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Enantioselective Heck–Matsuda Arylations via Chiral Anion Phase Transfer of Aryl Diazonium Salts

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Abstract

A mild, asymmetric Heck–Matsuda reaction of five-, six- and seven-membered ring alkenes and aryldiazonium salts is presented. High yields and enantioselectivities were achieved using Pd(0) and chiral anion co-catalysts, the latter functioning as a chiral anion phase-transfer (CAPT) reagent. For certain substrate classes, the chiral anion catalysts were modulated to minimize the formation of undesired by-products. More specifically, BINAM-derived phosphoric acid catalysts were shown to prevent alkene isomerization in cyclopentene and cycloheptene starting materials. DFT(B3LYP-D3) computations revealed that increased product selectivity resulted from a chiral anion dependent lowering of the activation barrier for the desired pathway.

Graphical abstract

An asymmetric Heck-Matsuda reaction of cyclopentene, cyclohexene, and cycloheptene derivatives has been developed using a Chiral Anion Phase Transfer (CAPT) Catalysis. These studies demonstrate that CAPT catalysis can be employed to control the enantio- and chemoselectivity of the Heck-Matsuda

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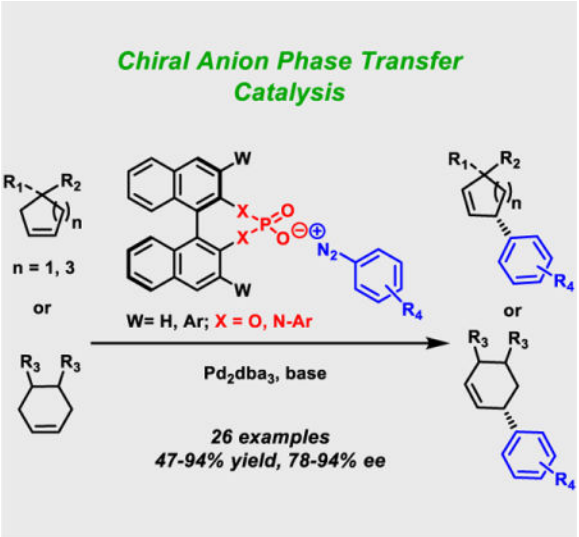
Supporting information for this article can be found under.



Keywords

Heck; Matsuda; Heck reaction; Chiral Anion Phase-Transfer Catalysis; Palladium; BINAM-derived phosphoric acid

The Heck–Matsuda arylation reaction[1] (Scheme 1) offers notable advantages over traditional cross-coupling chemistry.[2] Aryl diazonium salts, easily prepared from the corresponding anilines,[3] are much more reactive than their aryl halide and sulfonate counterparts.[4] Thus, reactions can typically be performed under milder conditions.[2b,5] Additionally, oxidation-sensitive ligands are not required, avoiding the need for rigorous exclusion of oxygen.[5] However, enantioselective variants of the Heck–Matsuda reaction are rare, largely because commonly employed chiral phosphine ligands are incompatible with diazonium salts.[6]

The groups of Correia[7] and Sigman[8] have addressed this challenge through the use of chiral bisoxazoline and pyridine oxazoline ligands, respectively. Correia and co-workers have developed arylative desymmetrizations of both cyclic and acyclic olefins (Scheme 1a), while the Sigman group has reported highly enantio and regioselective arylations of acyclic alkenyl alcohols of various chain lengths using a redox-relay strategy (Scheme 1b).[9] As an alternative approach, we envisioned the use of chiral anion phase transfer catalysis (CAPT) (Scheme 2).[10–12] In this strategy, an insoluble diazonium salt is transported into organic solution via anion exchange with a lipophilic phosphate salt to produce ion-pair **1**.[11a,12] After oxidative addition by a Pd(0) species and loss of N_2, the chiral phosphate remains as a counterion to the resulting cationic Pd(II) intermediate [2,11b] Migratory insertion of the olefin then provides intermediate **3**. This step is rendered enantioselective by virtue of the associated chiral anion.[11a] β-hydride elimination and olefin disassociation affords desired product **4** and Pd-hydride **5**. We envisioned **5** undergoing formal reductive elimination via two plausible pathways, either by deprotonation by the phosphate counterion (shown in Scheme 2) or by the inorganic base present in the mixture. Both pathways regenerate Pd(0) and chiral phosphate co-catalysts.

Notably, the outlined mechanism posits that the chiral anion is associated with the cationic palladium catalyst throughout the catalytic cycle. This hypothesis implies that the *anion might be leveraged to mediate reactivity and selectivity arising from any or all of the elementary steps in the catalytic cycle*. More specifically, alkene isomerization position by a palladium hydride intermediate (**5**), which has been previously noted as an issue of the Heck-Matsuda reaction of unactivated cyclic alkenes,[4b,13] might be subject to anion control. However, while the number of examples of chiral phosphate anion-controlled enantioselectivity is rapidly increasing, the use of these anions to influence reaction outcomes beyond enantioselectivity remains rare.[14] Herein, we demonstrate that CAPT catalysis can be employed to control the enantio- and chemoselectivity of the Heck-Matsuda reaction.

To test the viability of the hypothesis outlined above, cyclopentene **6** was treated with 5 mol % Pd_2dba_3, 1.4 equivalents of phenyldiazoniumtetrafluoroborate, 6 equivalents of Na_2CO_3, and 10 mol% **7a** as a phase-transfer catalyst in toluene. Under these conditions the desired product was formed in good yield and with a significant level of enantioselectivity (Table 1, entry 1). After examining various non-polar solvents, catalysts, inorganic bases, and reaction temperatures, the optimal results were obtained using a 3:2 mixture of benzene and MTBE as solvent, K_2CO_3 as the inorganic base, and H8-TCYP (**7a**) as the chiral anion at 10 °C (Table 1, entry 8). Notably, the reaction did not proceed in the absence of a phase-transfer catalyst (Table 1, entry 5) and was slowed in the absence of base, while, affording product in diminished enantioselectivity (Table 1, entry 6). These results are consistent with the proposed phase-transfer mechanism.

With an optimized set of conditions in hand, the scope of the aryl diazonium salt was examined (Table 2). Generally, substitution at the *meta*- and *para*- positions of this reagent was well-tolerated, affording products in good yields and enantioselectivities. Specifically, strongly electron-donating groups (Table 2, **8d–e**), and electron-withdrawing groups (Table 2, **8b–c**) were viable under the optimized reaction conditions. Disubstitution of the aryl diazonium salt was also well-tolerated (Table 2, **8f** and **8i**). In contrast, while high enantioselectivity was obtained with an ortho-substituted diazonium, the yield was diminished (Table 2, **8j**). Notably, enantioselectivities using various aryl diazonium salts under CAPT catalysis compare favorably with those previously reported for this class of substrate.[7a]

Given the results for disubstituted cyclopentene derivatives, we sought to expand the scope to mono-substituted analogues, with the aim of achieving high diastereo- and enantioselectivity. When cyclopentene **9** was subjected to the phase-transfer Heck–Matsuda conditions, the desired product was obtained as a single diastereomer in moderate enantioselectivity. Slight modification of reaction conditions, namely altering the inorganic base to Cs_2CO_3, improved the enantioselectivities up to 90% ee (Table 3). Substitution of the aryl diazonium salt with an electronically diverse set of substituents was well tolerated.

Examination of additional cyclopentene derivatives revealed divergent reactivity using spirocyclic substrates. For instance, reaction of olefin **11**, using BINOL-derived phosphoric

acid as a catalyst **7a**, produced a 3:2 mixture of the desired product **12** and isomerized starting material **13** (Table 4, entry 1).

Alkene isomer **13** likely arises from coordination of Pd-hydride **5** (Figure 1) to **11** followed by migratory insertion and β-hydride elimination. To inhibit this undesired isomerization pathway, we hypothesized that a more basic counterion would increase the rate of reductive elimination, thus decreasing the lifetime of the cationic Pd-hydride. A variety of chiral phosphoric acids with a more electron rich binapthyl diamine (BINAM) backbone were prepared.[12b,15] When **11** was subjected to the same reaction conditions, but with BINAM-derived phosphoric acids (BDPA, **7g-k**) as the catalyst, the desired product was generated without isomerization of starting material (Table 4, entries 2–8).

Furthermore, examination of BDPA catalysts with different *N*-aryl substituents and re-optimization of reaction conditions, allowed for the selective formation of the desired Heck-Matsuda adduct in good yield and high enantioselectivity (Table 4, entry 8). Various aryl diazonium salts were viable coupling partners using these conditions with enantioselectivities up to 92% (Table 5).[16]

Having established BDPAs as catalysts for the CAPT Heck-Matsuda reaction, we turned our attention to larger ring systems that had previous given low selectivity with either traditional ligands [7a] or BINOL-derived catalysts. To this end, tetrahydrophthalimide derivative **14** was subjected to CAPT conditions. The reaction of **14**, using **7a** as the catalyst, provided the Heck adduct in low enantioselectivity. Examination of BINAM-phosphate **7n**, using 4-fluorobenzenediazonium tetrafluoroborate as a coupling partner, afforded the Heck adduct in 84% ee and 40% yield. Due to presence of minor olefin isomers in the product,[17] the double bond was hydrogenated for analytical purposes without erosion of enantioselectivity (For further details See Supporting Information). Various aryl diazonium salts were viable coupling partners using these conditions with enantioselectivities up to 90% (Table 6).

Given the results for six-membered ring derivatives we looked to expand the scope to seven-membered analogue **16**. As had been previously observed with cyclopentenes, the reaction of olefin **16**, using **7a** as a catalyst, afforded the Heck adduct in 2.2:1 mixture of regioisomers and low enantioselectivity. In contrast, the reaction catalyzed by BDPA **7m** afforded the desired product with high regioselectivity and 78% ee (Scheme 3).

As an application of the developed method, hydantoin derivative **18**, an amino acid precursor, was arylated under chiral anion phase transfer conditions. The Heck-Matsuda reaction of **18** catalyzed by BINOL-derived phosphoric acid **7a**, generated **19** with 14% ee and 14:1 *dr*. In contrast, BDPA **7i** catalyzed the desired transformation to afford **19** as a single diastereomer in good yield and 81% ee, which was upgraded to 96% ee by a single recrystallization (Scheme 4). The corresponding amino acid derivative **20** was readily generated by reaction of **19** under basic conditions. Conformationally constrained amino acids similar to **20** are known to be S1P1 receptor agonists[18a,7h], and have been previously prepared from optically active starting materials.[18b]

The reductive elimination and isomerization steps[19] with both BINOL- and BINAM-derived phosphate counterions (Schemes 2 and S1) were investigated using density functional theory computations (B3LYP-D3).[20,21] The Gibbs free energies of activation computed at the $SMD_{(Toluene)}$/B3LYP-D3/6-31G**, SDD(Pd)//$SMD_{(Toluene)}$/B3LYP-D3/6-31G**,LANL2DZ(Pd) level of theory for reductive elimination step and isomerization of **11**. The Gibbs free energy of activation for the reductive elimination (Figure 1a) was found to be 2.2 kcal/mol lower with a BINAM-phosphate than with a BINOL-phosphate (See Table S3, Supporting Information). Presumably, the presence of less inductively withdrawing and more π-donating *N*-aryl substituents results in a more basic phosphate and consequently, a more favorable reductive elimination.

Calculations indicate that the chiral phosphate works in concert with a cationic (dba)Pd-hydride[22] in the isomerization step. The optimized geometries (Figure 1b) indicate that the alkene accepts the hydride from the palladium while the phosphate oxygen simultaneously abstracts a methylene proton. When comparing BINOL- and BINAM-phosphates, isomerization barriers were found to be higher than the reductive elimination by 2.5 and 5.5 kcal/mol, respectively (See Table S3, Supporting Information). These values are in agreement with the experimental observations, as the alkene isomerization occurs when BINOL-phosphates are employed as co-catalysts, but is circumvented with the use of BINAM-phosphates.

In conclusion, we have developed an asymmetric Heck-Matsuda reaction of cyclopentene, cyclohexene, and cycloheptene derivatives using a chiral ion-pairing strategy. These first examples of chiral counterion controlled enantioselective Heck reactions offer an alternative to and compliment the recent advances in asymmetric variants employing chiral ligand. In addition, these comprise the first successful examples of enantioselective Heck-Matsuda arylation of a 6-membered ring system. In the cases of cyclopentene and cycloheptene starting materials, undesired alkene isomerization was circumvented by the application of BINAM-derived phosphoric acids as catalysts for CAPT. Furthermore, mechanistic insights gained through DFT calculations suggest that the nature of the counterion is integral to achieving the desired selectivity. More importantly, these results suggest that BINOL/BINAM-derived phosphate counterions, that have almost exclusively been employed to control enantioselectivity, may offer a more general means to control reactivity and selectivity in transition metal mediated processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. The use of BDPA catalysts for the Heck-Matsuda reaction of **6** and **9** afforded the arylation products **8a** and **13a** in high yields as up to 65% and 52% ee, respectively (see supporting information, Table S1 and S2).
17. Unlike the reaction of with cyclopentene **11** and cycloheptene **16**, alkeneisomers are the result of isomerization of the alkene in the product **15** into conjugation with the maleimide carbonyl group(s).
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21. (a) All geometries were optimized at the $SMD_{(Toluene)}$/B3LYP-D3/6-31G**,LANL2DZ(Pd) level of theory.Gaussian09, Rev. D.01 is employed for all the computations.Frisch, MJ., et al. Gaussian09, Revision D.01. Gaussian, Inc.; Wallingford, CT: 2013. (c) The optimized geometries of the transition states and intermediates for the reductive elimination and isomerization steps are respectively given in Figures S1 and S2 in the SI.
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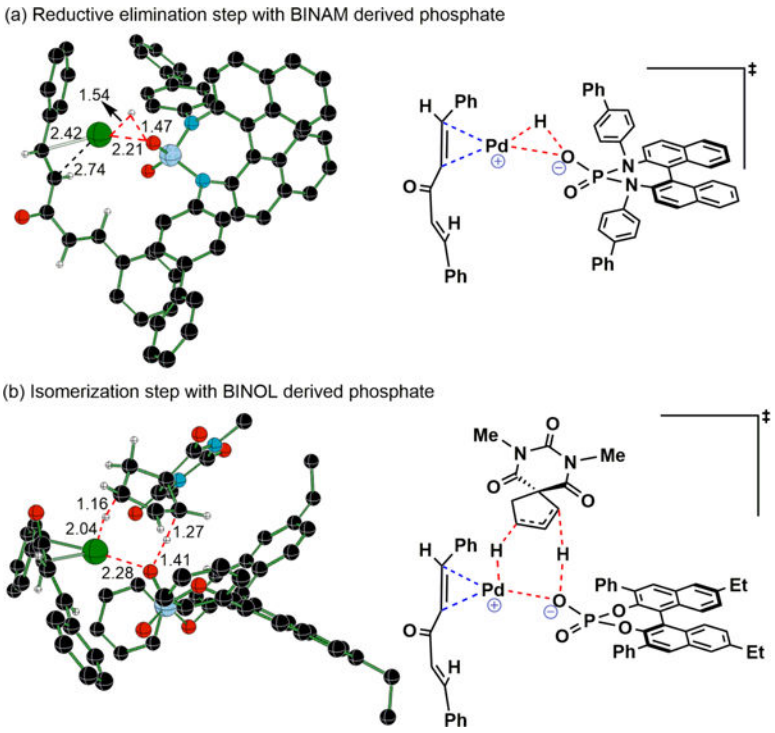
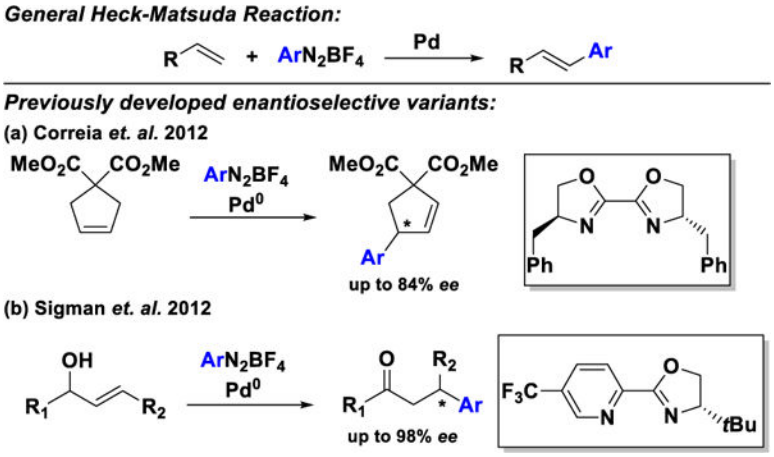


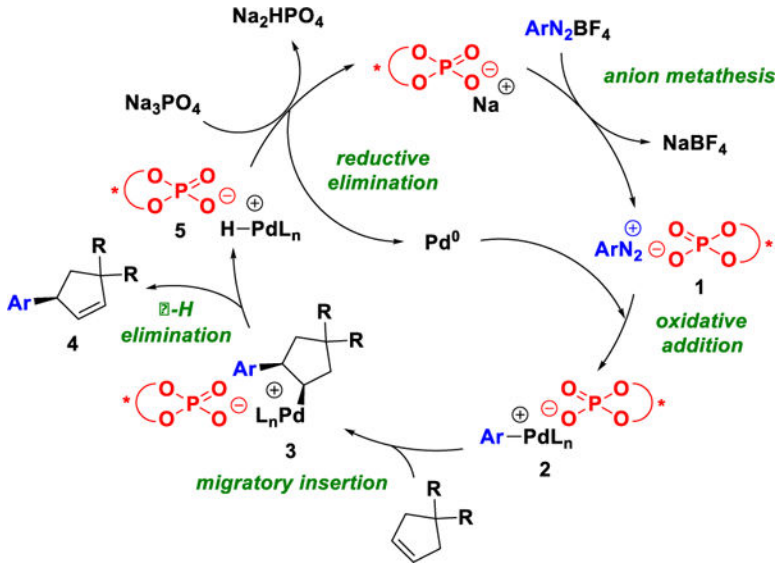
Figure 1.

Optimized transition state geometries for (a) reductive elimination and (b) isomerization of **11** in the presence of chiral phosphates at the $SMD_{(Toluene)}$/B3LYP-D3/6-31G**, LANL2DZ(Pd) level of theory. The distances are in Å. Only selected hydrogen atoms are shown for improved clarity. C=black, O=red, H=gray, N=cyan, P=blue and Pd=green.



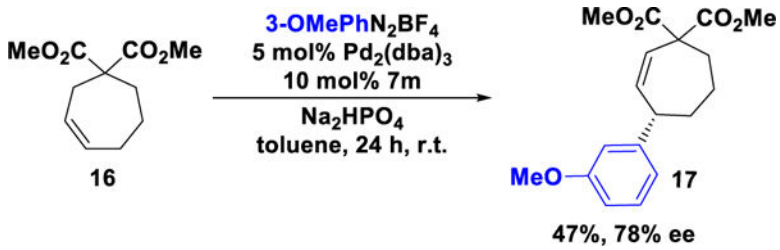
Scheme 1.

Heck–Matsuda reaction and enantioselective variants.

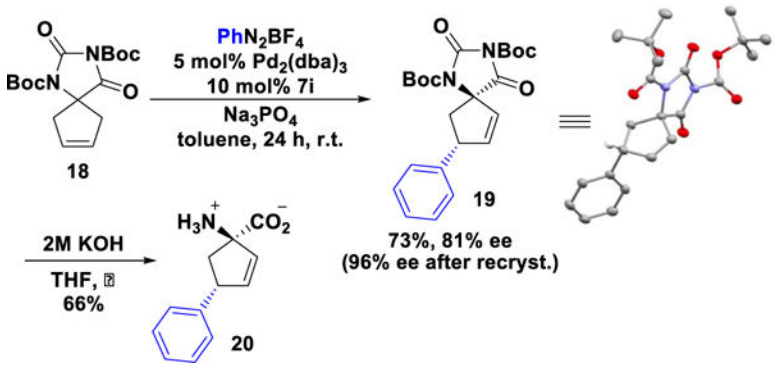


Scheme 2.

Enantioselective Heck–Matsuda reaction via chiral anion phase t ransfer catalysis.



Scheme 3.
Arylation of Cycloheptene **16**.



Scheme 4.
Enantioselective synthesis of amino acid **20**.

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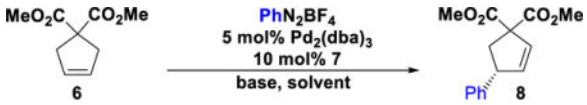
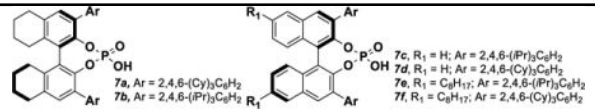
Table 1

Reaction Optimization[a]



entry	CAPT	solvent	base	temp	yield (%)[b]	ee (%)[c]
1	7a	toluene	Na_2CO_3	r.t.	76	49
2	7a	benzene	Na_2CO_3	r.t.	80	57
3	7a	MTBE	Na_2CO_3	r.t.	68	59
4	7a	benzene/MTBE 3:2	Na_2CO_3	r.t.	86	68
5	–	benzene/MTBE 3:2	Na_2CO_3	r.t.	9	–
6	7a	benzene/MTBE 3:2	–	r.t.	40	7
7	7a	benzene/MTBE 3:2	K_2CO_3	r.t.	97	70
8	7a	benzene/MTBE 3:2	K_2CO_3	10 °C	80	85
9	7b	benzene/MTBE 3:2	Na_2CO_3	r.t.	85	45
10	7c	benzene/MTBE 3:2	Na_2CO_3	r.t.	61	63
11	7d	benzene/MTBE 3:2	Na_2CO_3	r.t.	94	40
12	7e	benzene/MTBE 3:2	Na_2CO_3	r.t.	88	43
13	7f	benzene/MTBE 3:2	Na_2CO_3	r.t.	82	36



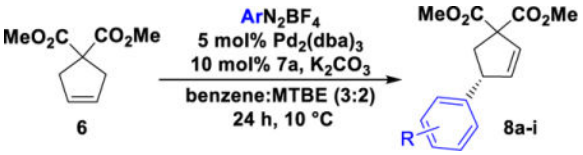
[a]Conditions: **6** (1 equiv, 0.027 mmol); phenyldiazonium tetrafluoroborate (1.4 equiv); $Pd_2(dba)_3$ (0.05 equiv); **7** (0.1 equiv); base (6 equiv); solvent (0.75 mL); 24 h.

[b]Yield determined by ^{1}H-NMR utilizing 1,4-dinitrobenzene as an internal standard.

[c]Enantiomeric excess determined by chiral HPLC. MTBE: Methyl *tert*-butyl ether.

Table 2

Aryl Diazonium Scope[a]



entry	R =	yield (%)[b]	ee (%)[c]
1	H (8a)	82	85
2	3-CF_3 (8b)	70	84
3	4-F (8c)	81	85
4	3-OMe (8d)	81	79
5	4-OMe (8e)	73	82
6	3,5-Me (8f)	79	82
7	4-fBu (8g)	82	87
8	4-Ph (8h)	66	85
9	4-OMe, 3-CI (8i)	80	80
10	2-F (8j)	15	94

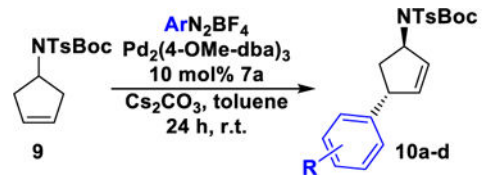
[a]Conditions: **6** (1 equiv, 0.054mmol); aryldiazonium tetrafluoroborate (1.4 equiv); $Pd_2(dba)_3$ (0.05 equiv); **7a** (0.10 equiv); K_2CO_3 (2 equiv); solvent (1.6 mL); 24 h.

[b]Isolated yields.

[c]Enantiomeric excess determined by chiral phase HPLC.

Table 3

Arylation of Monosubstituted Cyclopentene[a]



R =	yield [b]	ee [c]
4-F (**10a**)	86	90
3,5-Me (**10b**)	86	86
4-Ph (**10c**)	53	84
3-OMe (**10d**)	70	83

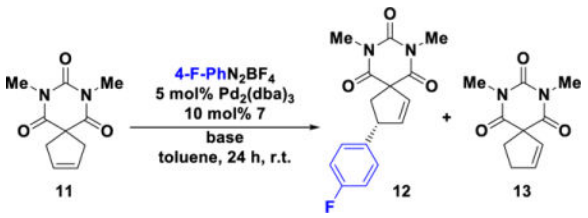
[a] Conditions: **9** (1 equiv, 0.05mmol); aryldiazonium tetrafluoroborate (1.5 equiv); Pd_2(4-MeO-dba)$_3$ (0.05 equiv); **7a** (0.10 equiv); Cs_2CO_3 (2 equiv); toluene (1.0 mL); 24 h.

[b] Isolated yields.

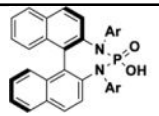
[c] Enantiomeric excess determined by chiral HPLC.

Table 4

Catalyst Control of Olefin Isomerization[a]



entry	CAPT	solvent	base	12 : 13	conv. (%)[b]	ee (%)[c]
1	7a	toluene	Na_2CO_3	3 : 2	50	40
2	7g	toluene	Na_2CO_3	>20:1	78	55
3	7g	toluene	Na_2HPO_4	>20:1	95	57
4	7h	toluene	Na_2HPO_4	>20:1	75	36
5	7i	toluene	Na_2HPO_4	>20:1	96	74
6	7j	tol/MTBE 1:1	Na_2HPO_4	>20:1	50	82
7	7k	tol/MTBE 1:1	Na_2HPO_4	>20:1	95	82
8	7k	MTBE	Na_2HPO_4	>20:1	95	87



7g, Ar = 4-Me-C_6H_4 ***7k***, Ar = 4-Adamantyl-C_6H_4
7h, Ar = 4-CF_3-C_6H_4 ***7l***, Ar = 3,5-$(OMe)_2$-C_6H_4[d]
7i, Ar = 4-*t*Butyl-C_6H_4 ***7m***, Ar = 3,5-$(O$*i*$Pr)_2$-C_6H_4[d]
7j, Ar = 4-Mes-C_6H_4 ***7n***, Ar = 1,4-Benzodioxane-C_6H_4[d]

[a]Conditions: **11** (1 equiv, 0.025mmol); 4-fluorophenyldiazonium tetrafluoroborate (1.2equiv); $Pd_2(dba)_3$ (0.05 equiv); **7** (0.1 equiv); base (2 equiv); solvent (0.50 mL); 24 h.

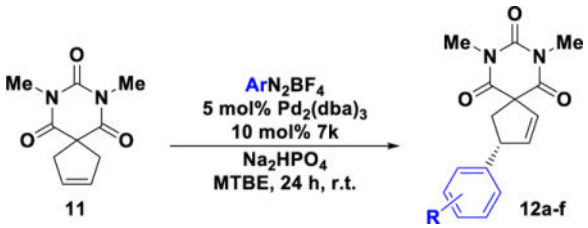
[b]Conversion determined by crude ^{1}HNMR.

[c]Enantiomeric excess determined by chiral HPLC.

[d]Low conversion.

Table 5

Aryl Diazonium Scope[a]



entry	R =	yield (%) [b]	ee (%)[c]
1	H (12a)	70	86
2	4-*t*Bu (12b)	92	92
3	4-Me (12c)	67	90
4	4-F (12d)	79	85
5	3-F (12e)	92	84
6	3-CF_3 (12f)	94	90

[a] Conditions: **11** (1 equiv, 0.025mmol); aryldiazonium tetrafluoroborate (1.5 equiv); $Pd_2(dba)_3$ (0.05 equiv); **7k** (0.10 equiv); Na_2HPO_4 (2 equiv); solvent (0.50 mL); 24 h.

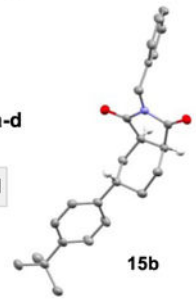
[b] Isolated yields.

[c] Enantiomeric excess determined by chiral phase HPLC.

Table 6

Arylation of Cyclohexene Derivatives[a]

entry	R =	yield (%)[b]	ee (%)[c]
1	4-F (**15a**)[d]	72	84
2	4-*t*Bu (**15b**)	72	88
3	4-OMe (**15c**)	66	86
4	3-CF_3 (**15d**)	78	90



[a]Conditions: **14** (1 equiv, 0.041mmol); aryldiazonium tetrafluoroborate (1.4 equiv); $Pd_2(dba)_3$ (0.05 equiv); **7n** (0.10 equiv); Na_2HPO_4 (2 equiv); solvent (1.0 mL); 24 h.

[b]Isolated yields for two steps.

[c]Enantiomeric excess determined by chiral phase HPLC.

[d]**15a′** was isolated in the first step in 84% ee and 40% yield (See SI).