Palladium-Imidazolium Carbene Catalyzed Heck Coupling Reactions and Synthesis of a Novel Class of Fluoroanthracenylmethyl PTC Catalysts

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PALLADIUM-IMIDAZOLIUM CARBENE CATALYZED HECK COUPLING
REACTIONS AND THE SYNTHESIS OF A NOVEL CLASS OF
FLUOROANTHRACENYL METHYL PTC CATALYSTS

By
Jiuqing Zhang

A thesis submitted to the faculty of
Brigham Young University
In partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry and Biochemistry
Brigham Young University
November 2005
ABSTRACT

PALLADIUM-IMIDAZOLIUM CARBENE CATALYZED HECK COUPLING REACTIONS AND THE SYNTHESIS OF A NOVEL CLASS OF FLUOROANTHRACENYLMETHYL PTC CATALYSTS

Jiuqing Zhang
Department of Chemistry and Biochemistry
Master of Science

Palladium catalyzed Heck coupling with aryl and alkenyl halides has become a powerful means of carbon-carbon bond formation. This standard synthetic method has been developed to a high level of utility using various catalysts, conditions and substrates. Yet significant drawbacks remain, including poor reactivity, the need for high temperatures and base, limited substrate generality, and selectivity. Mixed products often suffer from olefin migration following insertion.

N-Heterocyclic carbenes (NHC) have proven to be electron-rich donors which provide higher stability and reactivity than phosphines. In a previous paper reported by our research group the imidazolium-palladium carbene has proven to be highly efficient for the Suzuki-Miyaura cross couplings. The most active bis-2,6-diisopropylphenyl dihydroimidazolium chloride ligand 1 in that series together with palladium acetate were employed as the catalyst, to efficiently catalyze the Heck coupling of aryl diazonium ions with olefins with useful yields at room temperature. Added base is not needed either to
Phase-Transfer Catalysis (PTC) is a very useful approach and has been widely used in synthetic organic chemistry. A novel class of fluoroanthracenylmethyl PTC catalysts were synthesized and explored for asymmetric glycolate and glycine alkylation. Phosphorous pentoxide was used for the challenging electron-deficient electrophilic aromatic substitution step. These new catalysts proved to have high selectivities for glycine alkylation under mild conditions.
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Chapter 1. Palladium-Imidazolium Carbene Catalyzed Mizoroki-Heck Coupling with Aryl Diazonium Ions

1.1 Background

Palladium catalyzed Mizoroki-Heck reaction, discovered independently by Mizoroki\textsuperscript{1} and Heck\textsuperscript{2} and developed by Heck, has become a powerful means to form new carbon-carbon bonds (Scheme 1.1).\textsuperscript{3} This standard synthetic method has been developed as one of the simplest ways to obtain variously substituted olefins, dienes, and other unsaturated compounds, many of which are useful as dyes, UV screens, pharmaceuticals, and conjugated polymers.

![Chemical Reaction Image]

\[ \text{R}_1^1\text{-X} + \text{R}_2^2 \xrightarrow{[\text{Pd}][\text{L}] \text{base, heat}} \text{R}_1^1\text{R}_2^2 \]

\( \text{R}_1^1 = \text{aryl, alkenyl} \\
\text{X} = \text{N}_2^+, \text{I, OTf, Br, Cl} \)

Scheme 1.1 Heck coupling reaction

The reaction can be catalyzed by palladium complexes with phosphine ligands, and the phosphine-assisted approach\textsuperscript{4} has become a classical and well-established method to give excellent results in most cases. Yet significant drawbacks remain for this approach. Phosphine ligands are expensive, toxic, and unrecoverable. In large-scale industrial production, the phosphines might be a more serious economical burden than even palladium itself. Another reason is the poor reactivity often associated with fully ligated complexes of palladium. Usually the phosphine-assisted approach needs high temperatures and base, and has limited substrate generality and selectivity.\textsuperscript{5} Further
limitations are found in that amine or carbonate bases and often other additives, usually silver or thallium salts, must be screened in order to optimize the yield.\textsuperscript{6}

A new principle for designing catalysts for palladium-catalyzed reactions was proposed by Herrmann et al.\textsuperscript{7} Stable heterocyclic carbenes derived from the deprotonation of imidazolium salts such as 1 and 2 (Figure 1.1), turned out to be excellent ligands forming a wide range of complexes.\textsuperscript{8} Carbene ligands are electron-rich metal \(\sigma\)-donors\textsuperscript{9} which provide higher stability and reactivity than phosphines through strong \(\sigma\)-bond donation to the metal, together with attenuated back-bonding due to donation of the nitrogen lone pair of electrons.\textsuperscript{10} The combination of electronic effects renders the metal more electron-rich, allowing for a more favorable oxidative insertion step.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{imidazolium_salts.png}
\caption{Imidazolium salts}
\end{figure}

Typical NHC complexes, formed by treatment of an imidazolium salt with base and a metal, are air-stable and have recently been used for several catalytic applications including Suzuki cross-coupling and olefin metathesis reactions. In a previous paper reported by our research group the palladium-imidazolium carbene has proven to be highly efficient for the Suzuki-Miyaura cross coupling.\textsuperscript{11} The most active bis-2,6-diisopropylphenyl dihydroimidazolium chloride ligand 6 in that series was synthesized following a modified procedure of Arduengo (Scheme 1.2). Aqueous
glyoxal treated with aniline in refluxing *n*-propanal gave the diimine, which was reduced with sodium borohydride to give the diamine. Treatment with triethyl orthoformate produced the imidazolium chloride with 88% yield. The analogous dehydroimidazolium chloride ligand 7 could be prepared through the cyclization of the diimine using chloromethyl ethyl ether.

![Scheme 1.2 Synthesis of the imidazolium salts](image)

Scheme 1.2 Synthesis of the imidazolium salts

Scheme 1.3 illustrates the major steps of the Heck catalytic cycle. The entry into the catalytic cycle starts from the reduction of Pd(II) complexes to Pd(0), which is most likely accomplished by phosphine in the phosphine-assisted catalytic cycle. The oxidative addition proceeds as a concerted process in which C – X bond rupture is fast, and is very sensitive to the strength of C – X and M – X bonds. The order of reactivity is N$_2^+$ > I >> OTf > Br > Cl. The next step is the coordination of the Pd(II) complex to the olefin to be coupled, followed by the migratory insertion, which is the product-forming step of the Heck cycle, with a new C – C bond formed. It is this step which is most likely responsible for the regio- and stereodiscrimination as well as
substrate selectivity. As in the complexes of palladium with both monocarbenes and chelating bis-carbenes, the heterocyclic rings are turned out of the plane formed by the square-planar coordination shell of palladium. Thus, steric hindrance in the migratory insertion step of the Heck cycle should be low. This can also be used to explain the high efficiency of carbene ligands. $\beta$-Hydride elimination releases the double bond, and the palladium hydride is converted to Pd(0) by base. It should be noted that when diazonium salts were used as alternative leaving group instead of halides or triflates, the reaction does not require the presence of base, the addition of which leads to uncontrolled decomposition of diazonium salt.

\[
Pd(0)_{L_n} \xrightarrow{\text{B:H}X} Pd(0)_{L_n} \xrightarrow{R^1-X} R^1-Pd(0)_{L_n}X \xrightarrow{\text{oxidative addition}} H-Pd(II)_{L_n}X \xrightarrow{R^1} R^1-Pd(II)_{L_n}X \xrightarrow{\text{migratory insertion}} Pd(II)_{L_n}X \xrightarrow{R^1-Pd(II)_{L_n}X} \xrightarrow{\beta\text{-hydride elimination}} R^1\xrightarrow{\text{migratory insertion}} R^2
\]

Figure 1.2 Catalytic cycle of Heck coupling reaction

1.2 Palladium-Imidazolium Carbene Catalyzed Heck Coupling Reactions

In our research, catalysts formed from imidazolium salt 6 and palladium(II) acetate
were used, without added base and at room temperature, to catalyze the Heck coupling reactions, giving products with 80-90% yields.\textsuperscript{13}

![Scheme 1.3 Palladium-imidazolium catalyzed Heck coupling reaction](image)

Heck coupling of phenyl diazonium fluoroborate and styrene (Table 1.1) was used to screen the effect of several solvents. From the table we can see that THF gave the best results with 77% yield at room temperature within 5.5 hr. When the analogous dehydroimidazolium ligand 7 was used, the product yield was significantly lowered to 57% yield.

**Table 1.1** Effect of solvents

<table>
<thead>
<tr>
<th>solvent</th>
<th>time (hr)</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>4.5</td>
<td>77(57)\textsuperscript{b}</td>
</tr>
<tr>
<td>toluene</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>dioxane</td>
<td>7</td>
<td>57</td>
</tr>
<tr>
<td>ether</td>
<td>6</td>
<td>61</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yields are reported for isolated, chromatographed materials.

\textsuperscript{b} The analogous dehydroimidazolium chloride ligand was used.

The Heck couplings were explored with different diazonium salts and two styrenes at 1.2:1 stoichiometry (Table 1.2). The palladium-imidazolium catalyst loading is 2
mol% for all substitution patterns except for the yields in parentheses labeled with a and b. Good to excellent yields were obtained for all the substitution patterns, including methyl, methoxy, and bromo substrates. The more electron rich methoxyphenyl ions gave higher yields of 81% and 88% for the couplings with styrene and 76% and 81% for the couplings with p-methoxy styrene. The p-bromophenyl diazonium ion example showed complete chemoselectivity with exclusive reaction via the diazonium group in excellent 91% yield. The product obtained in this case could be used to run another Heck coupling reaction with added base and elevated temperature. With the loading of the palladium-imidazolium carbene catalyst reduced to 0.1 mol %, the yields are only slightly reduced to 72% and 87% respectively in the phenyl and p-methoxyphenyl diazonium ion cases. But when palladium acetate (2 mol%) was used without added imidazolium ligand in THF at room temperature for 12 h, the yield was significantly lowered to 21% in the phenyl diazonium ion case.

**Table 1.2 Heck coupling with styrenes**

<table>
<thead>
<tr>
<th>Ar</th>
<th>-H</th>
<th>-OMe</th>
<th>X</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>77 (72)a (21)b</td>
<td>75</td>
<td>86</td>
<td>81</td>
</tr>
<tr>
<td>-OMe</td>
<td>78</td>
<td>67</td>
<td>81</td>
<td>76</td>
</tr>
</tbody>
</table>

a Isolated yields using 0.1 mol % palladium acetate-imidazolium catalyst.
b Isolated yield without added imidazolium ligand.
Heck couplings of the diazonium salts with methyl acrylate and acrylonitrile in THF were also explored under the standard arylation conditions (Table 1.3). In general, longer reaction times were needed. The yields for the acrylonitrile were very low, with the \( p \)-bromophenyl diazonium ion having a reasonable 61\% yield and the electron-rich methoxyphenyl ions giving moderate yields of 51\% and 58\%. Methyl acrylate gave moderate to good yields for all the diazonium salts.

**Table 1.3** Heck coupling with acrylates

<table>
<thead>
<tr>
<th>Ar</th>
<th>X</th>
<th>( \text{yield (%)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Br} )</td>
<td>( -\text{CN} )</td>
<td>47 42 48 51 58 61</td>
</tr>
<tr>
<td>( \text{MeO} )</td>
<td>( -\text{CO}_2\text{Me} )</td>
<td>68 66 65 70 71 81</td>
</tr>
</tbody>
</table>

Table 1.4 shows the results for the \textit{in situ} aniline couplings. The anilines were treated with \textit{tert}-butyl nitrite followed by addition of boron trifluoride etherate at 0 °C to give the diazonium salts. Without separation, to the diazonium salts solution were directly added the coupling partners and the palladium-imidazolium carbene catalyst. Somewhat longer reaction times were needed, and moderate yields were obtained for most of the substrates. The more electron-rich \( p \)-methoxyphenyl diazonium ion gave the lowest yields of 21\% and 17\%. 

7
Table 1.4 In Situ aniline coupling

\[
\text{Ar-NH}_2 \xrightarrow{\text{1 eq}} \quad \xrightarrow{\text{BuONOBF}_3\cdot\text{OEt}_2, \text{THF, 0 °C}} \quad \xrightarrow{\text{2 mol% Pd(OAc)}_2\cdot\text{imid}} \quad \text{Ar-}N_2^+\text{BF}_4^- \xrightarrow{\text{1 eq, rt}} \quad \text{Ar-}X \xrightarrow{\text{Ar}} \quad \text{X}
\]

<table>
<thead>
<tr>
<th>Ar</th>
<th>H</th>
<th>-OMe</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>58</td>
<td>51</td>
</tr>
<tr>
<td>-OMe</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>MeO-</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>-Ar</td>
<td>62</td>
<td>53</td>
</tr>
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**1.3 Conclusion**

With ease and flexibility, this new active palladium acetate-imidazolium catalyst system readily couples olefins with diazonium ions at room temperature with useful yields. Added base is not needed either to form the carbene catalyst or for alkene product formation. When the ligand is omitted, the reaction occurs at a very slow rate at room temperature and with very low yield. A direct, single-flask operation was developed and found to be efficient with aniline substrates. This imidazolium-palladium-diazonium ion system could be used for the synthesis of more complex target compounds that require mild reaction conditions.
1.4 References


Chapter 2. Synthesis of a Novel Class of Fluoroanthracenylmethyl PTC Catalysts

2.1 Background

2.1.1 The Phase-Transfer Catalytic System

Phase-transfer catalysis (PTC) is a very useful approach that typically involves simple experimental operations, inexpensive reagents, and solvents.\(^1\) Due to these advantages, PTC has been widely used in synthetic organic chemistry.\(^2\) The most commonly used PTC catalysts are quaternary ammonium salts. In the last 25 years, the study of phase-transfer catalysis has been focused on the development of asymmetric PTC catalysts.\(^3\)

The alkylation of the prochiral substrate $A$ is used to illustrate the mechanism of the phase-transfer catalytic system (Figure 2.1).\(^4\) There are three main steps in the process. Step 1 is the deprotonation of the prochiral substrate ($A$) to form the enolate, which occurs at the solvent interface. In step 2, ion-exchange of the anion ($A^-$) with the chiral phase-transfer catalyst $R^*_4N^+$ produces an ammonium-enolate ion pair ($B$), which migrates to the organic phase. Step 3 is the rate limiting step, in which the alkylation of the ammonium-enolate ion pair creates the new chiral product ($P^*$).
2.1.2 Asymmetric Phase-Transfer Catalytic Reactions

Asymmetric phase-transfer catalytic reactions can be divided into two main types: carbon-carbon bond forming and carbon-hetero atom bond forming. The former plays an important role in organic synthesis. Under phase-transfer catalytic conditions, different types of C-C bond formation reactions have been studied, including the Michael addition, aldol reactions, and alkylations.

Scheme 2.1 shows an example of an asymmetric Michael addition using a PTC catalyst. A study by Corey showed that catalyst \( 9 \) can be used to catalyze the reaction of glycine imine \( 8 \) with acrylonitrile to produce \((S)-10\) with 85% yield and 91% ee.\(^5\) \((S)-10\) can be further elaborated to amino acid \( 11 \). Recently, catalyst \( 13 \) was used to synthesize chiral cyclohexenone derivatives \( 14 \) with 72% yield and 80% ee.\(^5\)
Phase-transfer aldol reactions of glycine imine 8 with an aldehyde would be a practical method for the synthesis of β-hydroxy-α-amino acids. Miller has reported that when glycine imine 8 was reacted with heptanal in the presence of catalyst 15, 17 was produced in 74% yield and with poor selectivity (12% ee for the syn product, and 7% ee for the anti product) (Scheme 2.2). Recently, a highly enantioselective aldol reaction of glycine imine 8 with aldehydes catalyzed by the C$_2$-symmetric chiral PTC catalyst 16 was published by Maruoka. In his research, product 18 was obtained in 76% yield with an antisy/syn ratio of 3.3:1, with the major anti isomer produced in 91% ee. Same type of reaction was reported by Castle and afforded the highest enantioselectivities recorded to date by using an inexpensive cinchona alkaloid derived salt.

**Scheme 2.1** Asymmetric Michael addition using cinchonidium PTC
Scheme 2.2 Phase-transfer catalyzed aldol reactions

The α-amino acids are the most widely employed and populated group of naturally occurring amino acids. Various methods have been developed for the synthesis of α-amino acids, including amination of α-halo acids, Strecker synthesis, and approaches through hydantoin and oxazolines. The phase-transfer catalyzed alkylation of glycine imine 8 was developed by O’Donnell in 1989, and has become another powerful method for the synthesis of α-amino acids (Scheme 2.3). Many successful PTC catalysts have been developed, which provide 19 with high levels of enantioselectivity for alkylation of glycine imine 8.

Scheme 2.3 Phase-transfer catalyzed alkylation
2.1.3 Chiral Phase-Transfer Catalysts

Chiral phase-transfer catalysts can be divided into two major types: chiral crown ethers and chiral quaternary ammonium salts. Catalysts derived from *cinchona* alkaloids 20-23 (Figure 2.2) have proven to be highly effective, and have been widely used in various phase-transfer catalytic systems.

![Figure 2.2 Structure of *cinchona* alkaloids](image)

N-benzyl derivatives of the *cinchona* alkaloids 24 and 25 were employed by O’Donnell as the first generation of *cinchona*-derived phase-transfer catalysts.\(^\text{10}\) O’Donnell has shown that PTC catalysts 24 and 25 led to the production of \((S)-19\) with 42-66% ee.

![Figure 2.3 First generation *cinchona*-derived phase-transfer catalyst](image)

In 1994, O’Donnell developed the second generation *cinchona*-derived phase-transfer catalysts 26 and 27 (Figure 2.4).\(^\text{11}\) The attachment of an allyl group to the secondary hydroxyl group could effectively block one tetrahedral face of the
ammonium cation and help increase the selectivity to 81% ee for the alkylation of glycine imine 8.

Figure 2.4 Second generation *cinchona*-derived phase-transfer catalysts

In recent years, new variations were designed for improved reactivity. A third generation of PTC catalysts 13, 16 and 28 have been developed. These catalysts show a steady improvement in selectivity and efficiency for the production of (S)-19 (Figure 2.5). 12 The structurally rigid, chiral spiro ammonium salts 16 derived from commercially available 1,1’-bi-2-naphthol was synthesized by Maruoka as a $C_2$-symmetric chiral phase-transfer catalyst, and showed a high enantioselectivity of 96% ee for the production of (S)-19. The $N$-9-anthracenylmethyl group in Corey’s catalyst 13 accentuates the steric constraints and provides stronger $\pi-\pi$ interactions which leads to a higher selectivity of 94% ee. Park and Jew’s catalyst 28, with fluoro substituents on the $N$-benzylic group, showed even higher selectivity than Corey’s catalyst. The excellent selectivity of Park and Jew’s catalyst might be due to a more rigid transition state structure caused by the electronic interactions involving water between C(9)-O allyl ether and 2’-F in the catalyst.
Figure 2.5 Third generation *cinchona*-derived phase-transfer catalysts

Based on the results shown above, we decided to synthesize a novel class of catalysts which combine both the size advantage of Corey’s catalyst and the electronegativity of Park and Jew’s catalyst, as shown below.\(^\text{13}\) We felt that this series of fluorinated anthracenyl methyl PTC catalysts could provide even higher levels of selectivity than both Corey’s and Park and Jew’s catalysts.

![New catalysts to be synthesized](image)

Figure 2.6 New catalysts to be synthesized

### 2.2 Synthesis of the Catalysts

A key to the synthesis of our target catalyst 29 is the preparation of the fluorinated bromomethyl anthracene 30, which can be synthesized through the cyclization of methyl ketone 32 followed by bromination. Carboxylic acid 33, which can be produced through the reduction of lactone 34, can be converted to methyl ketone 32 by treatment with methyl lithium. Fluorinated oxazoline 36, readily available from fluorinated benzoyl chloride, can be o-metallated and treated with fluorinated
benzaldehyde 37 to give alcohol 35, hydrolysis of which will give lactone 34 (Scheme 2.7).

**Figure 2.7** Retro synthesis of the new catalysts

Park and Jew’s study of the electronic factors in the catalytic enantioselective phase-transfer alkylation of glycine imine showed that the 2'-F substituent provides the best enantioselectivity.\textsuperscript{11c} Therefore, fluorinated anthracene 38 that has a fluoro group at the α position was initially selected as the target compound. 2-Fluorobenzoyl chloride 39 was used as the starting material. Reaction of 39 with 2-amino-2-methyl-1-propanol followed by treatment with thionyl chloride gave oxazoline 40 in 82% yield. The subsequent step failed to provide the desired compound 41. Instead of abstracting the proton at C-6, the butyl anion attacked C-2, leading to substituted product 42 with 91% yield (Scheme 2.4).
Scheme 2.4 Reactions starting from 2-fluorobenzoyl chloride

This result lead us to employ 2,5-difluorobenzoyl chloride 44 as the starting material. The electronegative fluoro group at C-5 increased the acidity of the hydrogen at C-6. Therefore, the proton at C-6 of oxazoline 45 was readily abstracted, and the desired compound 46 was obtained in 77% yield after heating with aqueous HCl at reflux temperature (100 °C) for 6 hr (Scheme 2.5).

Scheme 2.5 Reactions starting from 2,5-difluorobenzoyl chloride
The next step was reduction of lactone 46 to carboxylic acid 47 (Scheme 2.6). In Harvey's study, hydrogenation of lactone 48 catalyzed by Palladium on charcoal at 40 psi gave carboxylic acid 49 in near quantitative yield within 4 hours (equation A). Witiak also successfully reduced lactone 50 to 51 by refluxing 50 with zinc/copper sulphate in pyridine, to give the desired compound 51 with 92% yield within 20 hours (equation B).

**Scheme 2.6 Reduction of lactones**

When Harvey’s or Witiak’s condition was employed for the reduction of lactone 46, no reaction was observed. When the pressure of Harvey’s condition was increased from 40 psi to 800 psi, hydrogenation of lactone 46 catalyzed by palladium on charcoal successfully reduced 46 to the desired compound 47 with 98% yield in 8 hours (Scheme 2.7).
Scheme 2.7 Reduction of the lacton 46

Unfortunately, treatment of carboxylic acid 47 with methyl lithium failed to give the desired ketone 52. When acid 47 was transformed to amide 53, addition of methyl lithium still did not provide the desired compound (Scheme 2.8).

Scheme 2.8 Conversion of carboxylic acid to methyl ketone

Previous results have shown that the fluoro group at C-2 may be the reason for potential side reactions (Scheme 2.4), and could also be the reason why carboxylic acid 47 failed to be converted to the desired compound 52. 3-Fluorobenzoyl chloride 54 was then used as the starting material. As shown in Scheme 2.9, carboxylic acid 57 was successfully converted to methyl ketone 58 with 79% yield within 4.5 hours.
Polyphosphoric acid (PPA) was initially used for the cyclization of 58. The reaction was complicated, the work up was time-consuming, and only an unreproducible yield of 17% was obtained. Phosphorous pentoxide (P₂O₅) proved to be a more reliable reagent for this challenging electron-deficient electrophilic aromatic substitution step.¹⁶ When the reaction was run in o-dichlorobenzene (180 °C), 1,6-difluoro-10-methylantracene 59 was obtained in 75% isolated yield. The corresponding benzylic bromide 60 was then generated in 83% isolated yield after anthracene 59 was refluxed with NBS (N-bromosuccinimide)) and AIBN (azo-bis-isobutyronitrile) in benzene for 1 hour.

Scheme 2.9 Synthesis of 10-(Bromomethyl)-1,6-difluoroanthracene

Following a similar procedure, 10-(Bromomethyl)-1,8-difluoroanthracene 65 could be obtained in 85% isolated yield (Scheme 2.10).
Scheme 2.10 Synthesis of 10-(Bromomethyl)-1,8-difluoroanthracene

Trifluoroanthracenes 71 and 74 were prepared from oxazoline 66. All reaction conditions were the same as in the previous case except the condition for the conversion of carboxylic acid 68 to the methyl ketone 69. Previous reaction conditions (room temperature, 2 hours) gave the product with only 28% yield. When the reaction temperature was reduced to 0 °C, and the reaction time was changed to 0.5 hours, the yield was significantly increased to 79% (Scheme 2.11).

Scheme 2.11 Synthesis of trifluoroanthracene
Dihydrocinchonidine 75 was then reacted with 10-(bromomethyl)-1,8-difluoroanthracene 65 to give the quaternary ammonium bromide 76, treatment of which with allyl bromide and 50% KOH in CH₂Cl₂ at room temperature gave the desired catalyst 77 with 79% isolated yield (Scheme 2.12). Catalysts 78-81 were also prepared following the same procedure.

Scheme 2.12 Synthetic route and structures of new catalysts (77-81)
2.3 Application of the New Catalysts in Aldol and Alkylation Reactions

The aldol reaction was used to explore the activity and selectivity of the new catalyst 81. As shown in Table 2.1, the new catalyst 81 gave the product with higher selectivity (83% ee) than Park and Jew’s catalyst. But the activity is much lower (41% vs 79%).

Table 2.1 Phase-transfer catalyzed aldol reaction

<table>
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<tr>
<th></th>
<th>yield (%)\textsuperscript{a}</th>
<th>ee (%)\textsuperscript{b}</th>
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\textsuperscript{a}Chromatographed, isolated yields.  
\textsuperscript{b}Determined by chiral HPLC with comparison to racemic materials.

The new catalysts 77-79 were explored in the glycolate alkylation reaction (Table 2.2). In the reaction, 10 mol% of the catalyst, 5 equivalent of CsOH and 5 equivalent of benzyl bromide were used, and the reaction temperature was -35 °C. All three new
catalysts showed better activity and selectivity than Corey’s catalyst, but not as good as Park and Jew’s catalyst. Of the three new catalysts, 1,6-difluoro catalyst 78 gave the best selectivity (73% ee). Unfortunately, the trifluoro catalyst 79 didn’t give the product with good selectivity as anticipated. Only a mild selectivity of 60% ee was obtained.

**Table 2.2 Phase-transfer catalyzed glycolate alkylation**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>time (hr)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<sup>a</sup>Chromatographed, isolated yields.

<sup>b</sup>Determined by chiral HPLC with comparison to racemic materials.

The new catalysts 77-79 were also explored in the benzylation of glycine imine 8 in toluene/chloroform (7:3) with 50% aqueous KOH at -20 °C (Table 2.3). Corey’s catalyst gave the benzylated product 82 in 88% isolated yield with 85% ee. The new catalyst 77 gave a better selectivity of 98% ee, as good as park and Jew’s catalyst. But the selectivities for the new catalysts 78 and 79 were lower than Park and Jew’s catalyst.
Table 2.3 Phase-transfer catalyzed glycine benzylation

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>time (hr)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<sup>a</sup>Chromatographed, isolated yields.

<sup>b</sup>Determined by chiral HPLC with comparison to racemic materials.

Catalyst 77 was further explored in the glycine alkylation reactions using allyl, propargyl and alkyl bromide as the electrophiles (Table 2.4). The reaction condition for Park and Jew’s catalyst and the new catalyst 77 was in toluene/THF (7:3), at -20 °C, and using 50% KOH/H₂O as the base. The reaction condition for Corey’s catalyst was in methylene chloride, at -78 °C, and using CsOH•H₂O as the base. When the new catalyst 77 was used, allyl bromide reacted with glycine imine 8 to produce the product with excellent yield and selectivity (90% yield, 98% ee) in 11 hr. Methallyl bromide reacted at a slower rate, but also gave the product with high selectivity of 98% ee. Methyl iodide also gave the product with high selectivity (97% ee), but the
yield was much lower (66%). Compared with Corey’s catalyst 13 and Park and Jew’s catalyst 28, the new catalyst 77 gave the products with the best selectivity for all three electrophiles.

Table 2.4 Phase-transfer catalyzed glycine alkylation

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<th>time (hr)</th>
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</table>

<sup>a</sup>Chromatographed, isolated yields.
<sup>b</sup>Determined by chiral HPLC with comparison to racemic materials.

Different reaction conditions were applied in the glycine alkylation reaction to further study the activity and selectivity of the new catalyst 77 (Scheme 2.5). At 0 °C, only 12 hours was needed for the reaction to be completed, with slightly reduced selectivity (96% ee). At room temperature, the reaction time was reduced to 8 hours, and product 82 was still obtained with excellent selectivity of 91% ee.
Table 2.5 Effect of temperature

<table>
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<tr>
<th>temp (°C)</th>
<th>time (hr)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>23</td>
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</table>

<sup>a</sup>Chromatographed, isolated yields.

<sup>b</sup>Determined by chiral HPLC with comparison to racemic materials.

The tight-ion pair model of Corey can be used to rationalize the stereo induction (Figure 2.8). In the favored transition state A, the extended π-conjugation of the enolate and the imine adopt a face to face π-interaction with the quinoline and the t-butyl group of the ester fits into the space between the isoquinoline ring and the anthracenyl group. Because the back face is blocked by the isoquinoline group, alkylation has to occur from the front face, and gives the product with S configuration. The presence of the fluoro substituents accentuates the electron deficiency of the ammonium ion, which shortens the distance between the enolate oxygen and the ammonium ion of the catalyst. The more rigid conformation thus formed leads to improved selectivity. In the disfavored transition state B, the π-interaction between the
quinoline and the π-conjugated system of the enolate and the imine is lost, and the alkylation from the front face is hindered by the bulky anthracenyl group of the catalyst.

![Diagram of transition state arrangements of the glycine alkylation](image)

**Figure 2.8** Transition state arrangements of the glycine alkylation

### 2.4 Conclusion

New fluoroanthracenyl cinchonidinium catalysts were synthesized. These new catalysts demonstrate enhanced reactivity and selectivity for PTC glycine alkylation. Phosphorous pentoxide mediates intramolecular electrophilic substitution with the deactivated intermediates allowing for specific placement of fluoro groups.
2.5 References


Chapter 3. Experimental Details and Data

3.1 General Experimental

Air and water sensitive reactions were performed in flame-dried glassware under a nitrogen atmosphere. Air and moisture sensitive reagents were introduced via dry syringe or cannula. Methylene chloride, toluene, THF, diethyl ether, methanol, and triethylamine were dried by passing through columns of activated alumina. Benzene and pyridine were stored over molecular sieves. Reagents were purchased from Aldrich and Lancaster. Flash chromatography was carried out using 60-230 mesh silica gel. Radial chromatography was performed using 1 and 2 mm plates loaded with 230-400 mesh PF-254 gypsum bound silica. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F\textsubscript{254}, 0.25 mm pre-coated TLC plates. TLC plates were visualized using UV\textsubscript{254} and cerium molybdate (0.5 g Ce(NH\textsubscript{4})\textsubscript{2}(NO\textsubscript{3})\textsubscript{6}, 24.0 g (NH\textsubscript{4})\textsubscript{6}Mo\textsubscript{7}O\textsubscript{24}•4H\textsubscript{2}O, 500 mL H\textsubscript{2}O, 28 mL H\textsubscript{2}SO\textsubscript{4}) with charring. All \textsuperscript{1}H NMR spectra were obtained with either 300 or 500 MHz Varian spectrometers using TMS (0.0 ppm) or chloroform (7.26 ppm) as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet); and coupling constants are reported in hertz (Hz). \textsuperscript{13}C NMR was obtained with either 75 or 125 MHz Varian spectrometers using TMS (0.0 ppm), chloroform (77.2 ppm) as the internal standard. Mass spectral data (HRMS, EI, FAB) were obtained from the Brigham Young University mass spectrometry facility. Optical rotations were obtained using the sodium D line at
ambient temperature. Low temperatures were maintained using an immersion cooler with a cooling probe placed in an acetone bath.

3.2 Experimental Details and Data for Heck Coupling Reactions

**General Procedure for the Heck Reaction:**

To a flame dried flask under nitrogen were added arenediazonium tetrafluoroborate (0.125 mmol) and olefinic compound (0.1 mmol), followed by Pd(OAc)$_2$ 0.45 mg (0.002 mmol, 2 mol %) and dihydroimidazolium chloride salt ligand 0.85 mg (0.002 mmol, 2 mol %) in anhydrous THF (2 mL). The resulting suspension was stirred at rt for the time indicated. To the reaction mixture was added methylene chloride (10 mL). The methylene chloride solution was then washed 3 times with aqueous brine and dried over anhydrous magnesium sulphate. The solvent was concentrated by rotary evaporation and the crude material was purified by silica gel chromatography using ethyl acetate/hexanes (2-10%). The known compounds, with the isolated yields indicated, were characterized by the individual data shown below.

**General Procedure for the Heck Reaction beginning with the aniline compounds:**

To a flame dried flask was added dry THF at 0 °C (2 mL) followed by addition of the aniline compound (0.2 mmol). BF$_3$·OEt$_2$ (22.7 mg, 0.2 mmol) diluted with THF (2 mL) was then added. The mixture was stirred for 15 min, and to the solution was
added *tert*-butyl nitrite (23 mg, 0.22 mmol) diluted in THF (2 mL) and the stirring was continued for an additional 30 min. To the mixture were added the olefin compound (0.2 mmol), Pd(OAc)$_2$ (0.9 mg, 0.004 mmol), and N,N-bis(2,6-diisopropyl)dihydroimidazolium chloride (1.2 mg, 0.004 mmol) diluted in THF (3 mL). Stirring was continued and the reaction was worked up at the indicated time. The product was isolated and characterized as before.

**trans-Stilbene:** Yield: 76%; $^1$H NMR (CDCl$_3$) $\delta$ 7.11-7.38 (m, 10H), 6.91 (d, 2H); MS (EI) $m/z$ 180, 77.

**trans-2-methylstilbene:** Yield: 75%; $R_f$: 0.87 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.91-7.42 (m, 11H), 2.31 (s, 3H); MS (EI) $m/z$ 194, 91, 77.

**trans-3-methylstilbene:** Yield: 80%; $R_f$: 0.85 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.86-7.38 (m, 11H), 2.47 (s, 3H); MS (EI) $m/z$ 194, 91, 77.

**trans-4-methylstilbene:** Yield: 86%; $R_f$: 0.87 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.93-7.28 (m, 11H), 2.40 (s, 3H); MS (EI) $m/z$ 194, 91, 77.

**trans-2-methoxylstilbene:** Yield: 81%; $R_f$: 0.72 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.71-7.28 (m, 11H), 3.87 (s, 3H); MS (EI) $m/z$ 210, 107, 104, 77.
**trans-4-methoxylstilbene**: Yield: 88%; *Rf*: 0.76 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) δ 6.68-7.31 (m, 11H), 3.90 (s, 3H); MS (EI) m/z 210, 107, 104, 77.

**trans-4-Bromostilbene**: Yield: 91%; *Rf*: 0.68 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) δ 6.83- 7.32 (m, 11H); MS (EI) m/z 258, 260, 156, 77.

**trans-1-Phenylvinylnaphthlene**: Yield: 87 %; *Rf*: 0.56 (10% acetate: hexanes); $^1$H NMR (CDCl$_3$) δ 6.99-7.64 (m, 14H); $^{13}$C NMR (CDCl$_3$) δ 138.1 (d), 134.5 (s), 133.5 (s), 132.2 (s), 130.1 (s), 128.7 (d), 128.1 (d), 127.5 (s), 127.0 (d), 126.7 (s), 126.1 (s), 125.7 (s), 124.8 (s), 124.2 (s); MS (EI) m/z 230,127, 103, 77.

**trans-2-Phenylvinylnaphthlene**: Yield: 80%; *Rf*: 0.55 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) δ 6.89-7.74 (m, 14H); $^{13}$C NMR (CDCl$_3$) δ 138.6 (d), 134.7 (s), 133.8 (s), 132.1 (s), 130.1 (s), 129.4 (d), 128.6 (d), 127.5 (s), 127.1 (d), 126.6 (s), 126.1 (s), 125.7 (s), 124.4 (s), 124.0 (s); MS (EI) m/z 230, 127, 103, 77.

**trans-1,3-Bis-stilbene**: Yield: 57%; *Rf*: 0.51 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) δ 6.87- 7.69 (m, 18H); $^{13}$C NMR (CDCl$_3$) δ 138.5 (d), 134.3 (s), 133.1 (s), 132.7 (s), 130.3 (s), 128.9 (d), 128.4 (d), 127.7 (d), 127.0 (d), 126.7 (s), 126.1 (d), 125.7 (s), 125.1 (d), 124.6 (d); MS (EI) m/z 282, 127, 103, 77.

**trans-Cinnamic Acid Methyl Ester**: Yield: 68%; *Rf*: 0.50 (10 % ethyl acetate: 
hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 7.67-7.72 (d, 1H, $J$ = 10.0 Hz), 7.24-7.26 (m, 5H), 6.42-6.47 (d, 1H, $J$ = 10.0 Hz), 3.81 (s, 3H); MS (EI) $m/z$ 162, 103, 77.

**trans-2-Methyl-Cinnamic Acid Methyl Ester:** Yield: 66%; $R_f$: 0.51 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 7.96-8.01 (d, 1H, $J$ = 10.0 Hz), 7.21-7.26 (m, 4H), 6.33-6.38 (d, 1H, $J$ = 10.0 Hz), 3.82 (s, 3H) 2.44 (s, 3H); MS (EI) $m/z$ 176, 117, 91.

**trans-3-Methyl-Cinnamic Acid Methyl Ester:** Yield: 64%; $R_f$: 0.50 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 7.86-7.91 (d, 1H, $J$ = 10.0 Hz), 7.22-7.37 (m, 4H), 6.40-6.45 (d, 1H, $J$ = 10.0 Hz), 3.80 (s, 3H), 2.37 (s, 3H); MS (EI) $m/z$ 176, 117, 91.

**trans-4-Methyl-Cinnamic Acid Methyl Ester:** Yield: 65%; $R_f$: 0.49 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 7.87-7.92 (d, 1H, $J$ = 10.0 Hz), 7.22-7.37 (m, 4H), 6.40-6.45 (d, 1H, $J$ = 10.0 Hz), 3.80 (s, 3H), 2.37 (s, 3H); MS (EI) $m/z$ 176, 117, 91.

**trans-2-Methoxyl-Cinnamic Acid Methyl Ester:** Yield: 70%; $R_f$: 0.34 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 7.92-7.97 (d, 1H, $J$ = 10.0 Hz), 7.24-7.37 (m, 4H), 6.22-6.27 (d, 1H, $J$ = 10.0 Hz), 3.80 (s, 3H), 3.77 (s, 3H); MS (EI) $m/z$ 192, 133, 107.
**trans-4-Methoxyl-Cinnamic Acid Methyl Ester:** Yield: 71%; $Rf$: 0.35 (10 % ethyl acetate: hexanes); $^1H$ NMR (CDCl$_3$) $\delta$ 7.94-7.99 (d, 1H, $J = 10.0$ Hz), 7.21-7.37 (abba, 4H), 6.31-6.38 (d, 1H, $J = 10.0$ Hz), 3.85 (s, 3H), 3.75 (s, 3H); MS (EI) $m/z$ 192, 133, 107, 84.

**trans-4-Bromo-Cinnamic Acid Methyl Ester:** Yield: 81%; $Rf$: 0.42 (10 % ethyl acetate: hexanes); $^1H$ NMR (CDCl$_3$) $\delta$ 7.82-7.87 (d, 1H, $J = 10.0$ Hz), 7.24-7.37 (abba, 4H), 6.76-6.81 (d, 1H, $J = 10.0$ Hz), 3.80 (s, 3H); MS (EI) $m/z$ 242, 240, 181, 183, 102, 84.

**trans-3-(1-Naphthyl)-Propenoic Acid Methyl Ester:** Yield: 77%; $Rf$: 0.68 (10 % ethyl acetate: hexanes); $^1H$ NMR (CDCl$_3$) $\delta$ 7.66-7.71 (d, 1H, $J = 10.0$ Hz), 7.28-7.33 (m, 7H), 6.52-6.57 (d, 1H, $J = 10.0$ Hz), 3.81 (s, 3H); MS (EI) $m/z$ 212, 152, 84.

**trans-3-(2-Naphthyl)-Propenoic Acid Methyl Ester:** Yield: 71%; $Rf$: 0.68 (10 % ethyl acetate: hexanes); $^1H$ NMR (CDCl$_3$) $\delta$ 7.66-7.71 (d, 1H, $J = 10.0$ Hz), 7.28-7.33 (m, 7H), 6.52-6.57 (d, 1H, $J = 10.0$ Hz), 3.79 (s, 3H); MS (EI) $m/z$ 212, 152, 84.

**trans-1,3-Bis-cinnamic Acid Methyl Ester:** Yield: 54%; $Rf$: 0.51 (10 % ethyl acetate: hexanes); $^1H$ NMR (CDCl$_3$) $\delta$ 7.71-7.80 (m, 2H), 7.28-7.31 (m, 3H), 6.47-6.53(m, 2H), 3.81 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 157.8 (s), 157.1 (s), 133.1 (s), 130.3 (s), 128.4
(s), 127.7 (d), 127.0 (s), 125.3 (s), 123.7 (s), 117.7 (s), 114.6 (s), 57.3 (s), 56.7 (s); MS (EI) m/z 282, 127, 103; MS (EI) m/z 246, 161, 103, 77.

**trans-4-methoxystilbene**: Yield: 78%; Rf: 0.76 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.68-7.31 (m, 11H), 3.90 (s, 3H); MS (EI) m/z 210, 107, 104, 77.

**trans-4-methoxyl-2’-Methylstilbene**: Yield: 67%; Rf: 0.66 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.72-7.34 (m, 10H), 3.82 (s, 3H), 2.43 (s, 3H); MS (EI) m/z 224, 133, 91.

**trans-4-methoxyl-3’-Methylstilbene**: Yield: 77%; Rf: 0.66 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.77-7.34 (m, 10H), 3.81 (s, 3H), 2.42(s, 3H); MS (EI) m/z 224, 133, 91.

**trans-4-methoxyl-4’-Methylstilbene**: Yield: 81%; Rf: 0.64 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.76-7.34 (m, 10H); 3.82 (s, 3H), 2.40 (s, 3H); MS (EI) m/z 224, 133, 91.

**trans-4,2’-Dimethoxystilbene**: Yield: 76%; Rf: 0.54 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.76-7.34 (m, 10H), 3.82 (s, 3H), 3.71(s, 3H); MS (EI) m/z 240, 133, 123.
**trans-4,4’-Dimethoxylstilbene**: Yield: 81%; *Rf*: 0.50 (10 % ethyl acetate: hexanes);

$^1$H NMR $\delta$ (CDCl$_3$) 6.82-7.45 (m, 9H), 6.66-6.72 (d, 1H, $J = 12.0$ Hz), 3.82 (s, 6H);
MS (EI) $m/z$ 240, 133, 123.

**trans-4-methoxyl-4’-Bromostilbene**: Yield: 87%; *Rf*: 0.44 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.77-7.41 (m, 9H), 6.61-6.66(d, 1H, $J = 10.0$ Hz), 3.81 (s, 3H); MS (EI) $m/z$ 290, 288, 158, 156, 133.

**trans-1-(4’-methoxystyryl)naphthalene**: Yield: 75%; *Rf*: 0.40 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.97-7.82 (m, 12H), 6.71-6.75(d, 1H, $J = 8.0$ Hz), 3.83 (s, 3H); MS (EI) $m/z$ 260, 133, 127.

**trans-2-(4’-methoxystyryl)naphthalene**: Yield: 78%; *Rf*: 0.40 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 7.01-7.84 (m, 12H), 6.68-6.72(d, 1H, $J = 8.0$ Hz), 3.83 (s, 3H); MS (EI) $m/z$ 260, 133, 127.

**trans-1,3-Bis(4’-methoxyl)stilbene**: Yield: 32%; *Rf*: 0.35 (10 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$) $\delta$ 6.67-7.83 (m, 16H), 3.83 (s, 6H); $^{13}$C NMR (CDCl$_3$) $\delta$ 138.7 (s), 137.3 (d), 135.7 (s), 132.6 (d), 131.3 (s), 129.3 (d), 128.6 (d), 127.8 (d), 127.5 (d), 126.5 (s), 126.0 (d), 125.8 (s), 125.3 (s), 117.9 (s), 108.6 (s), 59.3 (s), 58.9 (s); MS (EI) $m/z$ 282, 127, 103; MS (EI) $m/z$ 246, 161, 103, 77.
trans-Cinnamonic acid: Yield, 47%; Rf: 0.37 (10 % ethyl acetate: hexanes); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.38-7.41 (d, 1H, \(J = 6.0\) Hz), 6.94-7.28 (m, 5H), 5.78-5.75 (d, 1H, \(J = 6.0\) Hz); MS (EI) \(m/z\) 129, 103, 51.

trans-2-Methylcinnamonic acid: Yield; 42%, Rf: 0.35 (10 % ethyl acetate: hexanes);
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.68-7.73 (d, 1H, \(J = 10.0\) Hz), 7.21-7.47 (m, 4H), 5.78-5.83 (d, 1H, \(J = 10.0\) Hz), 2.41 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 175.1 (s), 146.5 (s), 131.4 (s), 126.8 (s), 125.7 (s), 125.1 (s), 124.2 (s), 117.1 (s), 98.6 (s), 14.8 (s); MS (EI) \(m/z\) 143, 117, 91, 51.

trans-3-Methylcinnamonic acid: Yield; 41%, Rf: 0.37 (10 % ethyl acetate: hexanes);
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.67-7.72 (d, 1H, \(J = 10.0\) Hz); 7.25-7.49 (m, 4H), 5.81-5.86 (d, 1H, \(J = 10.0\) Hz), 2.31 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 174.2 (s), 147.1 (s), 130.4 (s), 127.5 (s), 125.6 (s), 125.2 (s), 124.9 (s), 115.1 (s), 100.7 (s), 17.8 (s); MS (EI) \(m/z\) 143, 117, 91, 51.

trans-4-Methylcinnamonic acid: Yield, 48%; Rf: 0.37 (10 % ethyl acetate: hexanes);
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.71-7.76 (d, 1H, \(J = 10.0\) Hz), 7.31-7.54 (m, 4H), 5.79-5.84 (d, 1H, \(J = 10.0\) Hz), 2.29 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 172.7 (s), 146.8 (s), 137.4 (s), 127.6 (s), 127.1, 125.7 (s), 125.3 (s), 117.1 (s), 96.7 (s), 19.8 (s); MS (EI) \(m/z\) 143, 117, 91, 51.
trans-2-Methoxycinnamonicitrile: Yield, 51%; \( Rf \): 0.31 (10 % ethyl acetate: hexanes); 
\(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.38-7.41 (d, 1H, \( J = 6.0 \) Hz), 6.94-7.76 (m, 4H), 6.86-6.89 (d, 1H, \( J = 6.0 \) Hz), 3.86 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 150.4 (s), 131.5 (s), 130.4 (s), 129.6 (s), 127.1 (s), 126.5 (s), 114.1 (s), 91.1 (s), 55.4 (s); MS (EI) \( m/z \) 159, 107, 77, 51.

trans-4-Methoxycinnamonicitrile: Yield, 58%; \( Rf \): 0.30 (10 % ethyl acetate: hexanes); 
\(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.39-7.42 (d, 1H, \( J = 6.0 \) Hz), 6.89-7.58 (abba, 4H), 6.88-6.91 (d, 1H, \( J = 6.0 \) Hz), 3.87 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 151.2 (s), 131.7 (s), 130.1 (s), 129.5 (s), 125.8 (s), 125.6 (s), 117.1 (s), 93.4 (s), 55.6 (s); MS (EI) \( m/z \) 159, 107, 77, 51.

trans-4-Bromocinnamonicitrile: Yield, 61%; \( Rf \): 0.35(10 % ethyl acetate: hexanes); 
\(^1\)H NMR (CDCl\(_3\)) \( \delta \) 8.19-8.21 (d, 1H, \( J = 4.0 \) Hz), 7.21-7.75 (abba, 4H), 5.67-5.69 (d, 1H, \( J = 4.0 \) Hz); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 130.8 (s), 129.2 (s), 128.5 (s), 128.1 (s), 127.9 (s), 127.7 (s), 127.4 (s), 115.8 (s), 104.5 (s); MS (EI) \( m/z \) 209, 207, 128, 101,51.

trans-1-Acrylonitrilenaphtalene: Yield: 37%; \( Rf \): 0.30 (10 % ethyl acetate: hexanes); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.28-7.69 (m, 8H), 5.57-5.60(d, 1H, \( J = 6.0 \) Hz); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 149.7 (s), 134.6 (s), 133.1 (s), 132.5 (s), 130.7 (s), 129.3 (s), 128.0 (s), 127.2 (s), 126.1 (s), 125.7 (s), 125.1 (s), 113.8 (s), 107.2 (s); MS (EI) \( m/z \) 179, 153,127, 51.
**trans-2-Acrylonitrlnaphthalene:** Yield: 39%; \( R_f \): 0.30 (10 \% ethyl acetate: hexanes); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.31-7.67 (m, 8H), 5.62-5.65(d, 1H, \( J = 6.0 \) Hz); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 151.2 (s), 134.8 (s), 133.6 (s), 133.1 (s), 129.7 (s), 128.6 (s), 128.3 (s), 127.2 (s), 126.8 (s), 125.6 (s), 124.1 (s), 116.5 (s), 104.2 (s); MS (EI) \( m/z \) 179, 153,127, 51.

### 3.3 Experimental Details and Data for the Preparation of New PTC Catalysts

**4-Fluoro-3-(4-fluorophenyl)isobenzofuran-1(3H)-one (56).**

![4-Fluoro-3-(4-fluorophenyl)isobenzofuran-1(3H)-one (56) molecular structure](image)

Dried oxazoline 55 (3.10 g, 16.0 mmol) was dissolved in dry THF (30 mL) and cooled to –40 °C. \( n \)-BuLi (12.5 mL, 1.6 M, hexane, 20.0 mmol) was added slowly and stirred for 2 h at –40 °C. 4-Fluorobenzaldehyde (2.08 g, 16.8 mmol) was added. The mixture was warmed to room temperature and stirred at 50 °C for 18 h. The mixture was quenched with saturated \( \text{NH}_4\text{Cl} \) solution and extracted with \( \text{CH}_2\text{Cl}_2 \). The combined organic extracts were dried over anhydrous \( \text{Na}_2\text{SO}_4 \), and concentrated *in vacuo* to afford a dark brown solid that was hydrolyzed by refluxing with HCl solution (4 N, 90 mL) for 6 h. The mixture was cooled and extracted with \( \text{CH}_2\text{Cl}_2 \).
The combined organic extracts were washed with 10% NaHCO₃ solution (to remove 3-fluorobenzoic acid), dried (Na₂SO₄), and concentrated to give a brown solid, which was chromatographed on a silica gel to afford 56 as a white needle (3.36 g, 85%). ¹H NMR (CDCl₃, 500 MHz) δ 7.79 (d, J = 7 Hz, 1H), 7.61-7.57 (m, 1H), 7.36-7.27 (m, 3H), 7.09-7.05 (m, 2H), 6.50 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 169.1, 163.4 (d, J(F, C) = 248 Hz), 157.2 (d, J(F, C) = 252 Hz), 135.4 (d, J(F, C) = 17 Hz), 132.3 (d, J(F, C) = 6 Hz), 130.9, 129.2 (d, J(F, C) = 9 Hz), 128.9, 121.9 (d, J(F, C) = 7 Hz), 121.5 (d, J(F, C) = 19.7 Hz), 116.2 (d, J(F, C) = 22 Hz), 79.9; HRMS (EI⁺) found 246.0490 (100), calcd 246.0492 for [C₁₄H₈F₂O₂]⁺.

1-(2-(4-fluorobenzyl)-3-fluorophenyl)ethanone (58).

To a solution of 57 (1.30 g, 5.2 mmol) in dry ether (85 mL) was added 8.2 mL of a 1.6 M solution of MeLi in ether (13.1 mmol), and the solution was stirred at room temperature for 2 h. The mixture was quenched with saturated NH₄Cl solution and extracted with CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo to afford a light brown liquid, which was chromatographed on a column of silica gel to afford 0.90 g 58 (79%). ¹H NMR (CDCl₃, 500 MHz) δ 7.46 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.32 (dt, J = 5.5, 7.5 Hz, 1H), 7.22 (t, J = 8.5 Hz, 1H), 7.15 (dd, J = 5.5, 8.5 Hz, 2H), 6.92 (t, J = 9.0 Hz, 2H), 4.26 (s, 2H), 2.47 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 201.5, 161.7 (d, J(F, C) = 245.4 Hz), 161.4 (d,
\[ J(F, C) = 242.1 \text{ Hz}, \quad 140.4, \quad 135.9, \quad 130.3 \quad (d, \quad J(F, C) = 6.9 \text{ Hz}), \quad 128.0 \quad (d, \quad J(F, C) = 9.1 \text{ Hz}), \quad 127.7 \quad (d, \quad J(F, C) = 16.0 \text{ Hz}), \quad 124.8 \quad (d, \quad J(F, C) = 2.6 \text{ Hz}), \quad 118.8 \quad (d, \quad J(F, C) = 23.8 \text{ Hz}), \quad 115.2 \quad (d, \quad J(F, C) = 20.7 \text{ Hz}), \quad 30.2, \quad 29.9 \quad (d, \quad J(F, C) = 4.3 \text{ Hz}); \] HRMS (EI⁺) found 246.0849 (100), calcd 246.0856 for \([C_{15}H_{12}F_2O]^+\).

1,6-difluoro-10-methylantracene (59).

Methyl ketone 58 (0.66 g, 2.7 mmol) and \(P_2O_5\) (2.67 g, 18.8 mmol) in dry \(o\)-dichlorobenzene were refluxed overnight. The black mixture formed was cooled to room temperature, quenched with water, neutralized by a solution of NaOH, and extracted with CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and concentrated \textit{in vacuo} to afford a dark brown liquid, which was chromatographed on a column of silica gel to afford 59 as a white solid (0.42 g, 69%). \(^1\)H NMR (CDCl₃, 300 MHz) \(\delta\) 8.27 (s, 1H), 7.56-7.68 (m, 2H), 7.53 (dd, \(J = 2.4, 12 \text{ Hz, 1H}\)), 7.25-7.18 (m, 1H), 7.15-7.08 (m, 1H), 6.94 (dd, \(J = 7.2, 10.8 \text{ Hz, 1H}\)), 2.67 (s, 3H); \(^{13}\)C NMR (CDCl₃, 75 MHz) \(\delta\) 160.6 (d, \(J(F, C) = 246 \text{ Hz}\)), 159.3 (d, \(J(F, C) = 252 \text{ Hz}\)), 132.2 (d, \(J(F, C) = 9 \text{ Hz}\)), 128.5, 124.9 (d, \(J(F, C) = 8.6 \text{ Hz}\)), 124.5 (d, \(J(F, C) = 30 \text{ Hz}\)), 120.3 (d, \(J(F, C) = 4.5 \text{ Hz}\)), 118.5 (d, \(J(F, C) = 6 \text{ Hz}\)), 117.0 (d, \(J(F, C) = 27.5 \text{ Hz}\)), 107.0 (d, \(J(F, C) = 20 \text{ Hz}\)), 106.9 (d, \(J(F, C) = 21.5 \text{ Hz}\)), 14.3; HRMS (EI⁺) found 228.0741 (100), calcd 228.0751 for \([C_{15}H_{10}F_2]^+\).
4-Fluoro-3-(2-fluorophenyl)isobenzofuran-1(3H)-one (61)

Dried oxazoline 55 (1.24 g, 6.4 mmol) was dissolved in dry THF (15 mL) and cooled to –40 °C. n-BuLi (5.0 mL, 1.6 M, hexane, 8.0 mmol) was added slowly and stirred for 2 h at –40 °C. 2-Fluorobenzaldehyde (0.84 g, 6.7 mmol) was added. The mixture was warmed to room temperature and stirred at 50 °C for 18 h. The mixture was quenched with saturated NH₄Cl solution and extracted with CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo to afford a dark brown solid that was hydrolyzed by refluxing with HCl solution (4 N, 35 mL) for 6 h. The mixture was cooled and extracted with CH₂Cl₂. The combined organic extracts were washed with 10% NaHCO₃ solution (to remove 3-fluorobenzoic acid), dried (Na₂SO₄), and concentrated to give a brown solid, which was chromatographed on a column of silica gel to afford 61 as a white needle (1.37 g, 84%). Rf: 0.51 (30 % ethyl acetate: hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 7.80 (d, J = 7.5 Hz, 1H), 7.59 (dt, J = 4.5, 8.4 Hz, 1H), 7.42 – 7.31 (m, 2H), 7.16 – 7.05 (m, 3H), 6.77 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.1, 161.1 (d, J = 249.4 Hz), 157.0 (d, J = 253.4 Hz), 134.7 (d, J = 17.0 Hz), 132.2 (d, J = 6.0 Hz), 131.7 (d, J = 8.6 Hz), 129.2 (d, J = 3.0 Hz), 128.6 (d, J = 3.0 Hz), 124.7 (d, J = 3.5 Hz), 122.2 (d, J = 12.5 Hz), 121.8 (d, J = 4.0 Hz), 121.3 (d, J = 19.0 Hz), 116.3 (d, J = 21.1 Hz), 74.9 (dd, J = 2.0, 4.5 Hz); HRMS (EI⁺) found 246.0477 (100), calcd 246.0492 for [C₁₄H₈F₂O₂]⁺.
1-(2-(2-Fluorobenzyl)-3-fluorophenyl)ethanone (63)

To a solution of 61 (2.50 g, 10.2 mmol) in EtOAc (50 mL) was added 10% palladium/charcoal catalyst (0.250 g). The mixture was stirred in a high-pressure bomb at 600 psi for 24 hr. The catalyst was removed by filtration, and the resulting solution was evaporated to dryness, to afford carboxylic acid 62 (2.50 g, 100%) as a white solid. To the solution of the acid (1.80 g, 6.76 mmol) in anhydrous Et$_2$O (120mL) was added MeLi (10.7mL, 1.0 M in hexane, 16.9 mmol), and the mixture was stirred at 0 °C for 1.5 hr. The reaction mixture was then quenched with saturated NH$_4$Cl (30 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 30mL). The combined organic extracts were washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, concentrated and purified via flash column chromatograph (10% EtOAc/hexanes), to provide methyl ketone 63 as a colorless oil (1.59 g, 79%). $R_f$: 0.50 (20 % ethyl acetate: hexanes); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.42 (d, $J$ = 8.0 Hz, 1H), 7.30 (dt, $J$ = 5.5, 8.5 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.00 – 6.94 (m, 3H), 4.29 (s, 2H), 2.47 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 201.5, 162.0 (d, $J$ = 245.9 Hz), 161.1 (d, $J$ = 243.8 Hz), 141.2, 130.3 (d, $J$ = 3.6 Hz), 128.0 (d, $J$ = 9.1 Hz), 127.9 (d, $J$ = 7.9 Hz), 127.1 (d, $J$ = 15.4 Hz), 126.1 (d, $J$ = 15.9 Hz), 124.4 (d, $J$ = 3.1 Hz), 124.0 (d, $J$ = 3.3 Hz), 118.5 (d, $J$ = 23.4 Hz), 115.2 (d, $J$ = 21.9 Hz), 29.9, 24.2; HRMS (EI$^+$) found 246.0854 (100), calcd 246.0856 for [C$_{15}$H$_{12}$F$_2$O]$^+$. 
1,8-Difluoro-10-methylantracene (64)

![Image of 1,8-Difluoro-10-methylantracene](image)

To a round flask containing 1-(2-(2-Fluorobenzyl)-3-fluorophenyl)ethanone 63 (1.00 g, 4.06 mmol) and P₂O₅ (4.04 g, 28.5 mmol) was added dry o-dichlorobenzene (25 mL). The solution was refluxed overnight. The black mixture formed was cooled to temperature, quenched with water, neutralized using 50% NaOH aqueous solution. NaOH Solution was kept being added until all black solid was dissolved and no heat was given out. The solution was extracted with Et₂O (7 x 60 mL). The combined organic layers were washed with H₂O followed by brine solution, then dried over Na₂SO₄, filtered, concentrated and purified through flash column chromatography (hexanes) to provide anthracene 64 as a white solid (0.760 g, 76%). Rf: 0.67 (5 % ethyl acetate: hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 8.65 (s, 1H), 7.79 (d, J = 9.5 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.03 – 6.99 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.4 (d, J = 252.6 Hz), 131.6, 130.6, 125.1 (d, J = 8.4 Hz), 122.5 (d, J = 17.4 Hz), 120.7 (d, J = 4.6 Hz), 111.3 (t, J = 6.0 Hz), 107.6 (d, J = 19.0 Hz), 14.6; HRMS (EI⁺) found 228.0749 (100), calcd 228.0751 for [C₁₅H₁₀F₂]⁺.

10-(Bromomethyl)-1,8-difluoroanthracene (65)

![Image of 10-(Bromomethyl)-1,8-difluoroanthracene](image)
A solution of AIBN (10.7 mg, 0.065 mmol), NBS (0.66 g, 3.7 mmol), and 64 (0.74 g, 3.2 mmol) in dry benzene (150 mL) was refluxed for 40 minutes. The mixture was concentrated in vacuo, and then dissolved in CCl₄ (80 mL). The white byproduct formed was removed by filtration, and the resulting solution was concentrated in vacuo to form a yellow solid, which was recrystallized from CCl₄ to afford the product as a yellow needle (0.85 g, 85%). Rf: 0.52 (5 % ethyl acetate: hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 9.02 (s, 1H), 8.04 (d, J = 9.0 Hz, 2H), 7.61 – 7.56 (m, 2H), 7.25 – 7.14 (m, 2H), 5.43 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 159.5 (d, J = 254.3 Hz), 131.3, 128.7, 127.1 (d, J = 8.5 Hz), 123.1 (d, J = 19.6 Hz), 119.7 (d, J = 5.0 Hz), 115.5 (t, J = 6.1 Hz), 108.5 (d, J = 20.0 Hz), 26.7; HRMS (EI⁺) found 305.9850 (100), calcd 305.9856 for [C₁₅H₉BrF₂]⁺.

2-(3,5-difluorophenyl)-4,4-dimethyl-4,5-dihydrooxazole (66).

2-Amino-2-methyl-1-propanol (5.05 g, 56.6 mmol) was dissolved in 14 mL CH₂Cl₂. The solution was added dropwise to a stirred solution of 3,5-difluorobenzoyl chloride (9.07 g, 51.4 mmol) in CH₂Cl₂ (11 mL) at 0 °C. Stirring was continued for 3.5 h. The white precipitate was filtered and washed with ethyl ether. The filtrate was concentrated under reduced pressure and the combined solid was dried in vacuo. Without purification, to the solid was added SOCl₂ (10.10 g, 84.9 mmol) and the mixture was stirred at room temperature for 2.5 h. Ether was added slowly to the
solution, and the white precipitate formed was collected by filtration, washed with cold ether, neutralized with NaOH solution (20%), and extracted with CH₂Cl₂. The combined organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford a light yellow solid (4.83 g, 81%). ¹H NMR (CDCl₃, 500 MHz) δ 7.47 – 7.45 (m, 2H), 6.93 – 6.89 (m, 1H), 4.12 (s, 2H), 1.30 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 162.9 (dd, J(F, C) = 12.2, 247.4 Hz), 160.3, 131.3 (d, J(F, C) = 10.1 Hz), 111.4 (dd, J(F, C) = 6.1, 21.0 Hz), 106.6 (t, J(F, C) = 25.2 Hz), 79.6, 68.1, 28.4.

4,6-difluoro-3-(4-fluorophenyl)isobenzofuran-1(3H)-one (67).

![Chemical structure of 4,6-difluoro-3-(4-fluorophenyl)isobenzofuran-1(3H)-one (67).]

84% yield. ¹H NMR (CDCl₃, 500 MHz) δ 7.48 (d, J = 7 Hz, 1H), 7.27 (dd, J = 5, 8 Hz, 2H), 7.15-7.07 (m, 3H), 6.48 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 167.9, 164.3 (dd, J(F, C) = 9, 253 Hz), 163.6 (d, J(F, C) = 248 Hz), 157.2 (dd, J(F, C) = 12, 255 Hz), 131.4 (d, J(F, C) = 17 Hz), 130.6, 130.0 (dd, J(F, C) = 5, 10 Hz), 129.2 (d, J(F, C) = 10 Hz), 116.0 (d, J(F, C) = 23 Hz), 110.5 (dd, J(F, C) = 26, 28 Hz), 108.8 (dt, J(F, C) = 4, 23 Hz), 79.9; HRMS (EI⁺) found 264.0401 (100), calcd 264.0395 for [C₁₄H₁₇F₃O₂]⁺.

1-(2-(4-fluorobenzyl)-3,5-difluorophenyl)ethanone (69).
79% yield. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.18-7.09 (m, 3H), 6.97-6.88 (m, 3H), 4.17 (s, 2H), 2.41 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 200.2, 161.8 (dd, $J$(F, C) = 11, 248 Hz), 161.5 (d, $J$(F, C) = 243 Hz), 161.0 (dd, $J$(F, C) = 13, 248 Hz), 141.1 (t, $J$(F, C) = 5 Hz), 135.6, 130.2 (d, $J$(F, C) = 8 Hz), 123.6 (d, $J$(F, C) = 20 Hz), 115.2 (d, $J$(F, C) = 22 Hz), 111.8 (dd, $J$(F, C) = 4, 22 Hz), 106.8 (dd, $J$(F, C) = 28, 30 Hz), 29.9, 29.5 (d, $J$(F, C) = 4 Hz); HRMS (EI$^+$) found 264.0769 (100), calcd 264.0762 for [C$_{15}$H$_{11}$F$_3$O]$^+$.

1,3,6-trifluoro-10-methylanthracene (70).

86% yield. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.26 (s, 1H), 7.80 (dd, $J$ = 6, 9.3 Hz, 1H), 7.56 (dd, $J$ = 2.7, 11.7 Hz, 1H), 7.37 (dt, $J$ = 1, 11.7 Hz, 1H), 7.18 (dt, $J$ = 2.7, 8.1 Hz, 1H), 6.84(dt, $J$ = 2.1, 8.4 Hz, 1H), 2.68 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 161.1 (d, $J$(F, C) = 247 Hz), 160.0 (dd, $J$(F, C) = 14, 255 Hz), 159.5 (dd, $J$(F, C) = 13, 245 Hz), 132.4 (d, $J$(F, C) = 9 Hz), 131.7 (d, $J$(F, C) = 9 Hz), 130.6 (dd, $J$(F, C) = 5, 9.5 Hz), 128.8 (dt, $J$(F, C) = 3.5, 8 Hz), 128.0, 119.0 (t, $J$(F, C) = 3 Hz), 117.0 (d, $J$(F, C) = 28 Hz), 106.8 (d, $J$(F, C) = 22 Hz), 103.0 (dd, $J$(F, C) = 5, 22 Hz), 100.6 (d, $J$(F, C) = 24 Hz, 100.2 (d, $J$(F, C) = 23 Hz), 14.4; HRMS (EI$^+$) found 246.0646 (100), calcd 246.0656 for [C$_{15}$H$_9$F$_3$]$^+$. 
10-(bromomethyl)-1,3,6-trifluoroanthracene (71).

70% yield. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.67(s, 1H), 8.04 (dd, $J = 6.5$, 9 Hz, 1H), 7.78 (d, $J = 11$ Hz, 1H), 7.61 (d, $J = 11$ Hz, 1H), 7.32 (dt, $J = 2.5$, 7.5 Hz, 1H), 7.00 (dt, $J = 2$, 8.5 Hz, 1H), 5.25 (s, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 161.9 (d, $J(F, C) = 250$ Hz), 160.5 (dd, $J(F, C) = 21$, 249 Hz), 160.2 (dd, $J(F, C) = 21$, 247 Hz), 133.0 (d, $J(F, C) = 10$ Hz), 131.9 (d, $J(F, C) = 9$ Hz), 130.7 (dd, $J(F, C) = 2$, 9 Hz), 128.3, 127.2, 123.0, 120.0 (d, $J(F, C) = 17$ Hz), 117.9 (d, $J(F, C) = 27$ Hz), 106.4 (d, $J(F, C) = 23$ Hz), 102.6 (dd, $J(F, C) = 5$, 23 Hz), 101.3 (dd, $J(F, C) = 24$, 31 Hz), 26.7; HRMS (EI$^+$) found 323.9758 (100), calcd 323.9761 for [C$_{15}$H$_9$F$_3$]$^+$. 

1-(2-(2-fluorobenzyl)-3,5-difluorophenyl)ethanone (72).

72% yield. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.15-7.11 (m, 2H), 6.99-6.90 (m, 4H), 4.21 (s, 2H), 2.42 (s, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 200.1, 162.1 (dd, $J(F, C) = 11$, 248.9 Hz), 161.0 (d, $J(F, C) = 243.8$ Hz), 161.1 (dd, $J(F, C) = 12.5$, 248.3 Hz), 130.3 (dd, $J(F, C) = 1.5$, 4.5 Hz), 128.0 (d, $J(F, C) = 8$ Hz), 126.8 (d, $J(F, C) = 15$ Hz), 124.0 (d, $J(F, C) = 4$ Hz), 122.0 (dd, $J(F, C) = 4.1$ 16.6 Hz), 115.2 (d, $J(F, C) = 22.1$ Hz),
111.4 (dd, \(J(F, C) = 4, 22.1\) Hz), 106.6 (d, \(J(F, C) = 27.1\) Hz), 106.4 (d, \(J(F, C) = 27.6\) Hz), 29.6, 23.8 (d, \(J(F, C) = 4.5\) Hz); HRMS (EI\(^+\)) found 264.0757 (100), calcd 264.0762 for \([C_{15}H_{11}F_3O]^{+}\).

**1,3,8-trifluoro-10-methylanthracene (73).**

![1,3,8-trifluoro-10-methylanthracene (73).](image)

69% yield. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta 8.55\) (s, 1H), 7.78 (d, \(J = 8.5\) Hz, 1H), 7.40 (d, \(J = 11.5\) Hz, 1H), 7.33 (dd, \(J = 1.5, 7.5\) Hz, 1H), 7.04-7.00 (m, 1H), 6.88 (t, \(J = 8\) Hz, 1H), 2.77 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 160.1\) (dd, \(J(F, C) = 12.9, 255.6\) Hz), 159.4 (d, \(J(F, C) = 254.1\) Hz), 159.3 (dd, \(J(F, C) = 10.6, 243.5\) Hz), 132.2, 130.6, 129.8, 125.8 (d, \(J(F, C) = 8.4\) Hz), 121.9 (d, \(J(F, C) = 17.5\) Hz), 120.4 (d, \(J(F, C) = 3.8\) Hz), 119.9 (d, \(J(F, C) = 16.6\) Hz), 111.9, 107.6 (d, \(J(F, C) = 19\) Hz), 103.3 (dd, \(J(F, C) = 4.2, 22\) Hz), 101.0 (dd, \(J(F, C) = 24.1, 31.9\) Hz), 14.7; HRMS (EI\(^+\)) found 246.0650 (100), calcd 246.0656 for \([C_{15}H_{9}F_3]^+\).

**10-(bromomethyl)-1,3,8-trifluoroanthracene (74).**

![10-(bromomethyl)-1,3,8-trifluoroanthracene (74).](image)

61% yield. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta 8.96\) (s, 1H), 7.99 (d, \(J = 9\) Hz, 1H), 7.66-7.56 (m, 2H), 7.17 (dd, \(J = 7.5, 10.2\) Hz, 1H), 7.04 (dt, \(J = 2.4, 10.5\) Hz, 1H),
5.31 (s, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 160.8 (dd, J(F, C) = 13, 249.4 Hz), 160.5 (dd, J(F, C) = 13, 257.4 Hz), 159.6 (d, J(F, C) = 254.9 Hz), 131.9 (d, J(F, C) = 4 Hz), 130.7 (dd, J(F, C) = 2, 9 Hz), 128.1, 127.8 (d, J(F, C) = 8.5 Hz), 122.5 (d, J(F, C) = 17.6 Hz), 120.5 (d, J(F, C) = 17 Hz), 119.4 (d, J(F, C) = 4.5 Hz), 116.05 (dt, J(F, C) = 2.5, 6 Hz), 108.5 (d, J(F, C) = 19.5 Hz), 102.8 (dd, J(F, C) = 5.0, 22.5 Hz), 101.9 (dd, J(F, C) = 23.6, 31.6 Hz), 26.5; HRMS (EI$^+$) found 323.9749 (99.2), calcd 323.9761 for [C$_{15}$H$_8$BrF$_3$]$^+$. 

**N-1',8'-Difluoroanthracenylmethylhydrocinchonidinium bromide (76)**

![Structure of N-1',8'-Difluoroanthracenylmethylhydrocinchonidinium bromide (76)](image)

A solution of 1,8-difluoro-10-methylanthracene 65 (0.566 g, 1.90 mmol) and (-)-hydrocinchonidine 75 (0.531 g, 1.73 mmol) in a mixture solvent of EtOH (1.30 mL), DMF (1.56 mL) and CHCl$_3$ (0.520 mL) was stirred at 100 °C for 4 hr. After cooling to room temperature, the solution was diluted with MeOH (0.43 mL), then the solution was added to Et$_2$O (70mL) dropwise with stirring. The solid precipitate was filtered and washed with ether (10 mL), to afford the product as a yellow solid (0.782 g, 75%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.85-8.80 (m, 3H), 8.60 (d, J = 6.5 Hz, 2H), 8.02 (d, J = 4.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.52 (dd, J = 6.5, 15.5 Hz, 1H), 7.19 (d, J = 5.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.02-6.93 (m, 4H), 6.80 (dd, J = 7.5, 10.2 Hz, 1H), 6.51 (q, J = 14.1 Hz, 2H), 4.95 (dt, J = 4.5, 10.5 Hz, 1H), 4.61 (q, J =
$^{1}H$ NMR (CDCl$_3$, 300 MHz) $\delta$ 9.40 (bs, 1H), 9.18 (bs, 1H), 9.03 (s, 1H), 8.96 (s, 1H), 8.14 (d, $J = 9.3$ Hz, 2H), 7.75-7.69 (m, 2H), 7.63-7.56 (m, 1H), 7.29-7.22 (m, 2H), 6.96-6.86 (m, 4H), 6.42-6.30 (m, 1H), 6.03 (d, $J = 13.8$ Hz, 1H), 5.71-5.40 (m, 3H), 5.02-4.98 (m, 1H), 4.62-4.44 (m, 3H),

$^{13}C$ NMR (CDCl$_3$, 125 MHz) $\delta$ 158.8, 158.3, 149.6, 147.2, 145.3, 134.7, 133.7, 129.5, 128.5, 127.8, 127.2, 124.5, 124.2, 122.5, 121.6, 120.2, 118.8, 117.3, 107.9, 67.5, 66.3, 66.0, 64.1, 54.8, 50.7, 37.5, 26.7, 26.4, 23.6, 23.4, 11.7; HRMS (EI$^+$) found 523.2561 (56.7), calcld 523.2556 for $[C_{34}H_{33}N_2F_2O]^+$. 

**O(9)-Allyl-N-1’,8’-Difluoroanthracenylmethylhydrocinchonidinium bromide (77)**

To a round bottom flask containing N-1’,8’-Difluoroanthracenylmethylhydrocinchonidinium bromide 76 (0.728 g, 1.20 mmol) in dichloromethane (2.5 mL) was added allyl bromide (0.310 mL, 3.61 mmol) and 50% aqueous KOH (0.337 mL). The reaction mixture was stirred at room temperature for 4 hr. The solution was diluted with water (6 mL) and extracted with methylene chloride (3 x 10 mL). The combined organic layer was dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude solid was recrystallized from CH$_2$Cl$_2$/hexanes to afford product 77 (0.536 g, 69%) as a yellow solid. $[\alpha]_D^{23}$ -295 (c 0.92, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 9.40 (bs 1H), 9.18 (bs, 1H), 9.03 (s, 1H), 8.96 (s, 1H), 8.14 (d, $J = 9.3$ Hz, 2H), 7.75-7.69 (m, 2H), 7.63-7.56 (m, 1H), 7.29-7.22 (m, 2H), 6.96-6.86 (m, 4H), 6.42-6.30 (m, 1H), 6.03 (d, $J = 13.8$ Hz, 1H), 5.71-5.40 (m, 3H), 5.02-4.98 (m, 1H), 4.62-4.44 (m, 3H),
2.76 (t, J = 10.2 Hz, 1H), 2.49 (t, J = 9.6 Hz, 1H), 2.18 (m, 1H), 2.08-1.95 (m, 1H), 1.86 (s, 1H), 1.56-1.25 (m, 5H), 0.66 (t, J = 6.9 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \delta 159.7, 158.68, 150.0, 148.9, 140.0, 135.3, 135.0, 133.4, 130.4, 128.6, 128.0, 127.9, 125.5, 123.7, 123.0, 122.8, 122.7, 122.5, 120.2, 119.5, 118.3, 118.1, 108.7, 108.1, 70.5, 66.5, 63.0, 55.5, 51.4, 37.3, 26.6, 26.4, 23.6, 23.5, 11.8; HRMS (EI\textsuperscript{+}) found 563.2878 (42.6), calcd 563.2874 for [C\textsubscript{37}H\textsubscript{37}N\textsubscript{2}F\textsubscript{2}O]\textsuperscript{+}.

3.4 Representative Procedure for the Enantioselective Catalytic Phase-Transfer Alkylations

3.4.1 Representative Procedure for the Enantioselective Catalytic Phase-Transfer Alkylation of 2-Benzhydryloxy-1-(2,5-dimethoxyphenyl)ethanone

To a flame dried round bottom flask was added 2-benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone (0.10 g, 0.276 mmol), O(9)-allyl-N-2’,3’,4’-trifluorobenzyl-hydrocinchonidinium bromide \textbf{28} (15.7 mg, 0.028 mmol), CH\textsubscript{2}Cl\textsubscript{2} (1.4 mL) and hexane (1.4 mL). The solution was cooled to -35 °C and then CsOH•H\textsubscript{2}O (0.232 g, 1.38 mmol) was added in one portion. The mixture stirred for 10 min at which time
benzyl bromide (0.165 mL, 1.38 mmol) was added dropwise. The mixture stirred at -35 °C for 13 h at which time the reaction was diluted with Et₂O (40 mL) and H₂O (2 x 15 mL) followed by a saturated aqueous solution of NaCl, then dried over MgSO₄. The mixture was filtered, the solvent removed in vacuo and the crude residue purified by column chromatography (15% EtOAc/hexane) to afford 0.116 g (93%) of the desired compound as a colorless oil.¹ The enantioselectivity was determined by chiral HPLC (DAICEL Chiralpack AD column, 10% EtOH/hexane, 1.0 mL/min, 23°C, λ = 254 nm, retention times: S (major) 7.3 min, R (minor) 6.4 min, 93 : 7 er). The absolute configuration was determined by the comparison of the optical rotation with the authentic sample synthesized by the reported procedure.

3.4.2 Representative Procedure for the Enantioselective Catalytic Phase-Transfer Alkylation of Glycinie Imine

To a mixture of N-(diphenylmethylene)glycine tert-butyl ester 3 (50 mg, 0.17 mmol) and chiral catalyst 77 (11 mg, 0.017 mmol) in toluene/THF (volume ratio = 7:3, 0.75 mL) was added benzyl bromide (0.10 mL, 0.85 mmol). The reaction mixture was then cooled to -40 °C, 50% aqueous KOH (0.25 mL) was added, and the solution was
stirred at -40 °C until starting material was consumed. The mixture was diluted with ether (30 mL), washed with water (2 x 10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (10% EtOAc/hexanes) afforded the desired product (S)-82 (56.4 mg, 86% yield) as a colorless oil. [α]D23 -169.6 (c 2.63, CHCl₃); The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, isopropanol:hexane = 0.5:100, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention times: R (minor) 10.2 min, S (major) 19.6 min, 98% ee). The absolute configuration was determined by the comparison of the optical rotation with the authentic sample synthesized by the reported procedure.²

3.5 References
