reaction with **1c** (see **3o**,**p**).

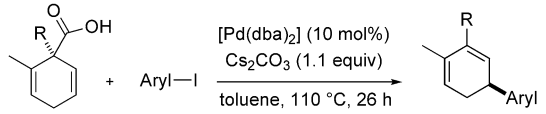
Encouraged by these results, we decided to study the stereospecificity of the decarboxylative coupling reaction. To this end, the chiral 2-methyl-2,5-cyclohexadiene-1-carboxylic acids **6a**,**b** were prepared in enantioenriched form by using a slightly modified procedure of a known asymmetric Birch reductive alkylation (Scheme 2, see the Supporting Information).[10] Amides **5a**,**b** were obtained from chiral amide **4** in good yields and good to excellent diastereoselectivities. Amide hydrolysis was achieved by desilylation and subsequent amide-to-ester transacylation followed by ester hydrolysis to give acids **6a**,**b** with high *ee* values and good yields.[11] For **6a** the *ee* value can be further increased to 99% by recrystallization. The relative configuration of the major isomer of **5a** was unambiguously assigned after desilylation by X-ray analysis of the corresponding alcohol (see the Supporting Information).



Scheme 2. Preparation of optically active 2-methyl-2,5-cyclohexadiene-1-carboxylic acid derivatives **6a**,**b**. TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

The enantiomerically enriched acid **6a** (93% *ee* after one recrystallization) was reacted with iodobenzene under optimized conditions to give diene **7a**, which was isolated in 62% yield. We were very pleased to find that **7a** was formed in 93% *ee*, which indicates that decarboxylation coupling occurred with perfect stereospecificity (Table 2, entry 1). Product **7a** with 99% *ee* was isolated starting from the highly enantiomerically enriched acid **6a** (Table 2, entry 2). As expected, also with substituted aryl iodides the reaction occurred with excellent stereospecificity, and products **7b–d** were isolated in good yields (Table 2, entries 3–7). Reaction of 1-iodonaphthalene with acid **6a** provided **7e** with 99% *ee* (Table 2, entry 8). Similar results were achieved using the benzylated acid **6b** to give stereospecifically the dienes **7f–h** in very good yields (Table 2, entries 9–11).

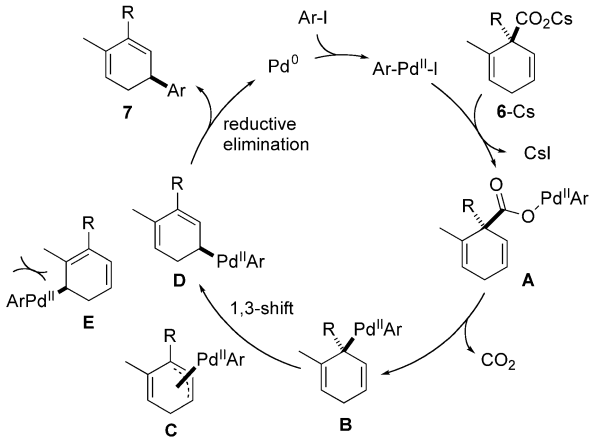
Table 2: Stereospecific Pd-catalyzed decarboxylative coupling of **6a**,**b** with various aryl iodides.



Entry	R	*ee* (**6**) [%][a]	Aryl	Yield [%][b]	*ee* (**7**) [%][c]
1	Me	93[d]	Ph	62	93 (**7a**)
2	Me	99[e]	Ph	63	99 (**7a**)
3	Me	93[d]	4-MeC_6H_4	66	93 (**7b**)
4	Me	99[e]	4-MeC_6H_4	68	99 (**7b**)
5	Me	93[d]	4-$MeOC_6H_4$	73	93 (**7c**)
6	Me	99[e]	4-$MeOC_6H_4$	72	99 (**7c**)
7	Me	99[e]	4-$NH_2C_6H_4$	77	99 (**7d**)
8	Me	99[e]	1-naphthyl	72	99 (**7e**)
9	Bn	94	Ph	81	94 (**7f**)
10	Bn	94	4-MeC_6H_4	92	94 (**7g**)
11	Bn	94	4-$NH_2C_6H_4$	93	94 (**7h**)

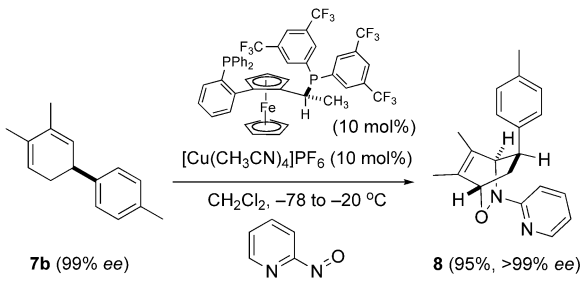
[a] Determined by GC analysis with a chiral stationary phase. [b] Yield of isolated product. [c] Determined by HPLC analysis with a chiral stationary phase. [d] After a single recrystallization. [e] After two recrystallizations.

Our proposed mechanism for the highly stereospecific Pd-catalyzed decarboxylative coupling reaction is shown in Scheme 3. Oxidative addition of aryl iodide to Pd^0 provides ArPdI, which undergoes ligand exchange with the cesium salt of **6** to give intermediate **A**. Decarboxylation provides the 2,5-cyclohexadienyl palladium species **B** with retention of stereochemistry. Stereospecific 1,3-Pd migration likely via allyl palladium complex **C** delivers the 2,4-cyclohexadienyl palladium intermediate **D**, which upon reductive elimination eventually affords arylated cyclohexadienes **7** along with the regenerated Pd^0 to complete the catalytic cycle. Alternatively, decarboxylation of **A** might directly lead to **C**. 1,3-Pd migration from **B** might also deliver the regiosiomeric palladium complex **E**. However, for steric reasons reductive elimination in **E** is slow and **B** can be regenerated through 1,3-Pd migration. In side reactions, **B**, **D**, and **E** can undergo β-H elimination to provide the corresponding arene directly (for **D**, **E**) or after tautomerization (for **B**).



Scheme 3. Suggested catalytic cycle (Ar = aryl).

The chiral product dienes are highly interesting building blocks in synthesis. To show their potential, we subjected diene **7b** to nitrosopyridine in our recently developed Cu-catalyzed nitroso Diels–Alder reaction (NDA).[12] Face and also regiochemistry was perfectly controlled, and product **8** was isolated as a single isomer with high yield (Scheme 4).[13] As previously shown, the chiral center at the diene moiety, in concert with the chiral Cu catalyst, steers the regioselectivity of the NDA reaction.[12]



Scheme 4. Regioselective nitroso-Diels–Alder reaction.

In conclusion, we have described a highly stereospecific Pd-catalyzed decarboxylative arylation of 2,5-cyclohexadiene-1-carboxylic acids. The resulting 5-arylated-1,3-cyclohexadienes are useful bulding blocks in synthesis.[14] The starting carboxylic acids are readily prepared by Birch

reduction. To our knowledge, this is the first report of the stereoselective formation of $C(sp^3)$–$C(sp^2)$ bonds through decarboxylative arylation.

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Keywords: asymmetric synthesis · Birch reduction · C–C bond formation · homogeneous catalysis · palladium

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[13] The assignment of the relative configuration is based on ^{1}H NMR analysis. The regiochemistry obtained in the nitroso-Diels–Alder reaction fits with our model (see Refs. [12a,b]) and further supports the correct assignment of the absolute configuration of **7b**.

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