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Controlling Olefin Isomerization in the Heck Reaction with Neopentyl Phosphine Ligands

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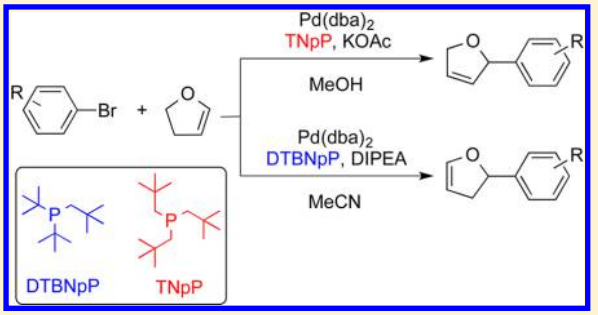
Supporting Information

ABSTRACT: The use of neopentyl phosphine ligands was examined in the coupling of aryl bromides with alkenes. Di-*tert*-butylneopentylphosphine (DTBNpP) was found to promote Heck couplings with aryl bromides at ambient temperature. In the Heck coupling of cyclic alkenes, the degree of alkene isomerization was found to be controlled by the choice of ligand with DTBNpP promoting isomerization to a much greater extent than trineopentylphosphine (TNpP). Under optimal conditions, DTBNpP provides high selectivity for 2-aryl-2,3-dihydrofuran in the arylation of 2,3-dihydrofuran, whereas TNpP provided high selectivity for the isomeric 2-aryl-2,5-dihydrofuran. A similar complementary product selectivity is seen in the Heck coupling of cyclopentene. Heck coupling of 2-bromophenols or 2-bromoanilides with 2,3-dihydrofurans affords 2,5-epoxybenzoxepin and 2,5-epoxybenzazepins, respectively.



INTRODUCTION

Since the seminal reports in the early 1970s by Mizoroki[1] and Heck[2] of the palladium-catalyzed reactions of organic halides with olefins, the Heck reaction has become one of the most used metal-catalyzed carbon−carbon bond forming methods.[3] Heck reactions with styrene and acrylate ester olefin coupling partners produce a single vinyl arene product. However, reactions with alkyl olefins bearing allylic protons result in product mixtures due to varying degrees of migration of the newly formed carbon−carbon double bond (Figure 1).

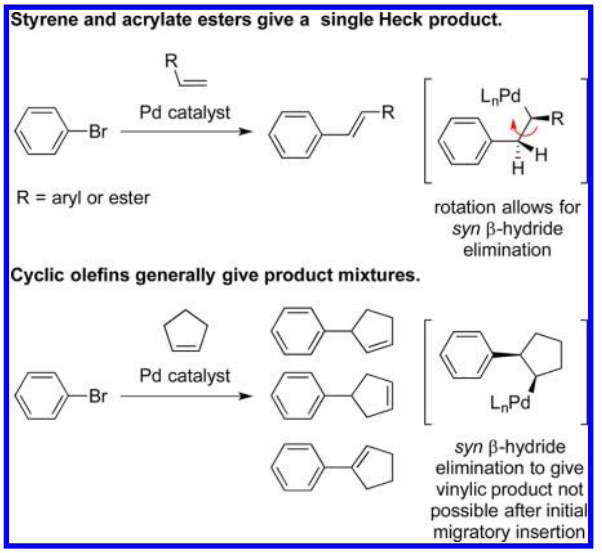


Figure 1. Product selectivity in the Heck reaction.

Santelli and co-workers found that a number of reaction conditions including base, solvent, and temperature affect the selectivity in the coupling of aryl bromides with linear and branched 1-alkenes when utilizing a tetraphosphine palladium catalyst.[4] Often isomerization can be suppressed with the addition of stoichiometric Ag(I) or Tl(I) salts.[5]

Cyclic olefins have the added complication of the thermodynamically favored 1-arylcycloalkene product being inaccessible via *syn* β-hydride elimination after the initial migratory insertion of the olefin into the Pd−Ar bond (Figure 1).[6] Under a large number of conditions, double bond migration is believed to occur via a "chain-walking" mechanism in which the hydridopalladium species does not undergo olefin exchange.[7] As a result, a mixture of allylic and homoallylic products is generally formed with only minor amounts of the vinylic product. Beller and co-workers reported conditions ($Pd_2(dba)_3$·dba, PCy_3, Na_2CO_3, DMA, 140 °C) for the Heck reaction of aryl bromides and cyclopentene where the double bond isomerization is a result of base-catalyzed isomerization and not the resulting hydridopalladium complexes.[8] As a result, sodium acetate gives the allylic olefin as the major product, whereas the more basic sodium carbonate provides the conjugated vinyl olefin as the major product.

Zhou and co-workers recently reported conditions for achieving excellent vinyl selectivity in the Heck coupling of cyclic olefins in which the resulting hydridopalladium complex is responsible for the isomerization.[6,9] In order to access the vinyl arene product, the hydridopalladium intermediate must be able to undergo olefin exchange of the initial allylic olefin

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product. Zhou proposes that stabilization of the hydridopalladium complex by the solvent (veratrole, DMPU) allows for the hydridopalladium complex to switch faces in order to undergo *syn* β-hydride elimination to give the thermodynamically most stable vinyl arene product.[6] Chelating ligands have been used to control the selectivity in the Heck reaction of cyclic olefins. The trend that stronger σ-donating ligands on palladium promote isomerization was observed.[10] *Trans*-chelating ligands also can affect the selectivity.[11]

Although a plethora of reaction conditions are reported for use in the Heck reaction, bulky, electron rich phosphines afford some of the most active catalysts.[12] Neopentylphosphines have received attention as bulky, electron rich phosphines (Figure 2). Catalysts derived from di-*tert*-butylneopentylphosphine

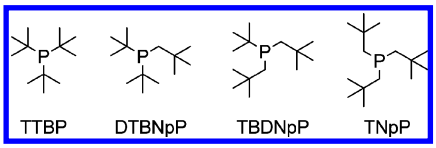


Figure 2. Neopentyl phosphine ligands.

(DTBNpP) have a reactivity similar to those derived from tri-*tert*-butylphosphine (TTBP), catalyzing the Suzuki, Sonogashira, and Buchwald–Hartwig couplings at room temperature.[13] *tert*-Butyldineopentylphosphine (TBDNpP) and trineopentylphosphine (TNpP) generally proved to be less reactive at ambient temperature, presumably due to their weaker electron donating ability.[13a] Recently, however, TNpP in combination with $Pd_2(dba)_3$ was found to be an extremely active catalyst in the Buchwald–Hartwig couplings of amines and enolates with sterically hindered aryl bromides and chlorides at temperatures from 80 to 100 °C.[13d,14] The surprising success of TNpP with sterically hindered substrates is believed to come from the added conformational flexibility of the neopentyl groups relative to the more static *tert*-butyl groups.

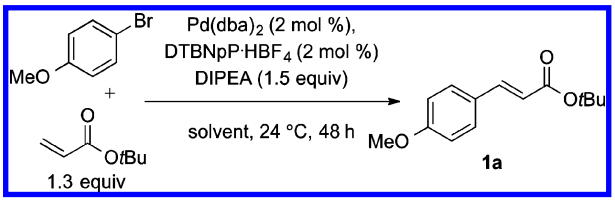
Herein, we report ligand controlled olefin isomerization in the Heck reaction of cyclic olefins utilizing DTBNpP and TNpP. DTBNpP was found to promote isomerization of the resulting olefins, whereas TNpP results in minimal isomerization under otherwise identical conditions. The catalyst derived from DTBNpP affords epoxybenzoxepins and epoxybenzazepins from 2,3-dihydrofuran (2,3-DHF) and 2-bromophenols or 2-bromoaniline derivatives.

RESULTS AND DISCUSSION

The Heck reaction of aryl bromides with acrylates and styrene utilizing DTBNpP as a ligand was first explored in an attempt to find mild reaction conditions. Our group previously reported that elevated temperatures (80–100 °C) were required for the coupling of aryl bromides with styrene in dioxane when DTBNpP was utilized as a ligand for palladium.[13b] A brief solvent screen revealed that the coupling of 4-bromoanisole with *tert*-butyl acrylate proceeded at room temperature in a number of polar aprotic solvents with DMF, providing the best conversion (Table 1, entries 1–7). Both *N*,*N*-diisopropylethylamine (DIPEA) and *N*,*N*-dicyclohexylmethylamine gave similar conversions to **1a** (entries 1 and 8). Very low conversion was obtained when TNpP was used as the ligand under these conditions (entry 9).

Electron rich and poor aryl bromides both gave high yields of the desired coupled products (**1**) with acrylate esters and

Table 1. Optimization of Room-Temperature Heck Reaction

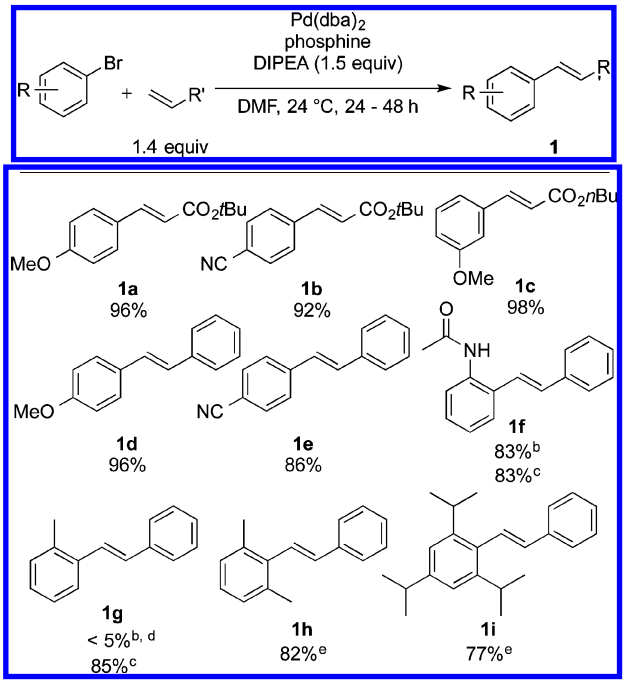


entry	solvent	% conv.[a]	entry	solvent	% conv.[a]
1	DMF	98	6	toluene	26
2	MeCN	77	7	MeOH	25
3	acetone	76	8[b]	DMF	98
4	DMSO	72	9[c]	DMF	3
5	dioxane	60			

[a]% conversion determined by relative GC areas of 4-bromoanisole and **1a**. [b]*N*,*N*-Dicyclohexylmethylamine (1.5 equiv) used as base. [c]TNpP (2 mol %) used as ligand.

styrene (Table 2). 2-Bromoacetanilide could be successfully coupled with styrene to produce **1f** in an 83% yield using

Table 2. Heck Reactions of Acrylates and Styrenes[a,b,c,d,e]



[a]Yields are an average of two 1 mmol reactions. Reaction conditions: ArBr (1 mmol), alkene (1.4 equiv), $Pd(dba)_2$ (2 mol %), DTBNpP (2 mol %), DIPEA (1.5 equiv), DMF, 24 °C. [b]Reaction performed at 80 °C with $Pd(dba)_2$ (2 mol %) and DTBNpP (2 mol %). [c]Reaction performed at 80 °C with $Pd(dba)_2$ (2 mol %) and TNpP (4 mol %). [d]Determined by GC analysis. [e]Reaction performed at 160 °C with $Pd(dba)_2$ (5 mol %) and TNpP (10 mol %).

DTBNpP at 80 °C; however 2-bromotoluene gave <5% conversion to **1g** under identical conditions. TNpP was previously shown to outperform DTBNpP with sterically hindered substrates in both the Buchwald–Hartwig and the Suzuki couplings, so the use of TNpP with 2-bromotoluene and other hindered *ortho*-substituted aryl bromides was examined.[14]

Although TNpP gave low conversions at ambient temperature for nonhindered substrates (Table 1, entry 9) it gave a good yield (85%) of **1g** at 80 °C. Di-*ortho*-substituted products **1h** and **1i** could also be formed in good yield utilizing TNpP,

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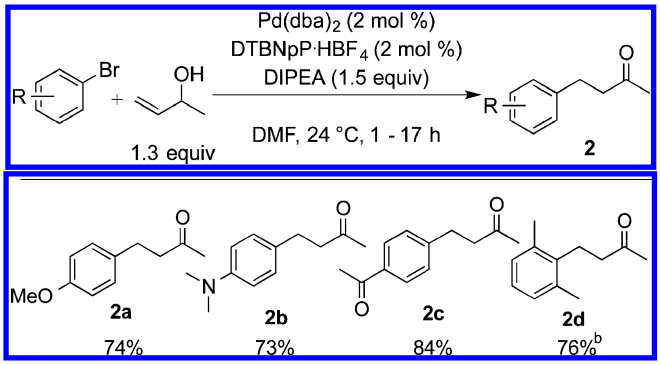
although a higher temperature (160 °C) and catalyst loading (5 mol % $Pd(dba)_2$) were required.

3-Buten-2-ol also reacted with a number of aryl bromides under the standard reaction conditions to give the corresponding methyl ketone as the major product (Table 3). The

Table 3. Heck Reactions with 3-Buten-2-ol[a,b]

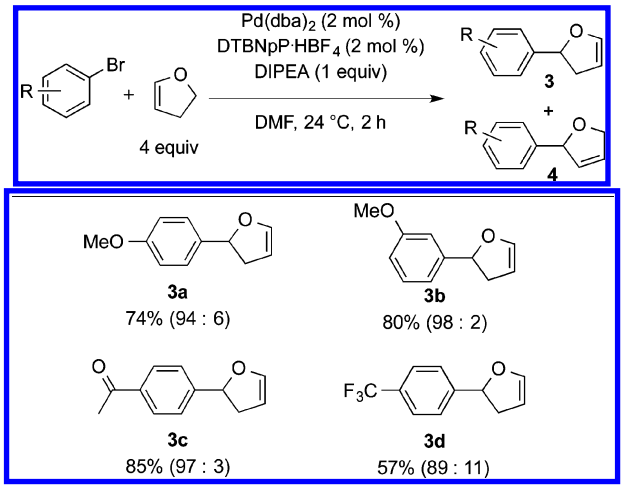


[a]Yields are an average of two 1 mmol reactions. [b]Reaction performed with $Pd(dba)_2$ (5 mol %), TNpP (10 mol %), 160 °C.

reactions producing products **2a** and **2b** from the electron rich aryl bromides were remarkably fast, reaching completion within 2 h at 24 °C. 3-Buten-2-ol could be coupled with the sterically hindered aryl bromide, 2-bromo-1,3-dimethylbenzene, utilizing TNpP as the ligand to produce **2d** in a yield of 76%.

Next, Heck reactions were examined utilizing 2,3-DHF as the olefin coupling partner (Table 4). The conditions optimized for

Table 4. Heck Reactions with 2,3-DHF[a]

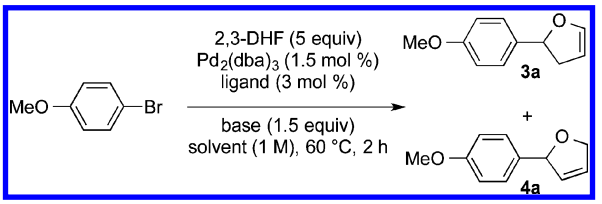


[a]Isolated yields of **3** are an average of two 1 mmol scale reactions. Ratios in parentheses (**3**:**4**) are of the crude reaction mixture and were determined by GC peak area.

acrylates and styrene gave high selectivity for 2,3-DHF products (**3**) within 2 h at ambient temperature. Both electron rich and poor aryl bromides produced good yields and selectivity for the 2,3-DHF product (**3**).

Once again, TNpP failed to give a high conversion at ambient temperature. When utilizing DTBNpP at 60 °C, a number of different solvents produced good yields of the 2,3-DHF product (**3**), so the use of TNpP was explored at 60 °C. Surprisingly, TNpP produced the opposite selectivity to that seen with DTBNpP, producing the 2,5-DHF product (**4**), under otherwise identical conditions (Table 5). Conditions

Table 5. Optimization of Heck Reaction with 2,3-DHF[a]



entry	solvent	base	ligand	3a:4a[a]	yield (%)[a]
1	MeCN	DIPEA	DTBNpP	88:12	79
2	MeCN	DIPEA	TNpP	29:71	79
3	MeCN	KOAc	DTBNpP	66:34	86
4	MeCN	KOAc	TNpP	15:85	92
5	MeOH	DIPEA	DTBNpP	72:28	20[b]
6	MeOH	DIPEA	TNpP	17:83	83
7	MeOH	KOAc	DTBNpP	60:40	82
8	MeOH	KOAc	TNpP	8:92	95
9	MeOH	KOAc	TNpP[c]	4:96	98
10	MeCN	DIPEA	TTBP	89:11	72
11	MeOH	KOAc	TTBP	90:10	68
12	MeCN	DIPEA	PCy_3	6:94	32[b]
13	MeOH	KOAc	PCy_3	1:99	37[b]
14[d]	MeOH	KOAc	PCy_3	1:99	52[b]
15[d]	MeOH	KOAc	TNpP	1:99	98

[a]Product ratios and yields were determined by GC using an internal standard on a 0.25 mmol scale; yield refers to the total yield of both product isomers (**3a** and **4a**). [b]Reaction did not reach completion. [c]6 mol % of TNpP was used in the reaction. [d]Reaction conducted at 80 °C for 17 h.

were then optimized with TNpP for the 2,5-DHF product (**4**). Methanol and potassium acetate proved to be the best solvent and base combination with TNpP to give the highest selectivity for the 2,5-DHF product (**4**) (entries 8 and 9). Under a series of different conditions, DTBNpP consistently gave selectivity for the 2,3-DHF product (**3**) (entries 1, 3, 5, and 7), whereas TNpP gave selectivity for the 2,5-DHF product (**4**) (entries 2, 4, 6, and 8). Although the choice of base and solvent affects the product selectivity, ligand choice seems to be the most important factor in controlling double bond isomerization. TTBP gave excellent selectivity for the 2,3-DHF product (**3**) under both sets of optimized conditions (entries 10 and 11), although in lower yields than achieved with DTBNpP. Tricyclohexylphosphine (PCy_3) produced 2,5-DHF product **4** with good selectivity, but the reactions failed to reach completion under the two sets of optimized conditions (entries 12 and 13). The reaction utilizing PCy_3 still failed to reach completion at 80 °C for 17 h, whereas TNpP still gave excellent yield and selectivity for product **4** at 80 °C (entries 14 and 15).

The substrate scope was examined after optimized conditions were found (Table 6). The DTBNpP conditions gave good yields and selectivity for a number of 2,3-DHF products (**3**) derived from electron rich and deficient aryl bromides. The conditions with TNpP worked well, producing excellent selectivity for the 2,5-DHF products **4a**, **4b**, and **4f**. However, the products **4c**, **4d**, and **4e** derived from electron deficient aryl bromides gave lower selectivity for 2,5-DHF product (**4**), while requiring higher temperatures and reaction times. Not surprisingly, the DTBNpP-derived catalyst gave low conversions with the more hindered 2-bromotoluene, affording only a 35% yield of *ortho*-substituted **3g**, although with high selectivity for the 2,3-DHF product. The conditions to produce 2,5-DHF (**4**) utilizing the more conformationally flexible TNpP

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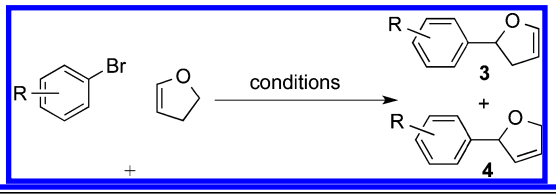
Table 6. Heck Reaction with 2,3-DHF[a,b,c]



Ar-Br	conditions[a]	ratio **3** : **4**[b]	% yield[c]
MeO–Br	A	87 : 13	66 (**3a**)
	B	3 : 97	82 (**4a**)
MeO, Br	A	97 : 3	81 (**3b**)
	B	4 : 96	72 (**4b**)
O, Br	A	96 : 4	86 (**3c**)
	C	13 : 87	80 (**4c**)
F_3C–Br	A	97 : 3	57 (**3d**)
	C	19 : 81	64 (**4d**)
NC–Br	A	90 : 10	72 (**3e**)
	C	23 : 77	60 (**4e**)
Br	A	96: 4	61 (**3f**)
	B	4 : 96	72 (**4f**)
Br	A	98 : 2	35 (**3g**)
	C	2 : 98	70 (**4g**)
S, Br	A	95 : 5	66 (**3h**)
	C	2 : 98	62 (**4h**)
Cl–Br	A	94 : 6	64 (**3i**)
	C	3 : 97	90 (**4i**)

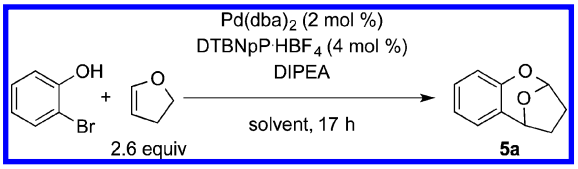
[a]Conditions: A: 2,3-DHF (5 equiv), $Pd_2(dba)_3$ (1.5 mol %), DTBNpP (3 mol %), DIPEA (1.5 equiv), MeCN, 60 °C, 2 h. B: 2,3-DHF (2.5 equiv), $Pd_2(dba)_3$ (1.5 mol %), TNpP (6 mol %), KOAc (1.5 equiv), MeOH, 60 °C, 2–5 h. C: 2,3-DHF (5 equiv), $Pd_2(dba)_3$ (1.5 mol %), TNpP (6 mol %), KOAc (1.5 equiv), MeOH, 80 °C, 5–17 h. [b]Ratios are based on GC peak areas of reaction mixture. [c]Isolated yields of major isomer.

produced a good yield (70%) and excellent selectivity (98%) for **4g**. The heterocyclic compound 3-bromothiophene produced good yield and selectivity for products **3h** and **4h**. However, 2-bromopyridine failed to react under optimized conditions. 1-Bromo-4-chlorobenzene and 2,3-DHF selectively coupled at the carbon containing the bromine to give 4-chlorophenyl products **3i** and **4i** in good yield and selectivity. 4-Chlorotoluene failed to react with 2,3-DHF under both sets of optimized conditions. The activated aryl chloride 4-chloroacetophenone produced 76% conversion to product in 17 h with the DTBNpP-derived catalyst at 80 °C with excellent selectivity for the 2,3-DHF product **3c** (98:2). 4-Chloroacetophenone failed to react with 2,3-DHF with the catalyst system derived from TNpP.

When the conditions optimized for the 2,3-DHF products (**3**) were applied to 2-bromophenol, a mixture of DHF products **3** and **4** were formed along with a small amount of 2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepin (**5a**) (Table 7, entry 2). A structure similar to that of **5a** is found in the core of the spiroxins, a family of marine-derived antitumor antibiotics.[15] A catalytic amount of 2-propanol was found to promote formation of **5a**, although its role is not clear at this time (entry 4). It was found that lowering the equivalents of DIPEA from 1.5 to 1.0 resulted in the formation of **5a** without contamination by the 2,3-DHF product (**3**) (entries 5–7). This effect is presumably due to slower reductive elimination of the hydridopalladium species with the lower base concentration. As a result, there is ample time for the palladium–hydride bond to reinsert across the 2,3-DHF product (**3**) to allow reductive elimination of the carbon–oxygen bond (Scheme 1, path A). The cyclization could also occur via the formation of a carbocation intermediate that is then trapped by the pendant alcohol (path B).[16] Acetone and MeCN were both found to be viable solvents for the cyclization reaction. Holzapfel and co-workers previously reported the formation of **5a** via a Heck reaction between 2-hydroxyarylmercuric salts and 2,3-DHF with 1 equiv of $Pd(OAc)_2$ in THF.[17]

The 2-bromophenol substrates were shown to tolerate both electron donating and withdrawing groups *para* to the OH (Table 8). Next, 2-bromoaniline was examined to see if it would give epoxybenzazepins similar to the structure found at the core of the recently reported pyrroloiminoquinone alkaloid, atkamine.[18] Unfortunately 2-bromoaniline failed to react with 2,3-DHF to give product **5e**. However, cyclization proceeded with the addition of an acetyl or tosyl protecting group to the

Table 7. Optimization for the Formation of 5a



entry	solvent	*T* (°C)	DIPEA (equiv)	additive	yield (%)[a]
1	DMF	24	1		0
2	MeCN	80	1.5		5
3	acetone	80	1.5		8
4	acetone	80	1.5	*i*PrOH (0.5 equiv)	26
5	MeCN	80	1		54
6	acetone	80	1		55
7	acetone	80	1	*i*PrOH (0.5 equiv)	61

[a]Yield determined by ^{1}H NMR analysis of the reaction mixture with an internal standard.

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Scheme 1. Plausible Mechanisms for Formation of 5a

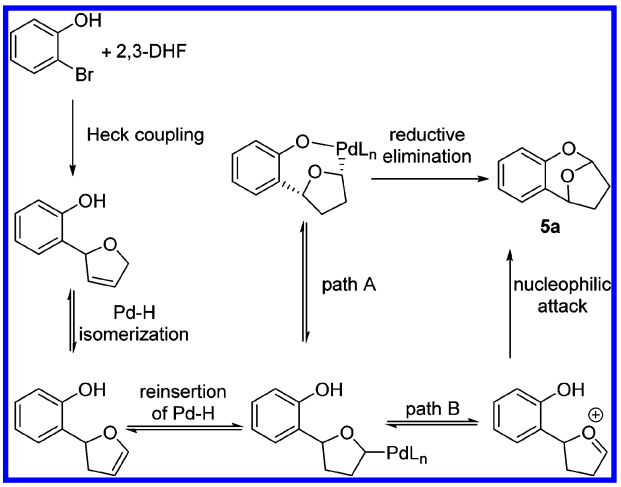
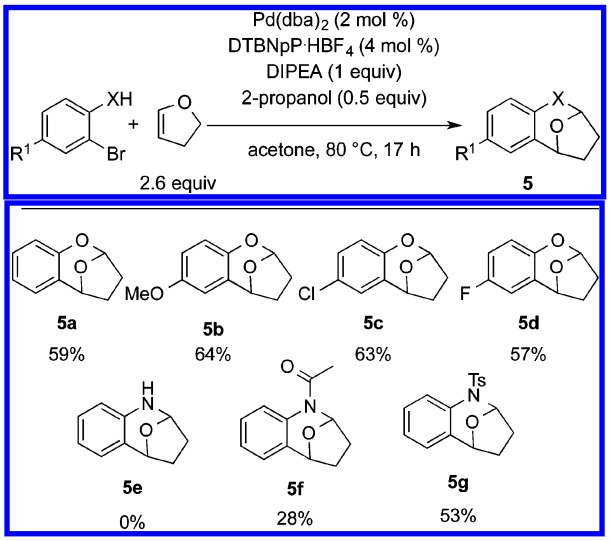


Table 8. Heck Reaction of 2-Bromo-Phenols and Anilines with 2,3-DHF Producing 5[a]



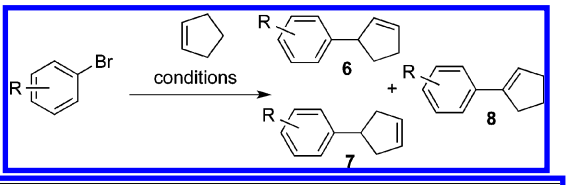
[a]Yields are an average of two 1 mmol reactions.

aniline starting material to produce **5f** and **5g**, with the tosyl group providing a higher yield.

Cyclopentene was next explored as a coupling partner in the Heck reaction (Table 9). The conditions optimized for DTBNpP at 80 °C gave allylic olefin product **6** as the major product, albeit with poor selectivity (Table 9, conditions A). When conditions optimized for TNpP at 80 °C were used, **6** was once again formed as the major product, but with much better selectivity (Table 9, conditions B). When utilizing TNpP as the ligand, there was minimal isomerization producing only traces of the vinylic product **8** (2−3%). Both sets of conditions (A and B) produced measurable amounts of the homoallylic product **7** that could not be isolated from allylic product **6** via column chromatography. The TNpP conditions (B) produced less of the homoallylic product **7** compared to the DTBNpP conditions (A).

When the cyclization conditions (Table 9, conditions C) for the formation of **5** where applied to the coupling of 2-bromophenol and cyclopentene, no cyclized product was observed. However, the vinylic product **8d** was formed in excellent selectivity (>99%) and in high yield (90%). Cyclization may not occur due to the increased stability of

Table 9. Heck Reaction of Cyclopentene[a,b,c]



Ar-Br	conditions [a]	ratio ((6+7) : 8) [b]	% yield [c]
MeO–Br	A	63 : 37	55 + 18 (**6a** + **7a**)
	B	98 : 2	66 + 10 (**6a** + **7a**)
	C	1 : 99	93 (**8a**)
O–Br	B	97 : 3	84 + 10 (**6b** + **7b**)
	C	<1 : 100	94 (**8b**)
NC–Br	B	97 : 3	58 + 13 (**6c** + **7c**)
	C	2 : 98	83 (**8c**)
OH–Br	B	97 : 3	67 + 4 (**6d** + **7d**)
	C	<1 : 100	90 (**8d**)
NHAc–Br	B	97 : 3	74 + 16 (**6e** + **7e**)
	C	9 : 91	58 (**8e**)

[a]Conditions: A: cyclopentene (4 equiv), $Pd(dba)_2$ (5 mol %), DTBNpP·HBF_4 (5 mol %), DIPEA (1.5 equiv), acetone, 80 °C, 24 h. B: cyclopentene (4 equiv), $Pd(dba)_2$ (5 mol %), TNpP (10 mol %), KOAc (1.5 equiv), MeOH, 80 °C, 24 h. C: cyclopentene (4 equiv), $Pd(dba)_2$ (5 mol %), DTBNpP·HBF_4 (10 mol %), DIPEA (1 equiv), 2-propanol (0.5 equiv), acetone, 80 °C, 17 h. [b]Ratios are based on GC peak areas of reaction mixture. [c]Isolated yields, **6** and **7** were isolated as a mixture and individual yields are based on ratios obtained via NMR spectroscopy of the isolated mixture. Ratios for **6** and **7** matched (±2%) when determined from the reaction mixture via GC or from the isolated mixture after column chromatography via ^{1}H NMR spectroscopy.

the trisubstituted olefin, which does not allow for reinsertion of the hydridopalladium complex to allow for reductive elimination of the carbon oxygen bond. Alternatively, decreased stability of the potential carbocation intermediate necessary for cyclization may disfavor formation of the bicyclic ether product. When the cyclization conditions (C) were applied with other aryl halide coupling partners, the vinyl product was still obtained with excellent selectivity and good yields. The cyclization conditions apparently allow for more efficient olefin exchange of the hydridopalladium intermediates so that *syn* β-hydride elimination may occur to form the most stable conjugated vinylic product (**8**).

To help verify that the double bond isomerization is due to the hydridopalladium species generated during the reaction, a mixture of Heck products **6a** and **7a** was subjected to a hydridopalladium species generated from isobutyryl chloride (Scheme 2).[19] Subjecting **6a** and **7a** to the in situ generated palladium(II) hydride catalyst resulted in isomerization of the olefin to give **8a** as the major component. Heating Heck products **6a** and **7a** to 80 °C in the presence of DIPEA for 24 h resulted in no observable isomerization by GC analysis. As a result, it appears migration of the olefin under the reaction conditions is due to hydridopalladium species generated during the reaction and not the base, unlike the system reported by Beller and co-workers for the Heck reaction with cyclic olefins.[8]

The results with 2,3-DHF and cyclopentene show a common pattern. The catalyst derived from DTBNpP favors formation

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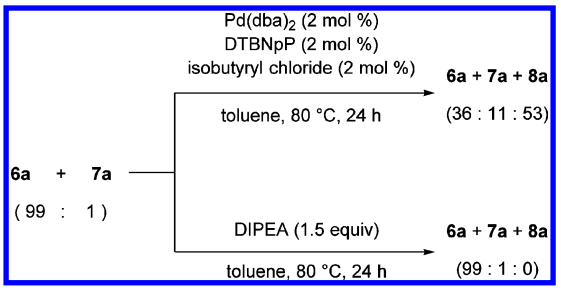
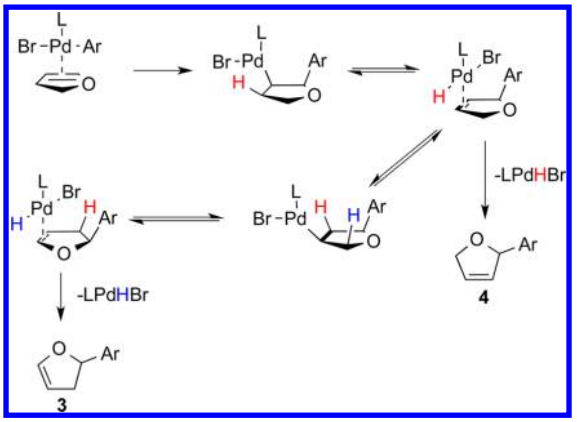
Scheme 2. Source of Double Bond Migration



of products resulting from isomerization to form the most stable alkene product (**3** or **8**, Scheme 3). In contrast, the

Scheme 3. Isomerization of DHF Products through Reversible Insertion/Elimination Steps



TNpP-derived catalyst forms the less stable nonconjugated product in each case (**4** or **6**/**7**). These products result from the initial β-hydride elimination, without further isomerization to the more stable products. It is possible that the DTBNpP-derived palladium-hydride is more stable than the TNpP analogue, resulting in more extensive isomerization. Alternatively, the alkene product may coordinate more strongly to the DTBNpP complex than the TNpP complex, which again would allow for more extensive isomerization.

Fu and co-workers reported that ligand steric hindrance plays a critical role in the reductive elimination of HCl from $(R_3P)_2PdHCl$.[20] The reductive elimination of HCl from $(TTBP)_2PdHCl$ occurs at 20 °C in the presence of 35 equiv of *N*,*N*-dicyclohexylmethylamine, whereas reductive elimination of HCl with the less sterically hindered tricyclohexylphosphine complex does not occur under identical conditions. Using hydroxide as the base, elimination of HBr from $(Cy_3P)_2PdHBr$ was achieved at 75 °C.[21] Given that TTBP promotes more alkene isomerization in the Heck coupling of 2,3-DHF compared to PCy_3, the rate of HX elimination from the L_2PdHBr complexes does not appear to be the determining factor in the product selectivity. DTBNpP has similar steric demand to TTBP based on calculated steric parameters and reactivity profiles.[13a] The flexible TNpP ligand is able to adopt less sterically demanding conformations that may be more comparable to PCy_3.[14] Therefore, it would appear that the steric effect on palladium-hydride stability is not the primary factor in determining the product selectivity.

As a result, we hypothesize that the selectivity in the isomerization of the resulting Heck products is primarily due to the relative electron donating abilities of the phosphine ligands. The more electron rich palladium centers containing TTBP or DTBNpP as a ligand bind to the olefin product more tightly due to stronger π-backbonding. The strong bonding allows for the hydridopalladium species to undergo reversible insertion/elimination to give the thermodynamically more stable product **3** or **8**, while preventing reductive elimination of HBr. In contrast, the tricyclohexylphosphine and TNpP hydridopalladium species dissociate from the olefin faster due to the weaker π-backbonding, allowing for reductive elimination of HBr before reinsertion of the hydridopalladium species and isomerization can occur (Scheme 3). The same trend holds with the use of chelating ligands in the coupling of cyclic olefins.[10]

The electronic nature of the aryl halide also affects the product selectivity in Heck couplings of 2,3-DHF. Electron deficient aryl halides decreased the selectivity for product **4** when using TNpP (**4c**, **4d**, **4e**, Table 6), but had little effect on the selectivity with the DTBNpP-derived catalyst. In contrast, lower selectivity was observed with the electron rich 4-bromoanisole using DTBNpP (**3a**, Table 6). These observations may support our hypothesis. The more electron deficient 2-aryl-DHF products may act as better backbonding acceptors, which results in increased isomerization with the TNpP-derived catalyst. In contrast, the more electron rich product formed from 4-bromoanisole, may bind less tightly because it is a poorer back-bonding acceptor. This decreases the amount of isomerization, decreasing the selectivity for product **3**.

With the cyclopentene couplings, the base concentration also plays a crucial role, as the hydridopalladium must switch faces of the alkene to allow for *syn* β-hydride elimination to form the vinylic product **8**. With a lower concentration of base, the hydridopalladium species survives long enough after dissociation from the olefin to switch faces of the cycloalkane, thus allowing *syn* β-hydride elimination to the conjugated product. At higher base concentrations, the elimination of HBr occurs too readily after dissociation of the hydridopalladium species to allow isomerization to vinylic product **8**. As seen in Table 9, only a 37% selectivity of **8a** was produced with 1.5 equiv of DIPEA compared to 99% selectivity for **8a** with 1.0 equiv of DIPEA.

CONCLUSIONS

DTBNpP in combination with $Pd(dba)_2$ was shown to catalyze the Heck reaction of aryl bromides at ambient temperature. Although the TNpP-derived catalyst showed minimal activity at ambient temperature, it showed increased reactivity with sterically hindered substrates at elevated temperatures. DTBNpP and TNpP were found to promote different degrees of isomerization in the coupling of cyclic olefins, allowing selective production of arylated cycloalkene isomers. DTBNpP promoted isomerization of the initial olefin product, whereas TNpP did not. A catalytic method for the formation of 2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepins (**5**) having a structure similar to that found at the core of a number of biologically active natural products was found. We propose that the greater electron donating ability of DTBNpP relative to TNpP allows for stronger coordination of the olefin products to the electron rich palladium center. This, in turn, promotes isomerization while preventing reductive elimination of HBr, giving ample time to form the thermodynamically more stable products through reversible migratory insertion/β-hydride elimination steps. The findings reported should aid in ligand selection for

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future palladium-catalyzed reactions involving olefin isomerization due to hydridopalladium species.

EXPERIMENTAL SECTION

General Experimental Methods. DTBNpP, TNpP, and TTBP were obtained from FMC, Lithium Division. 2-Bromoacetanilide,[22] *N*-(2-bromophenyl)-4-methylbenzenesulfonamide,[23] and $Pd(dba)_2$[24] were prepared from known literature procedures. Anhydrous DMF was stored in a nitrogen-filled glovebox. MeCN was distilled over CaH_2 under nitrogen gas. Acetone and methanol were vigorously bubbled with nitrogen gas for at least 15 min immediately prior to use. All other reagents were obtained from commercial sources and used as received. Reaction temperatures refer to previously equilibrated oil bath temperatures. $Pd(dba)_2$ and $Pd_2(dba)_3$ gave similar results in the coupling reactions involving 2,3-DHF; the use of $Pd_2(dba)_3$ was not tested in the other Heck couplings.[25] HRMS was obtained on a magnetic sector mass spectrometer using EI ionization and operating in the positive ion mode.

General Procedure A - Heck Reaction of Acrylate Esters and Styrene (Table 2). To a 4 mL borosilicate glass vial were added $Pd(dba)_2$ (2 or 5 mol %), phosphine (2, 4, or 10 mol %), and DMF (1 mL) inside a glovebox. The vial was fitted with a septa screw cap and removed from the glovebox. To the vial were added aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to adding DMF in the glovebox), olefin (1.4 equiv), and DIPEA (1.5 equiv, 0.26 mL; 1.5 mmol). The vial was then stirred at 24−160 °C (reactions heated to 160 °C were performed in a pressure tube with adequate shielding) for 24−48 h. After cooling to ambient temperature, the reaction mixture was subjected directly to flash chromatography on silica gel.

*tert-Butyl (E)-3-(4-Methoxyphenyl)acrylate (**1a**).*[26] General Procedure A was followed using 4-bromoanisole (0.125 mL, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol), and *tert*-butyl acrylate (0.20 mL, 1.4 mmol) while stirring for 24 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2.5% EtOAc/hexanes) to give **1a** (228 mg, 0.97 mmol, 97%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, J = 15.9 Hz, 1H), 7.44 (m, 2H), 6.87 (m, 2H), 6.24 (d, J = 16.0 Hz, 1H), 3.81 (s, 3 H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.5, 141.2, 139.1, 132.7, 128.4, 124.0, 118.5, 113.2, 81.3, 28.2.

*tert-Butyl (E)-3-(4-Cyanophenyl)acrylate (**1b**).*[27] General Procedure A was followed using 4-bromobenzonitrile (182 mg, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol), and *tert*-butyl acrylate (0.20 mL, 1.4 mmol) while stirring for 24 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−4% EtOAc/hexanes) to give **1b** (214 mg, 0.93 mmol, 93%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 16.0 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 161.3, 143.3, 129.7, 127.6, 117.9, 114.4, 80.3, 55.5, 28.4.

*Butyl (E)-3-(3-Methoxyphenyl)acrylate (**1c**).*[28] General Procedure A was followed using 3-bromoanisole (0.127 mL, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol), and *n*-butyl acrylate (0.20 mL, 1.4 mmol) while stirring for 24 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2.5% EtOAc/hexanes) to give **1c** (227 mg, 0.98 mmol, 98%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (d, J = 16.0 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.03 (m, 1H), 6.91 (dd, J = 8.1, 2.3 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 4.20 (t, J = 6.7 Hz, 2H), 3.80 (s, 3H), 1.71−1.65 (m, 2H), 1.43 (sex, J = 7.5 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.0, 160.1, 144.5, 136.0, 129.9, 120.8, 118.7, 116.2, 113.0, 64.5, 55.3, 30.9, 19.3, 13.8.

*(E)-1-Methoxy-4-styrylbenzene (**1d**).*[29] General Procedure A was followed using 4-bromoanisole (0.125 mL, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol), and styrene (0.16 mL, 1.4 mmol) while stirring for 48 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2% EtOAc/hexanes) to give **1d** (202 mg, 0.96 mmol, 96%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (d, J = 7.4 Hz, 2H), 7.43 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.3 Hz, 2H), 7.05 (d, J = 16.3 Hz, 1H), 6.96 (d, J = 16.3 Hz, 1H), 6.88 (m, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5, 137.9, 130.5, 128.8, 128.4, 127.9, 127.4, 126.8, 126.5, 114.3, 55.5.

*(E)-4-Styrylbenzonitrile (**1e**).*[30] General Procedure A was followed using 4-bromobenzonitrile (182 mg, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol), and styrene (0.16 mL, 1.4 mmol) while stirring for 48 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−3% EtOAc/hexanes) to give **1e** (177 mg, 0.86 mmol, 86%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (d, J = 8.4 Hz, 2H), 7.55−7.50 (m, 4H), 7.37 (t, J = 7.3 Hz, 2H), 7.31 (m, 1H), 7.18 (d, J = 16.3 Hz, 1H), 7.06 (d, J = 16.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.9, 136.4, 132.6, 132.5, 129.0, 128.9, 127.1, 127.0, 126.8, 119.2, 110.7.

*(E)-N-(2-Styrylphenyl)acetamide (**1f**).*[31] General Procedure A was followed using 2′-bromoacetanilide[35] (214 mg, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol), and styrene (0.16 mL, 1.4 mmol) while stirring for 24 h at 80 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−3% EtOAc/hexanes) to give **1f** (194 mg, 0.82 mmol, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (br s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.47−7.43 (m, 3H), 7.32 (t, J = 7.4 Hz, 2H), 7.26−7.24 (m, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.11−7.07 (m, 2H), 6.89 (d, J = 16.2 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.3, 137.3, 134.8, 131.2, 130.9, 128.8, 128.2, 128.1, 126.8, 126.5, 125.8, 125.1, 123.8, 24.0.

*(E)-1-Methyl-2-styrylbenzene (**1g**).*[30] General Procedure A was followed using 2-bromotoluene (0.120 mL, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), TNpP (4 mol %, 9.8 mg; 0.04 mmol), and styrene (0.16 mL, 1.4 mmol) while stirring for 24 h at 80 °C. The crude product was purified by flash chromatography on silica gel using hexanes to give **1g** (165 mg, 0.85 mmol, 85%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57 (d, J = 7.2 Hz, 1H), 7.50 (m, 2H), 7.35−7.30 (m, 3H), 7.26−7.22 (m, 1H), 7.20−7.15 (m, 3H), 6.98 (d, J = 16.1 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.9, 136.6, 136.0, 130.6, 130.2, 128.9, 127.8, 127.7, 126.8, 126.4, 125.6, 20.1.

*(E)-1,3-Dimethyl-2-styrylbenzene (**1h**).*[32] General Procedure A was followed using 2-bromo-1,3-dimethylbenzene (0.133 mL, 1.00 mmol), $Pd(dba)_2$ (5 mol %, 28.8 mg, 0.05 mmol), TNpP (10 mol %, 24.4 mg; 0.10 mmol), and styrene (0.16 mL, 1.4 mmol) while stirring for 24 h at 160 °C. The crude product was purified by flash chromatography on silica gel using hexanes to give **1h** (172 mg, 0.83 mmol, 83%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (d, J = 7.3 Hz, 2H), 7.32 (m, 2H), 7.23 (m, 1H), 7.08 (d, J = 16.6 Hz, 1H), 7.05−7.04 (m, 3H), 6.57 (d, J = 16.6 Hz, 1H), 2.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.8, 137.1, 136.4, 134.2, 128.8, 128.1, 127.7, 127.1, 126.9, 126.5, 21.2.

*(E)-1,3,5-Triisopropyl-2-styrylbenzene (**1i**).*[32] General Procedure A was followed using 1-bromo-1,3,5-triisopropylbenzene (0.260 mL, 1.00 mmol), $Pd(dba)_2$ (5 mol %, 28.8 mg, 0.05 mmol), TNpP (10 mol %, 24.4 mg; 0.10 mmol), and styrene (0.16 mL, 1.4 mmol) while stirring for 24 h at 160 °C. The crude product was purified by flash chromatography on silica gel using hexanes to give **1i** (234 mg, 0.83 mmol, 76%) as a clear colorless solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.27−7.24 (m, 1H), 7.19 (d, J = 16.6 Hz, 1H), 7.03 (s, 2H), 6.49 (d, J = 16.6 Hz, 1H), 3.82 (sept, J = 6.8 Hz, 2H), 2.90 (sept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.9, 146.9, 137.9, 134.1, 133.2, 128.9, 127.7, 127.2, 126.5, 120.8, 34.5, 30.4, 24.3, 24.2.

General Procedure B - Heck Reaction of 3-Buten-2-ol (Table 3). To a 4 mL borosilicate glass vial were added $Pd(dba)_2$ (2 or 5 mol %), phosphine (2 or 10 mol %), and DMF (1 mL) inside a glovebox. The vial was fitted with a septa screw cap and removed from the

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glovebox. To the vial were added aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to adding DMF in the glovebox), 3-buten-2-ol (1.3 equiv, 0.115 mL, 1.3 mmol), and DIPEA (1.5 equiv, 0.26 mL; 1.5 mmol). The vial was then stirred at 24−160 °C (reactions heated to 160 °C were performed in a pressure tube behind a blast shield) for 2−24 h. After cooling to ambient temperature, the reaction mixture was subjected directly to flash chromatography on silica gel.

*4-(4-Methoxyphenyl)butan-2-one (**2a**).*[33] General Procedure B was followed using 4-bromoanisole (0.125 mL, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), and DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol) while stirring for 1 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (8% EtOAc/hexanes) to give **2a** (134 mg, 0.75 mmol, 75%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.08 (m, 2H), 6.81 (m, 2H), 3.76 (s, 3H), 2.83 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.1, 158.1, 133.1, 129.3, 114.0, 55.3, 45.5, 30.2, 29.0.

*4-(4-(Dimethylamino)phenyl)butan-2-one (**2b**).*[34] The above general procedure was followed using 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), and DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol) while stirring for 2 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (3−4% EtOAc/hexanes) to give **2b** (138 mg, 0.72 mmol, 72%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.04 (m, 2H), 6.67 (m, 2H), 2.89 (s, 6H), 2.80 (m, 2H), 2.70 (m, 2H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.5, 149.3, 129.1, 129.0, 113.1, 45.7, 40.9, 30.2, 29.0.

*4-(4-Acetylphenyl)butan-2-one (**2c**).*[35] General Procedure B was followed using 4-bromoacetophenone (199 mg, 1.00 mmol), $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), and DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol) while stirring for 17 h at 24 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (5−8% EtOAc/hexanes) to give **2c** (162 mg, 0.85 mmol, 85%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (m, 2H), 7.28 (m, 2H), 2.95 (t, J = 7.5 Hz, 2H), 2.79 (t, J = 7.5 Hz, 2H), 2.57 (m, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.3, 197.8, 147.0, 135.4, 128.8, 128.7, 44.6, 30.2, 29.7, 26.7.

*4-(2,6-Dimethylphenyl)butan-2-one (**2d**).* General Procedure B was followed using 2-bromo-1,3-dimethylbenzene (0.133 mL, 1.00 mmol), $Pd(dba)_2$ (5 mol %, 28.8 mg, 0.05 mmol), and PNp_3 (10 mol %, 24.4 mg; 0.10 mmol) while stirring for 17 h at 160 °C. The crude product was purified by flash chromatography on silica gel using a solvent gradient (5−8% EtOAc/hexanes) to give **2d** (135 mg, 0.77 mmol, 77%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.03−6.98 (m, 3H), 7.91−2.88 (m, 2H), 2.59−2.56 (m, 2H), 2.30 (s, 6H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.3, 137.8, 136.2, 128.4, 126.2, 42.8, 30.0, 23.8, 19.9; HRMS: m/z calcd for $C_{12}H_{16}O$ (M^+) 176.1201, found 176.1204.

General Procedure C − Heck Reaction of 2,3-Dihydrofuran at 24 °C (Table 4). To a 4 mL borosilicate glass vial were added $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol), DTBNpP·HBF_4 (2 mol %, 6.1 mg; 0.02 mmol), and DMF (1 mL) inside a glovebox. The vial was fitted with a septa screw cap and removed from the glovebox. To the vial were added aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to adding DMF in the glovebox), 2,3-DHF (4 equiv, 0.30 mL, 4.0 mmol), and DIPEA (1.0 equiv, 0.175 mL; 1.0 mmol). The vial was then stirred at 24 °C for 2 h. After cooling to ambient temperature, the reaction mixture was subjected directly to flash chromatography on silica gel.

*2-(4-Methoxyphenyl)-2,3-dihydrofuran (**3a**).*[36] General Procedure C was followed using 4-bromoanisole (0.125 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−3% EtOAc/hexanes) to give **3a** (130 mg, 0.74 mmol, 74%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (m, 2H), 6.92 (m, 2H), 6.45 (dt, J = 2.6, 2.4 Hz, 1H), 5.49 (dd, J = 10.6, 8.6 Hz, 1H), 4.97 (dt, J = 2.6, 2.5 Hz, 1H), 3.82 (s, 3H), 3.05 (ddt, J = 15.2, 10.6, 2.4 Hz, 1H), 2.63 (ddt, J = 15.2, 8.5, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 145.4, 135.2, 127.2, 114.1, 99.2, 82.4, 55.4, 37.8.

*2-(3-Methoxyphenyl)-2,3-dihydrofuran (**3b**).*[37] General Procedure C was followed using 3-bromoanisole (0.127 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2% EtOAc/hexanes) to give **3b** (141 mg, 0.80 mmol, 80%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (m, 1H), 6.92 (m, 2H), 6.82 (m, 1H),6.44 (m, 1H), 5.48 (dd, J = 10.5, 8.5 Hz, 1H), 4.94 (m, 1H), 3.80 (s, 3H), 3.06 (ddt, J = 15.2, 10.8, 2.3 Hz, 1H), 2.59 (ddt, J = 15.2, 8.4, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 145.5, 144.9, 129.8, 118.0, 113.3, 111.3, 99.2 82.4, 55.4, 38.0.

*1-(4-(2,3-Dihydrofuran-2-yl)phenyl)ethanone (**3c**).*[38] General Procedure C was followed using 4-bromoacetophenone (199 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−5% EtOAc/hexanes) to give **3c** (164 mg, 0.87 mmol, 87%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (m, 2H), 7.44 (m, 2H), 6.47 (dt, J = 2.6, 2.4 Hz, 1H), 5.57 (dd, J = 10.8, 8.2 Hz, 1H), 4.97 (dt, J = 2.6, 2.6 Hz, 1H), 3.13 (ddt, J = 15.2, 8.5, 2.4 Hz, 1H), 2.60 (s, 3H), 2.57 (ddt, J = 15.2, 8.2, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.7, 148.5, 145.4, 136.5, 128.7, 125.6, 99.1, 81.6, 37.9, 26.6.

*2-((4-Trifluoromethyl)phenyl)-2,3-dihydrofuran (**3d**).*[38] General Procedure C was followed using 4-bromobenzotrifluoride (0.140 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−0.5% EtOAc/hexanes) to give **3d** (124 mg, 0.58 mmol, 58%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (m, 2H), 7.48 (m, 2H), 6.47 (dt, J = 5.0, 2.4 Hz, 1H), 5.57 (dd, J = 10.8, 8.2 Hz, 1H), 4.97 (dt, J = 2.6, 2.5 Hz, 1H), 3.14 (ddt, J = 15.2, 10.8, 2.4 Hz, 1H), 2.57 (ddt, J = 15.2, 8.0, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.4, 145.5, 130 (q, J = 32.4 Hz), 126.0, 125.7 (q, J = 3.9 Hz), 124.4 (q, J = 270 Hz), 99.2, 81.6, 38.1.

General Procedure D - Synthesis of 2,3-Dihydrofurans (3) (Table 6, Conditions A). To a 4 mL borosilicate glass vial were added $Pd_2(dba)_3$ (1.5 mol %, 13.7 mg, 0.015 mmol) and DTBNpP (2.9 mol %, 6.3 mg; 0.029 mmol) inside a glovebox. The vial was fitted with a septa screw cap and removed from the glovebox. To the vial were added MeCN (1 mL), aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to removing from glovebox), 2,3-dihydrofuran (5.3 equiv, 0.40 mL, 5.3 mmol), and DIPEA (1.5 equiv, 0.26 mL; 1.5 mmol). The vial was then placed in an oil bath preheated to 60 °C for 2 h. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on silica gel.

*2-(4-Methoxyphenyl)-2,3-dihydrofuran (**3a**).*[36] General Procedure D was followed using 4-bromoanisole (0.125 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−3% EtOAc/hexanes) to give **3a** (118 mg, 0.67 mmol, 67%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (m, 2H), 6.92 (m, 2H), 6.45 (dt, J = 2.6, 2.4 Hz, 1H), 5.49 (dd, J = 10.6, 8.6 Hz, 1H), 4.97 (dt, J = 2.6, 2.5 Hz, 1H), 3.82 (s, 3H), 3.05 (ddt, J = 15.2, 10.6, 2.4 Hz, 1H), 2.63 (ddt, J = 15.2, 8.5, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 145.4, 135.2, 127.2, 114.1, 99.2, 82.4, 55.4, 37.8.

*2-(3-Methoxyphenyl)-2,3-dihydrofuran (**3b**).*[37] General Procedure D was followed using 3-bromoanisole (0.127 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2% EtOAc/hexanes) to give **3b** (145 mg, 0.82 mmol, 82%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (m, 1H), 6.92 (m, 2H), 6.82 (m, 1H),6.44 (m, 1H), 5.48 (dd, J = 10.5, 8.5 Hz, 1H), 4.94 (m, 1H), 3.80 (s, 3H), 3.06 (ddt, J = 15.2, 10.8, 2.3 Hz, 1H), 2.59 (ddt, J = 15.2, 8.4, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 145.5, 144.9, 129.8, 118.0, 113.3, 111.3, 99.2 82.4, 55.4, 38.0.

*1-(4-(2,3-Dihydrofuran-2-yl)phenyl)ethanone (**3c**).*[38] General Procedure D was followed using 4-bromoacetophenone (0.199 g, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−5% EtOAc/hexanes) to give **3c** (162 mg, 0.86 mmol, 86%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (m, 2H), 7.44 (m, 2H), 6.47 (dt, J = 2.6, 2.4 Hz, 1H), 5.57 (dd, J = 10.8, 8.2 Hz, 1H), 4.97 (dt, J = 2.6, 2.6 Hz, 1H),

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3.13 (ddt, J = 15.2, 8.5, 2.4 Hz, 1H), 2.60 (s, 3H), 2.57 (ddt, J = 15.2, 8.2, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.7, 148.5, 145.4, 136.5, 128.7, 125.6, 99.1, 81.6, 37.9, 26.6.

*2-((4-Trifluoromethyl)phenyl)-2,3-dihydrofuran (**3d**).*[38] General Procedure D was followed using 4-bromobenzotrifluoride (0.140 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−0.5% EtOAc/hexanes) to give **3d** (125 mg, 0.58 mmol, 58%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (m, 2H), 7.48 (m, 2H), 6.47 (dt, J = 5.0, 2.4 Hz, 1H), 5.57 (dd, J = 10.8, 8.2 Hz, 1H), 4.97 (dt, J = 2.6, 2.5 Hz, 1H), 3.14 (ddt, J = 15.2, 10.8, 2.4 Hz, 1H), 2.57 (ddt, J = 15.2, 8.0, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.4, 145.5, 130 (q, J = 32.4 Hz), 126.0, 125.7 (q, J = 3.9 Hz), 124.4 (q, J = 270 Hz), 99.2, 81.6, 38.1.

*4-(2,3-Dihydrofuran-2-yl)benzonitrile (**3e**).* General Procedure D was followed using 4-bromobenzonitrile (0.183 g, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−3% EtOAc/hexanes) to give **3e** (125 mg, 0.73 mmol, 73%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (m, 2H), 7.45 (m, 2H), 6.46 (dt, J = 2.6, 2.4 Hz, 1H), 5.56 (dd, J = 10.9, 8.0 Hz, 1H), 4.97 (dt, J = 2.6, 2.5 Hz, 1H), 3.15 (ddt, J = 15.2, 11.0, 2.4 Hz, 1H), 2.53 (ddt, J = 15.2, 7.9, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.7, 145.5, 132.6, 126.3, 119.0, 99.2, 81.4, 38.1; HRMS: m/z calcd for $C_{11}H_9NO$ (M^+) 171.0684, found 171.0680.

*2-(3,5-Dimethylphenyl)-2,3-dihydrofuran (**3f**).* General Procedure D was followed using 1-bromo-3,5-dimethylbenzene (0.136 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) to give **3f** (108 mg, 0.62 mmol, 62%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.99 (s, 2H), 6.94 (s, 1H), 6.45 (dt, J = 2.6, 2.4 Hz, 1H), 5.45 (dd, J = 10.6, 8.6 Hz, 1H), 4.96 (dt, J = 2.6, 2.5 Hz, 1H), 3.05 (ddt, J = 15.2, 10.7, 2.4 Hz, 1H), 2.61 (ddt, J = 15.2, 8.6, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.5, 143.1, 138.3, 129.5, 123.6, 99.3, 82.7, 38.0, 21.5; HRMS: m/z calcd for $C_{12}H_{14}O$ (M^+) 174.1045, found 174.1052.

*2-(o-Tolyl)-2,3-dihydrofuran (**3g**).*[39] A slight modification of General Procedure D was followed using 2-bromotoluene (0.183 g, 1.00 mmol). The reaction was performed at 80 °C for 5 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) to give **3g** (57 mg, 0.35 mmol, 35%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (m, 1H), 7.22−7.14 (m, 3H), 6.48 (dt, J = 2.6, 2.4 Hz, 1H), 5.68 (dd, J = 10.8, 8.6 Hz, 1H), 4.93 (dt, J = 2.6, 2.5 Hz, 1H), 3.10 (ddt, J = 15.0, 10.8, 2.4 Hz, 1H), 2.45 (ddt, J = 15.0, 8.5, 2.3 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.5, 141.3, 134.2, 130.6, 127.5, 126.3, 124.9, 99.0, 80.2, 37.1, 19.4.

*2-(Thiophen-3-yl)-2,3-dihydrofuran (**3h**).* General Procedure D was followed using 3-bromothiophene (0.094 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using hexanes to give **3h** (101 mg, 0.67 mmol, 67%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (dd, J = 5.0, 3.0 Hz, 1H), 7.22 (m, 1H), 7.09 (dd, J = 5.0, 1.2 Hz, 1H), 6.39 (m, 1H), 5.57 (dd, J = 10.5, 8.1 Hz, 1H), 4.95 (m, 1H), 3.01 (ddt, J = 15.1, 10.5, 2.4 Hz, 1H), 2.64 (ddt, J = 15.1, 8.1, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.2, 143.9, 126.5, 125.7, 121.2, 99.2, 78.8, 36.9; HRMS: m/z calcd for C_8H_8OS (M^+) 152.0296, found 152.0297.

*2-(4-Chlorophenyl)-2,3-dihydrofuran (**3i**).*[40] General Procedure D was followed using 1-bromo-4-chlorobenzene (0.116 g, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using hexanes to give **3i** (116 mg, 0.64 mmol, 64%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32−7.27 (m, 4H), 6.42 (m, 1H), 5.47 (dd, J = 10.7, 8.2 Hz, 1H), 4.94 (m, 1H), 3.06 (ddt, J = 15.2, 10.8, 2.4 Hz, 1H), 2.54 (ddt, J = 15.2, 8.2, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.4, 141.7, 133.4, 128.8, 127.1, 99.1, 81.7, 38.0.

General Procedure E - Synthesis of 2,5-Dihydrofurans (4) (Table 6, Conditions B and C). To a 4 mL borosilicate glass vial were added $Pd_2(dba)_3$ (1.5 mol %, 13.7 mg, 0.015 mmol), TNpP (6 mol %, 14.7 mg; 0.06 mmol), and potassium acetate (1.5 equiv, 0.150 g; 1.5 mmol) inside a glovebox. The vial was fitted with a septa screw cap and removed from the glovebox. To the vial were added methanol (1 mL), aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to removing from glovebox), and 2,3-dihydrofuran (2.5−5.3 equiv). The vial was then placed in an oil bath preheated to 60−80 °C for 2−12 h. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on silica gel.

*2-(4-Methoxyphenyl)-2,5-dihydrofuran (**4a**).*[41] General Procedure E was followed using 4-bromoanisole (0.125 mL, 1.00 mmol) and 2,3-dihydrofuran (0.19 mL, 2.5 mmol). The reaction mixture was heated to 60 °C for 2 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−4% EtOAc/hexanes) to give **4a** (140 mg, 0.80 mmol, 80%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (m, 2H), 6.88 (m, 2H), 6.04 (m, 1H), 5.86 (m, 1H), 5.74 (m, 1H), 4.87−4.82 (m, 1H), 4.75−4.71 (m, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 134.3, 130.2, 128.1, 126.9, 114.1, 87.7, 75.7, 55.5.

*2-(3-Methoxyphenyl)-2,5-dihydrofuran (**4b**).* General Procedure E was followed using 3-bromoanisole (0.127 mL, 1.00 mmol) and 2,3-dihydrofuran (0.19 mL, 2.5 mmol). The reaction mixture was heated to 60 °C for 5 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−4% EtOAc/hexanes) to give **4b** (132 mg, 0.74 mmol, 74%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25 (dd, J = 7.8, 7.8 Hz, 1H), 6.89 (m, 1H), 6.86 (m, 1H), 6.80 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.01 (m, 1H), 5.88 (m, 1H), 5.76 (m, 1H), 4.88−4.84 (m, 1H), 4.78−4.74 (m, 1H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0, 143.9, 130.1, 129.7, 126.8, 118.8, 113.4, 112.0, 87.9, 76.0, 55.4; HRMS: m/z calcd for $C_{11}H_{11}O_2$ (M^+) 175.0759, found 175.0753.

*1-(4-(2,5-Dihydrofuran-2-yl)phenyl)ethanone (**4c**).* General Procedure E was followed using 4-bromoacetophenone (0.199 g, 1.00 mmol) and 2,3-dihydrofuran (0.40 mL, 5.3 mmol). The reaction mixture was heated to 80 °C for 5 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−5% EtOAc/hexanes) to give **4c** (150 mg, 0.80 mmol, 80%) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (m, 2H), 6.38 (m, 2H), 6.04 (m, 1H), 5.87 (m, 1H), 5.82 (m, 1H), 4.90−4.86 (m, 1H), 4.80−4.76 (m, 1H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.8, 147.5, 136.6, 129.4, 128.7, 127.1, 126.3, 87.3, 76.1, 26.6; HRMS: m/z calcd for $C_{12}H_{12}O_2$ (M^+) 188.0837, found 188.0841.

*2-((4-Trifluoromethyl)phenyl)-2,5-dihydrofuran (**4d**).* General Procedure E was followed using 4-bromobenzotrifluoride (0.140 mL, 1.00 mmol) and 2,3-dihydrofuran (0.40 mL, 5.3 mmol). The reaction mixture was heated to 80 °C for 7 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) to give **4d** (141 mg, 0.66 mmol, 66%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (m, 2H), 7.42 (m, 2H), 6.06 (m, 1H), 5.88 (m, 1H), 5.84 (m, 1H), 4.89 (m, 1H), 4.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.4, 130.2 (q, J = 32.4 Hz), 129.6, 127.4, 126.7, 125.7 (q, J = 3.8 Hz), 124.4 (q, J = 270 Hz), 87.4, 76.3; HRMS: m/z calcd for $C_{11}H_9OF_3$ (M^+) 214.0605, found 214.0602.

*4-(2,5-Dihydrofuran-2-yl)benzonitrile (**4e**).* General Procedure E was followed using 4-bromobenzonitrile (0.183 g, 1.00 mmol) and 2,3-dihydrofuran (0.40 mL, 5.3 mmol). The reaction mixture was heated to 80 °C for 12 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (3−6% EtOAc/hexanes) to give **4e** (103 mg, 0.60 mmol, 60%) as a clear, colorless oil, which solidified to a white solid upon sitting. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (m, 2H), 7.41 (m, 2H), 6.10 (m, 1H), 5.88−5.82 (m, 2H), 4.89 (m, 1H), 4.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.7, 132.6, 129.2, 127.7, 127.0, 119.0, 111.7, 87.3, 76.4; HRMS: m/z calcd for $C_{11}H_9NO$ (M^+) 171.0684, found 171.0680.

*2-(3,5-Dimethylphenyl)-2,5-dihydrofuran (**4f**).* General Procedure E was followed using 1-bromo-3,5-dimethylbenzene (0.136 mL, 1.00 mmol) and 2,3-dihydrofuran (0.19 mL, 2.5 mmol). The reaction mixture was heated to 60 °C for 2 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−3% EtOAc/hexanes) to give **4f** (125 mg, 0.72 mmol, 72%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.91 (m, 3H), 6.00 (m,

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1H), 5.86 (m, 1H), 5.72 (m, 1H), 4.88−4.83 (m, 1H), 4.76−4.72 (m, 1H), 2.30 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.1, 138.2, 130.2, 129.6, 126.6, 124.3, 88.1, 75.9, 21.4; HRMS: m/z calcd for $C_{12}H_{14}O$ (M^+) 174.1045, found 174.1049.

*2-(o-Tolyl)-2,5-dihydrofuran (**4g**).*[42] General Procedure E was followed using 2-bromotoluene (0.120 mL, 1.00 mmol) and 2,3-dihydrofuran (0.40 mL, 5.3 mmol). The reaction mixture was heated to 80 °C for 5 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2% EtOAc/hexanes) to give **4g** (112 mg, 0.70 mmol, 70%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (m, 1H), 7.19−7.12 (m, 3H), 6.03−5.98 (m, 2H), 5.90 (m, 1H), 4.87−4.83 (m, 1H), 4.78−4.74 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.1, 135.2, 130.5,129.2, 127.7, 126.9, 126.33, 126.30, 85.2, 75.7, 19.1.

*2-(Thiophen-3-yl)-2,5-dihydrofuran (**4h**).* General Procedure E was followed using 3-bromothiophene (0.094 mL, 1.00 mmol) and 2,3-dihydrofuran (0.40 mL, 5.3 mmol). The reaction mixture was heated to 80 °C for 17 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (20−40% CH_2Cl_2/hexanes) to give **4h** (97 mg, 0.63 mmol, 63%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (dd, J = 5.0, 3.0 Hz, 1H), 7.20 (m, 1H), 7.02 (dd, J = 5.0, 1.2 Hz, 1H), 6.04 (m, 1H), 5.91 (m, 1H), 5.88 (m, 1H), 4.82 (m, 1H), 4.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.5, 129.3, 127.1, 126.3, 126.2, 121.8, 83.6, 75.4; HRMS: m/z calcd for C_8H_8OS (M^+) 152.0296, found 152.0291.

*2-(4-Chlorophenyl)-2,3-dihydrofuran (**4i**).*[10b] General Procedure E was followed using 1-bromo-4-chlorobenzene (0.116 g, 1.00 mmol) and 2,3-dihydrofuran (0.40 mL, 5.3 mmol). The reaction mixture was heated to 80 °C for 17 h. The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) to give **4i** (165 mg, 0.91 mmol, 91%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31−7.29 (m, 2H), 7.25−7.22 (m, 2H), 6.03 (m, 1H), 5.83 (m, 1H), 5.75 (m, 1H), 4.87−4.82 (m, 1H), 4.77−4.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.7, 133.6, 129.7, 128.7, 127.9, 127.1, 87.2, 75.9.

General Procedure F - The Synthesis of Product 5 (Table 8). To a 4 mL borosilicate glass vial were added $Pd(dba)_2$ (2 mol %, 11.5 mg, 0.02 mmol) and DTBNpP·HBF_4 (4 mol %, 12.2 mg; 0.04 mmol) inside a glovebox. The vial was fitted with a septa screw cap and removed from the glovebox. To the vial were added acetone (1 mL), aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to removing from the glovebox), 2,3-DHF (2.6 equiv, 0.20 mL, 2.6 mmol), 2-propanol (0.5 equiv, 0.038 mL, 0.5 mmol), and DIPEA (1.0 equiv, 0.175 mL; 1.0 mmol). The vial was then stirred at 80 °C for 24 h. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on silica gel.

*2,3,4,5-Tetrahydro-2,5-epoxybenzo[b]oxepine (**5a**).*[43] General Procedure F was followed using 2-bromophenol (0.116 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (20−30% CH_2Cl_2/hexanes) to give **5a** (97 mg, 0.60 mmol, 60%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15 (dt, J = 8.0, 1.6 Hz, 1H), 6.95 (dd, J = 7.4, 1.5 Hz, 1H), 6.84 (dd, J = 7.4, 1.0 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 5.94 (m, 1H), 5.13 (m, 1H), 2.31−2.17 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.2, 128.9, 127.5, 124.6, 120.2, 116.3, 100.6, 77.4, 35.9, 33.6.

*7-Methoxy-2,3,4,5-tetrahydro-2,5-epoxybenzo[b]oxepine (**5b**).* General Procedure F was followed using 2-bromo-4-methoxyphenol (203 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) to give **5b** (97 mg, 0.60 mmol, 60%) as a clear, light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.71−6.67 (m, 2H), 6.51 (d, J = 2.6 Hz, 1H), 5.91 (m, 1H), 5.06 (m, 1H), 3.73 (s, 3H), 2.25−2.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.3, 143.9, 127.9, 116.9, 114.2, 110.2, 100.5, 77.3, 55.9, 35.9, 33.2; HRMS: m/z calcd for $C_{11}H_{12}O_3$ (M^+) 192.0786, found 192.0789.

*7-Chloro-2,3,4,5-tetrahydro-2,5-epoxybenzo[b]oxepine (**5c**).* General Procedure F was followed using 2-bromo-4-chlorophenol (208 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−0.5% EtOAc/hexanes) to give **5c** (126 mg, 0.64 mmol, 64%) as a clear, light yellow oil, which solidified to a white solid upon sitting. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.08 (dd, J = 8.6, 2.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 5.92 (m, 1H), 5.07 (m, 1H), 2.26−2.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.9, 128.8, 128.7, 124.9, 124.5, 117.7, 100.7, 77.0, 35.7, 33.5; HRMS: m/z calcd for $C_{10}H_9O_2Cl$ (M^+) 196.0291, found 196.0295.

*7-Fluoro-2,3,4,5-tetrahydro-2,5-epoxybenzo[b]oxepine (**5d**).* General Procedure F was followed using 2-bromo-4-fluorophenol (191 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel eluted with 25% CH_2Cl_2/hexanes to give **5d** (106 mg, 0.59 mmol, 59%) as a clear, colorless oil, which solidified to a white solid upon sitting. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.83 (dt, J = 8.7, 3.0 Hz, 1H), 6.70−6.66 (m, 2H), 5.92 (m, 1H), 5.07 (m, 1H), 2.26−2.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.6 (d, J = 237.6 Hz), 146.1 (d, J = 1.6 Hz), 128.2 (d, J = 6.8 Hz), 117.2 (d, J = 7.9 Hz), 115.3 (d, J = 22.9 Hz), 111.2 (d, J = 23.6 Hz), 100.5, 77.0, 35.8, 33.3; HRMS: m/z calcd for $C_{10}H_9FO_2$ (M^+) 180.0594, found 180.0585.

*1-(2,3,4,5-Tetrahydro-1H-2,5-epoxybenzo[b]azepin-1-yl)ethan-1-one (**5f**).* General Procedure F was followed using 2′-bromoacetanilide[35] (214 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel eluted with CH_2Cl_2 to give **5f** (58 mg, 0.28 mmol, 28%) as a cloudy white oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04 (br s, 1H), 7.22(ddd, J = 8.4, 6.8, 2.2 Hz, 1H) 7.05−7.00 (m, 2H), 6.28 (br s, 1H), 5.13 (d, J = 6.2 Hz, 1H), 2.40−2.34 (m, 4H), 2.26−2.16 (m, 1H), 2.11−2.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.2, 134.7, 130.7, 127.9, 124.4, 123.9, 122.7, 86.4, 78.7, 36.1, 32.2, 24.7; HRMS: m/z calcd for $C_{12}H_{13}NO_2$ (M^+) 203.0946, found 203.0946.

*1-Tosyl-2,3,4,5-tetrahydro-1H-2,5-epoxybenzo[b]azepine (**5g**).* General Procedure F was followed using *N*-(2-bromophenyl)-4-methylbenzenesulfonamide[36] (326 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel eluted with 50% CH_2Cl_2/hexanes to give **5g** (169 mg, 0.53 mmol, 53%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (d, J = 8.4 Hz, 1H), 7.58 (m, 2H) 7.20 (m, 1H), 7.14 (m, 2H), 7.03 (ddd, J = 7.5, 7.4, 1.0 Hz, 1H), 6.87 (dd, J = 7.5, 1.4 Hz, 1H), 6.47 (m, 1H), 4.87 (m, 1H), 2.43−2.35 (m, 1H), 2.33 (s, 3H), 2.13−1.97 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.9, 135.7, 133.3, 131.0, 129.4, 128.1, 127.9, 124.9, 124.7, 123.2, 87.8, 77.7, 36.9, 31.4, 21.7; HRMS: m/z calcd for $C_{17}H_{17}NO_3S$ (M^+) 315.0929, found 315.0922.

General Procedure G - Heck Reaction with Cyclopentene To Produce 6 (Table 9, Conditions B). To a pressure tube were added $Pd(dba)_2$ (5 mol %, 28.8 mg, 0.05 mmol), TNpP (10 mol %, 24.4 mg; 0.10 mmol), and potassium acetate (1.5 equiv, 0.15 g, 1.5 mmol) inside a glovebox. The tube was fitted with a Teflon screw cap and removed from the glovebox. To the tube were added methanol (1 mL), aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to removing from the glovebox), and cyclopentene (4 equiv, 0.36 mL, 4 mmol) under a positive pressure of N_2. The reaction mixture was then stirred at 80 °C for 24 h. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on silica gel.

*1-(Cyclopent-2-en-1-yl)-4-methoxybenzene (**6a**).*[16] General Procedure G was followed using 4-bromoanisole (0.125 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel eluted with hexanes to give **6a** and **7a** as a (68:10) mixture: (135 mg, 0.78 mmol, 78%) as a clear, colorless oil. **6a**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.08 (m, 2H), 6.82 (m, 2H) 5.90 (m, 1H), 5.74 (m, 1H), 3.83 (m, 1H), 3.75 (s, 3H), 2.50−2.43 (m, 1H), 2.40−2.33 (m, 2H), 1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.0, 138.7, 134.7, 131.6, 128.1, 113.9, 55.3, 50.6, 34.0, 32.5.

*1-(4-(Cyclopent-2-en-1-yl)phenyl)ethan-1-one (**6b**).*[16] General Procedure G was followed using 4-bromoacetophenone (199 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2% EtOAc/hexanes) to give **6b** and **7b** as a (83:8) mixture: (169 mg, 0.91 mmol, 91%) as a yellow oil. **6b**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (m, 2H), 7.26 (m, 2H)

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5.97 (m, 1H), 5.75 (m, 1H), 3.94 (m, 1H), 2.56 (s, 3H), 2.51−2.40 (m, 3H), 1.74−1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.8, 152.3, 135.4, 133.5, 132.8, 128.7, 127.5, 51.4, 33.7, 32.6, 26.6.

*4-(Cyclopent-2-en-1-yl)benzonitrile (**6c**).*[44] General Procedure G was followed using 4-bromobenzonitrile (182 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2% EtOAc/hexanes) to give **6c** and **7c** as a (83:8) mixture: (169 mg, 0.91 mmol, 91%) as a light yellow oil. **6c**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (m, 2H), 7.29 (m, 2H) 6.01 (m, 1H), 5.73 (m, 1H), 3.94 (m, 1H), 2.54−2.40 (m, 3H), 1.72−1.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.3, 133.5, 133.0, 132.4, 128.2, 119.3, 110.0, 51.6, 33.7, 32.6.

*2-(Cyclopent-2-en-1-yl)phenol (**6d**).*[45] General Procedure G was followed using 2-bromophenol (116 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) to give **6d** and **7d** as a (67:4) mixture: (114 mg, 0.71 mmol, 71%) as a clear colorless oil. **6d**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (m, 2H), 7.15−7.11 (m, 2H) 6.89 (dt, J = 7.5, 1.0 Hz, 1H), 6.82 (dd, J = 7.9, 0.6 Hz, 1H), 6.10 (m, 1H), 5.92 (m, 1H), 5.31 (br s, 1H), 4.11−4.06 (m, 1H), 2.63−2.55 (m, 1H), 2.53−2.43 (m, 2H), 1.86−1.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.3, 134.4, 133.5, 130.9, 129.0, 127.7, 120.8, 116.2, 47.2, 32.9, 31.7.

*N-(2-(Cyclopent-2-en-1-yl)phenyl)acetamide (**6e**).*[46] General Procedure G was followed using 2′-bromoacetanilide[35] (214 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (15−25% EtOAc/hexanes) to give **6e** and **7e** as a (73:18) mixture: (183 mg, 0.91 mmol, 91%) as a white solid. **6e**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (br s, 1H), 7.65 (d, J = 7.6 Hz, 1H) 7.17−7.13 (m, 2H), 7.08 (m, 1H), 6.00 (m, 1H), 5.76 (m, 1H), 4.00 (m, 1H), 2.53−2.34 (m, 3H), 2.08 (s, 3H), 2.08 (s,3H), 1.71−1.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.8, 137.4, 135.3, 133.6, 133.0, 128.3, 126.9, 125.6, 124.8, 47.6, 32.7, 31.7, 24.1.

General Procedure H - Heck Reaction with Cyclopentene To Produce 8 (Table 9, Conditions C). To a pressure tube were added $Pd(dba)_2$ (5 mol %, 28.8 mg, 0.05 mmol) and DTBNpP·HBF_4 (10 mol %, 30.4 mg; 0.10 mmol) inside a glovebox. The vial was fitted with a septa screw cap and removed from the glovebox. To the vial were added acetone (1 mL), aryl bromide (1 mmol, if a solid, the aryl bromide was added prior to removing from the glovebox), cyclopentene (4 equiv, 0.36 mL, 4 mmol), and DIPEA (1.0 equiv, 0.18 mL, 1.0 mmol). The vial was then stirred at 80 °C for 17 h. After cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on silica gel.

*1-(Cyclopent-1-en-1-yl)-4-methoxybenzene (**8a**).*[47] General Procedure H was followed using 4-bromoanisole (0.125 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel eluted with hexanes to give **8a**: (163 mg, 0.93 mmol, 93%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 (m, 2H), 6.83 (m, 2H) 6.03 (m, 1H), 3.77 (s, 3H), 2.66 (m, 2H), 2.49 (m, 2H), 1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.8, 142.0, 129.9, 126.9, 124.0, 113.8, 55.4, 33.50, 33.48, 23.6.

*1-(4-(Cyclopent-1-en-1-yl)phenyl)ethan-1-one (**8b**).*[48] General Procedure H was followed using 4-bromoacetophenone (199 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) to give **8b**: (178 mg, 0.95 mmol, 95%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (m, 2H), 7.49 (m, 2H) 6.34 (m, 1H), 2.72 (m, 2H), 2.58 (s, 3H), 2.56 (m, 2H), 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.7, 142.0, 141.6, 135.6, 129.8, 128.7, 125.8, 33.8, 33.2, 26.7, 23.5.

*4-(Cyclopent-1-en-1-yl)benzonitrile (**8c**).*[44] General Procedure H was followed using 4-bromobenzonitrile (182 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−1% EtOAc/hexanes) and a second column eluted with CH_2Cl_2 to give **8c**: (139 mg, 0.82 mmol, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (m, 2H), 7.47 (m, 2H) 6.35 (m, 1H), 2.69 (m, 2H), 2.56 (m, 2H), 2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.32, 141.26, 132.2, 130.8, 126.1, 119.3, 110.0, 33.7, 33.0, 23.3.

*2-(Cyclopent-1-en-1-yl)phenol (**8d**).*[45] General Procedure H was followed using 2-bromophenol (0.116 mL, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (0−2% EtOAc/hexanes) and a second column eluted with CH_2Cl_2 to give **8d**: (146 mg, 0.91 mmol, 91%) as a light brown solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20 (dd, J = 3.8, 1.5 Hz, 1H), 7.15 (m, 1H) 6.94−6.91 (m, 2H), 6.15 (m, 1H), 5.68 (s, 1H), 2.75 (m, 2H), 2.62 (m, 2H), 2.03 (pent, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.1, 140.2, 129.3, 128.3, 128.1, 124.2, 120.5, 115.7, 36.3, 34.1, 23.1.

*N-(2-(Cyclopent-1-en-1-yl)phenyl)acetamide (**8e**).*[46] General Procedure H was followed using 2′-bromoacetanilide[35] (214 mg, 1.00 mmol). The crude product was purified by flash chromatography on silica gel using a solvent gradient (10−20% EtOAc/hexanes to give **8e**: (116 mg, 0.57 mmol, 57%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (d, J = 8.2 Hz, 1H), 7.57 (br s, 1H) 7.22 (t, J = 7.3 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 5.90 (m, 1H), 2.67 (m, 2H), 2.58 (m, 2H), 2.14 (s, 3H), 2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.2, 141.0, 134.8, 130.4, 128.6, 127.9, 127.8, 124.1, 121.5, 36.9, 34.0, 24.9, 23.5.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all products in Tables 2, 3, 4, 6, 8, and 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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