## Supplementary Information File

# Identifying the Roles of Amino Acids, Alcohols and 1,2Diamines as Mediators in Coupling of Haloarenes to Arenes 

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## General experimental information

All the reactions were performed in oven-dried or flame-dried apparatus and preparation of the substrates was carried out under argon atmosphere using dry solvents. Diethyl ether, tetrahydrofuran, dichloromethane and hexane were dried with a Pure-Solv 400 solvent purification system by Innovative Technology Inc., U.S.A. A glove box (Innovative Technology Inc., U.S.A.) was used to weigh out the super-electron-donor (SED) into the reaction flask. All the reagents were bought from commercial suppliers and used without further purification unless stated otherwise. A Büchi rotary evaporator was used to concentrate the reaction mixtures. Thin layer chromatography (TLC) was performed using aluminum-backed sheets of silica gel and visualized under a UV lamp ( 254 nm ). The plates were developed using vanillin or $\mathrm{KMnO}_{4}$ solution. Column chromatography was performed to purify compounds by using silica gel 60 (200-400 mesh).

Proton $\left({ }^{1} \mathrm{H}\right)$ and deuterium $\left({ }^{2} \mathrm{H}\right)$ NMR spectra were recorded at 400 MHz on a Bruker DPX 400 spectrometer or at 500 MHz on a Bruker DRX 500 spectrometer. Carbon NMR $\left({ }^{13} \mathrm{C}\right)$ spectra were recorded at 100 MHz or 125 MHz respectively. The chemical shifts are quoted in parts per million (ppm) by taking tetramethylsilane as a reference $(\delta=0)$ but calibrated on the residual non-deuterated solvent signal. Signal multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; coupling constants are given in Hertz (Hz).

Infra-Red spectra were recorded on a Perkin Elmer Spectrum One FT IR Spectrometer either pressed as discs in KBr or as films applied on NaCl crystal plates or using Shimadzu FT-IR Spectrophotometer (Model IRAffinity-1) with a MIRacle Single Reflection Horizontal ATR Accessory. Melting points were determined on a Gallenkamp Melting point apparatus. High resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service Centre, Swansea. The spectra were recorded using electron ionization (EI), chemical ionization (CI), fast atom bombardment (FAB) or electrospray ionization (ESI) techniques as stated for each compound.

## Coupling Reactions between Dimethyliodobenzene 33 and Benzene



Standard procedure (See Scheme 2 and Figure 3 in the paper):
The mixture of 2,6-dimethyl-1-iodobenzene $33(232 \mathrm{mg}, 1.0 \mathrm{mmol})$, potassium tertbutoxide (if not specified, $224 \mathrm{mg}, 2.0 \mathrm{mmol}$ ) and additive (if not specified, 0.2 mmol ) in 10 mL benzene was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at $130^{\circ} \mathrm{C}$ for 18 hours behind a shield. After cooling to room temperature, the reaction was quenched by water ( 30 mL ). The mixture was extracted with diethyl ether $(15 \mathrm{~mL})+$ hexane $(15 \mathrm{~mL})$. The organic layer was dried over sodium sulfate. Filtration and concentration gave a residue, which was purified by careful chromatography, eluting with hexane. The products are recovered starting material 2,6-dimethyl-1-iodobenzene and a mixture of biphenyl and 2,6-dimethylbiphenyl. The ratio of biphenyl to 2,6-dimethylbiphenyl is around 4 to 1 if not specified.

Table 1. Additives used in the coupling of $\mathbf{3 3}$ with benzene

| Additive Structure | Additive <br> $(\mathrm{mmol})$ | KOtBu (mmol) | Recovered 33 | Product <br> (biphenyl 35 + 2,6- <br> dimethylbiphenyl 34) <br> $(\mathrm{mg})$ |
| :---: | :---: | :---: | :---: | :---: |
| No additive <br> (blank reaction) | ---- | 2.0 | $93 \%$ | $<0.5$ |
| No additive <br> (blank reaction, <br> repeat) | ---- | 2.0 | $88 \%$ | $<0.5$ |
| $\mathrm{H}^{\mathrm{O}}$ <br> -OH | 0.2 | 3.0 | $25 \%$ | 44 |
| $\mathbf{8}$ |  |  |  |  |


|  | 0.2 | 3.0 | 54\% | 32 |
| :---: | :---: | :---: | :---: | :---: |
|  <br> 41 | 0.2 | 2.0 | 92\% | $<0.5$ |
|  <br> 42 | 0.2 | 2.0 | 94\% | $<0.5$ |
|  <br> 43 | 0.2 | 3.0 | 70\% | 16 |
|  <br> 44 | 0.2 | 2.0 | 22\% | 45 |
|  | 0.2 | 3.0 | 92\% | $<0.5$ |
|  <br> 49 | 0.2 | 2.0 | 19\% | 43 |
|  <br> 50 | 0.2 | 2.0 | 93\% | $<0.5$ |


|  <br> 51 | 0.2 | 2.0 | 57\% | 22 |
| :---: | :---: | :---: | :---: | :---: |
|  <br> 52 | 0.2 | 2.0 | 52\% | 18 |
|  <br> 53 | 0.2 | 2.0 | 0 | 42 |
|  <br> 54 | 0.2 | 2.0 | 33\% | 32 |
| $\begin{gathered} \text { EtOAc } \\ 55 \end{gathered}$ | 0.2 | 2.0 | 41\% | 19 |
|  <br> 56 | 0.2 | 3.0 | 0 | 44 |
|  <br> 57 | 0.2 | 3.0 | 0 | 35 |
|  <br> 58 | 0.3 | 3.0 | 74\% | 9 |
|  <br> 59 | 0.2 | 3.0 | 0 | 32 |


|  <br> 60 | 0.2 | 3.0 | 0 | 64 |
| :---: | :---: | :---: | :---: | :---: |
|  <br> 61 | 0.2 | 3.0 | 52\% | 10 |
|  | 0.2 | 3.0 | 50\% | 5 |
|  | 0.2 | 2.0 | 39\% | 9 |
|  <br> 63 | 0.2 | 3.0 | 50\% | 7 |
| $\begin{gathered} \mathrm{Bu}_{2} \mathrm{NH} \\ 64 \end{gathered}$ | 0.2 | 2.0 | 92\% | $<0.5$ |
|  <br> 65 | 0.2 | 3.0 | 0 | 46 |


|  <br> 75 | 0.2 | 2.0 | 55\% | 11 |
| :---: | :---: | :---: | :---: | :---: |
| Additional Examples (AE1-6): |  |  |  |  |
|  <br> AE 1 | 0.3 | 3.0 | 85\% | 4 |
|  <br> AE 2 | 0.2 | 2.0 | 82\% | 5 |
|  <br> AE 3 | 0.2 | 2.0 | 21\% | 12 |
|  <br> AE 4 | 0.2 | 2.0 | 45\% | 17 |
|  <br> AE 5 | 0.2 | 2.0 | 80\% | 4 |
|  <br> AE 6 | 0.2 | 3.0 | 95\% | 0 |

## Preparation of Piperazinediones



Chloroacetyl chloride ( $5.65 \mathrm{~g}, 50 \mathrm{mmol}$ ) was added dropwise to a solution of $n$ propylamine ( $5.9 \mathrm{~g}, 100 \mathrm{mmol}$ ) in DCM ( 80 mL ) cooled in an ice-water bath. The resulting suspension was stirred in the cooling bath for 1 h , diluted with ether ( 80 mL ), and filtered. The clear solution was concentrated. The residue was dissolved in ether ( 30 mL ) and the solid was filtered again. Concentration of the filtrate gave 2 -chloro-N-propylacetamide $(6.71 \mathrm{~g}, 99 \%)$ as a pure pale yellow liquid. The product was used without further purification. ${ }^{1}$


Oil-free $\mathrm{NaH}(288 \mathrm{mg}, 12.0 \mathrm{mmol})$ was added carefully portion-wise to a solution of 2-chloro-N-propylacetamide ( $1.355 \mathrm{~g}, 10 \mathrm{mmol}$ ) in dry DMF $(20 \mathrm{~mL})$ in a glovebox. After the completion of the addition, the mixture was moved out of the glovebox and stirred at room temperature for 30 min . Then the mixture was diluted with ether ( 70 mL ) and filtered. The filtrate was concentrated and purified by column (hexane/EtOAc $=50 / 50$ to $100 \%$ EtOAc). 1,4-Di- $n$-propylpiperazine-2,5-dione 44 ( $723 \mathrm{mg}, 73 \%$ ) was obtained as a white solid. $\mathrm{mp}, 41-42^{\circ} \mathrm{C}$; [Found: (FTMS+) $(\mathrm{M}+\mathrm{H})^{+}$199.1439, $\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{2}(\mathrm{M}+\mathrm{H})$ requires 199.1441]; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right): \delta 0.92(6 \mathrm{H}, \mathrm{t}, J=7.4 \mathrm{~Hz}), 1.58(4 \mathrm{H}, \mathrm{m}), 3.35(4 \mathrm{H}, \mathrm{m}), 3.95(4 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR (100 MHz, $\mathrm{CDCl}_{3}$ ): $\delta 10.6,19.4,47.0,49.4,163.0$.



To a suspension of 2-amino-2-methylpropanoic acid ( $5.25 \mathrm{~g}, 50.97 \mathrm{mmol})$ in MeOH $(60 \mathrm{~mL})$, cooled in an ice-water bath, was added thionyl chloride ( $3.9 \mathrm{~mL}, 53.7 \mathrm{mmol}$ ) dropwise over about 20 min . The resulting solution was heated to $55-60{ }^{\circ} \mathrm{C}$ for 4 h , then cooled to room temperature, and concentrated. More $\mathrm{MeOH}(50 \mathrm{~mL})$ was added, and concentrated under vacuum. The white solid obtained was used in the next reaction without purification.
Crude methyl 2-amino-2-methylpropanoate hydrogen chloride salt was dissolved in water. $\mathrm{NaHCO}_{3}(12.9 \mathrm{~g}, 153 \mathrm{mmol})$ was added, followed by chloroform ( 30 mL ). The 2-chloroacetyl chloride ( $4.4 \mathrm{~mL}, 55 \mathrm{mmol}$ ) in chloroform ( 5 mL ) was added dropwise. The mixture was stirred at room temperature overnight.

The organic layer was separated. The aqueous layer was extracted with chloroform $(30 \mathrm{~mL})$. The combined organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. Column purification (EtOAc) gave methyl 2-(2-chloroacetamido)-2methyl propanoate, $(5.47 \mathrm{~g}, 56 \%$ over two steps $)$ as a white solid that was used directly in the next step. ${ }^{2}$



A solution of 2-(2-chloroacetamido)-2-methyl propanoate ( $850 \mathrm{mg}, 4.41 \mathrm{mmol}$ ) and $n-\mathrm{BuNH}_{2}$ in ethanol $(15 \mathrm{~mL})$ was heated at $55{ }^{\circ} \mathrm{C}$ for 3 h , and the mixture was cooled to room temperature. The volatiles were removed on a rotary evaporator. The residue was dissolved in EtOAc and washed with aqueous potassium carbonate solution (5 mL , containing $\mathrm{K}_{2} \mathrm{CO}_{3}(1.0 \mathrm{~g})$. The organic layer was separated and concentrated.
The residue was dissolved in $\mathrm{MeOH}(5 \mathrm{~mL})$ and THF ( 5 mL ), sealed in a pressure tube and heated to $150{ }^{\circ} \mathrm{C}$ overnight behind a shield. The mixture was cooled to room temperature. The solvent was removed under vacuum, and the residue was purified by column chromatography (EtOAc). 1-Butyl-3,3-dimethylpiperazine-2,5-dione $\mathbf{5 0}$ was
obtained as a white solid, ( $645 \mathrm{mg}, 74 \%$ over two steps). $\mathrm{mp} 78-80^{\circ} \mathrm{C}$; $v_{\text {max }}$ (neat) $/ \mathrm{cm}^{-1}$ 3073, 2963, 2930, 2872, 1682, 1645, 1450, 1427, 1298, 1196, 825, 785; [Found: (FTMS) $(\mathrm{M}+\mathrm{H})^{+}$199.1438, $\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{~N}_{2} \mathrm{O}_{2}(\mathrm{M}+\mathrm{H})$ requires 199.1441]; ${ }^{1} \mathrm{H}$ NMR ( 400 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 0.94(3 \mathrm{H}, \mathrm{t}, J=7.3 \mathrm{~Hz}), 1.29-1.38(2 \mathrm{H}, \mathrm{m}), 1.49(6 \mathrm{H}, \mathrm{s}), 1.50-1.58$ $(2 \mathrm{H}, \mathrm{m}), 3.4(2 \mathrm{H}, \mathrm{t}, J=7.4 \mathrm{~Hz}), 3.96(2 \mathrm{H}, \mathrm{s}), 7.55(1 \mathrm{H}$, broad)$){ }^{13} \mathrm{C}$ NMR ( 100 MHz , $\left.\mathrm{CDCl}_{3}\right): \delta 13.2,19.4,27.3,28.2,45.8,49.4,55.5,165.7,168.6$.


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(ii) Mel


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To a solution of 1-butyl-3,3-dimethylpiperazine-2,5-dione 50 ( $220 \mathrm{mg}, 1.11 \mathrm{mmol}$ ) in THF ( 8 mL ) cooled in an ice-water bath under argon was added $n$-BuLi $(0.5 \mathrm{~mL}, 1.25$ mmol ) dropwise. The mixture was stirred at room temperature for 10 min , then it was cooled in ice-water bath again. Iodomethane $(0.2 \mathrm{~mL})$ was added and the mixture was stirred at room temperature overnight. The reaction was quenched by water ( 30 mL ). The mixture was extracted with EtOAc ( $2 \times 30 \mathrm{~mL}$ ). The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. Purification by column chromatography (EtOAc) gave 1-butyl-3,3,4-trimethylpiperazine-2,5-dione 49 as a yellow oil ( $118 \mathrm{mg}, 50 \%$ ). $v_{\max }($ neat $) / \mathrm{cm}^{-1} 2959,2932,2875,1651,1456,1429,1400,1379,1308,1211,1153$, 989, 752; [Found: (FTMS) $(\mathrm{M}+\mathrm{H})^{+}$213.1594, $\mathrm{C}_{11} \mathrm{H}_{21} \mathrm{~N}_{2} \mathrm{O}_{2}(\mathrm{M}+\mathrm{H})$ requires 213.1598]; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 0.85(3 \mathrm{H}, \mathrm{t}, J=7.3 \mathrm{~Hz}), 1.25-1.29(2 \mathrm{H}$, m), 1.39-1.50 ( $2 \mathrm{H}, \mathrm{m}$ ), $1.43(6 \mathrm{H}, \mathrm{s}), 2.89(3 \mathrm{H}, \mathrm{s}), 3.13(2 \mathrm{H}, \mathrm{t}, J=7.4 \mathrm{~Hz}), 3.89(2 \mathrm{H}$, s); ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 13.2,19.3,24.2,27.2,28.0,45.7,48.9,60.1$, 163.6, 168.0.


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2-Chloroacetyl chloride ( $10 \mathrm{~mL}, 125 \mathrm{mmol}$ ) was added dropwise to a solution of dimethylamine in water ( $130 \mathrm{~mL}, 1.0 \mathrm{~mol}$ ) cooled in an ice-water bath, at such a rate that the temperature of the reaction did not exceed $20^{\circ} \mathrm{C}$. Once the addition was finished, the solution was stirred at room temperature overnight.
$\mathrm{NaOH}(10 \mathrm{~g}, 250 \mathrm{mmol}$ ) was added to the solution, which was stirred at room temperature for 4 h . Then $\mathrm{NaI}(1.0 \mathrm{~g})$ was added. A Dean-Stark apparatus was set up, and benzene $(200 \mathrm{~mL})$ was added. The mixture was heated to reflux, and water was separated. The mixture was cooled to room temperature, and the solid was filtered off. The filtrate was concentrated. The product 2-(dimethylamino)- $N, N$-dimethyl acetamide 51 was obtained as colourless liquid, ( $13.02 \mathrm{~g}, 80 \%$ ). ${ }^{1} \mathrm{HNMR}(400 \mathrm{MHz}$, $\left.\mathrm{CDCl}_{3}\right): \delta 2.27(6 \mathrm{H}, \mathrm{s}), 2.92(3 \mathrm{H}, \mathrm{s}), 3.05(3 \mathrm{H}, \mathrm{s}), 3.08(2 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR ( 100 MHz , $\mathrm{CDCl}_{3}$ ): $35.0,36.4,45.1,61.5,169.4$. $^{3}$


The mixture of dimethylamine ( $50 \mathrm{~mL}, 7.9 \mathrm{M}$ in water) and diethyl ether $(200 \mathrm{~mL})$ was dried with $\mathrm{Na}_{2} \mathrm{SO}_{4}$. The ether solution of dimethylamine was decanted into a flask containing methyl 2-bromoacetate $(8.0 \mathrm{~g}, 52.28 \mathrm{mmol})$. A white precipitate appeared immediately. The mixture was stirred at room temperature overnight, and then was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. After filtration, the filtrate was concentrated. The residue was distilled to give methyl $\mathrm{N}, \mathrm{N}$-dimethylglycinate as a colorless liquid, $(4.65 \mathrm{~g}, 76 \%)$. ${ }^{1} \mathrm{HNMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 2.37(6 \mathrm{H}, \mathrm{s}), 3.19(2 \mathrm{H}, \mathrm{s}), 3.75(3 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR (100 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta 45.2,51.4,60.3,170.9 .{ }^{4}$

## Reaction of cis-Cyclohexanediol 59 with potassium $\boldsymbol{t}$-butoxide



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A mixture of cis-cyclohexane-1,2-diol 59 ( $116 \mathrm{mg}, 1.0 \mathrm{mmol}$ ), $t$-BuOK ( $400 \mathrm{mg}, 3.57$ mmol ) and dry benzene $(10 \mathrm{~mL})$ was sealed in a pressure tube in glovebox. It was heated to $130{ }^{\circ} \mathrm{C}$ for 18 h behind a shield. The reaction was quenched with water ( 30 mL ). The aqueous phase was neutralized by 2 N hydrochloric acid. EtOAc ( 30 mL ) and (2,4-dinitrophenyl)hydrazine ( $100 \mathrm{mg}, 0.5 \mathrm{mmol}$ ) were added. The mixture was stirred at room temperature overnight.

The organic layer was separated and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$. Filtration and concentration gave a residue that was purified by column chromatography ( $\mathrm{DCM} \rightarrow \mathrm{DCM}: \mathrm{MeOH}=$ 95:5). 2-(2-(2,4-Dinitrophenyl)hydrazono)cyclohexan-1-ol $\mathbf{8 2}$ was obtained as a yellow solid.

The hydrazone obtained was not stable in air and decomposed over some hours. One of the products of this process was ketone 2-(2-(2,4-dinitrophenyl)hydrazono)cyclohexan-1-one (83), a yellow solid that presented as a mixture of two geometric isomers. mp $159-161^{\circ} \mathrm{C}$. [Found: (FTMS) $(\mathrm{M}+\mathrm{H})^{+}$ 293.0880, $\mathrm{C}_{12} \mathrm{H}_{13} \mathrm{~N}_{4} \mathrm{O}_{5}(\mathrm{M}+\mathrm{H})$ requires 293.0880]; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ 1.99-2.01 ( $4 \mathrm{H}, \mathrm{m}$ ), 2.67-2.70 ( $2 \mathrm{H}, \mathrm{m}$ ), 2.84-2.87 ( $2 \mathrm{H}, \mathrm{m}$ ), $8.21(1 \mathrm{H}, \mathrm{d}, J 9.6 \mathrm{~Hz}), 8.36$ $(1 \mathrm{H}$, ddd, $J=0.8,2.8,9.6 \mathrm{~Hz}), 9.15(1 \mathrm{H}, \mathrm{d}, J=2.8 \mathrm{~Hz}), 14.84(1 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR $(100$ $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 21.8,22.1,22.3,23.2,26.9,33.7,40.8,41.1,116.7,118.0,122.9$, 123.1, 129.6, 130.3, 131.3, 139.8, 142.4, 144.7, 195.3, 198.7.

## Independent synthesis of $\mathbf{8 3}$



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To a solution of trans-cyclohexane-1,2-diol $\mathbf{6 0}(580 \mathrm{mg}, 5.0 \mathrm{mmol})$, sodium bromate ( $906 \mathrm{mg}, 6.0 \mathrm{mmol}$ ) in acetonitrile ( 10 mL ) and water ( 5 mL ) at room temperature was added a solution of sodium bisulfite ( $625 \mathrm{mg}, 6.0 \mathrm{mmol}$ ) in water ( 8 mL ) via a syringe pump in 40 min . After completion of the addition, the mixture was stirred at room temperature for 3 h . The mixture was extracted with ether ( 60 mL ). The organic layer was washed with aqueous sodium thiosulfate, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. ${ }^{5}$

The crude product was dissolved in EtOAc $(40 \mathrm{~mL})$ at room temperature, and $(2,4-$ dinitrophenyl)hydrazine ( $500 \mathrm{mg}, 2.5 \mathrm{mmol}$ ) were added. The mixture was stirred at room temperature for 5 h . The organic layer was separated, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. Purification by column chromatography (DCM $\rightarrow$ hexane:EtOAc = 50:50) gave 2-(2-(2,4-dinitrophenyl)hydrazono)cyclohexan-1-ol 82 as a yellow solid.
The hydrazone obtained was not stable in air and decomposed over a few hours. One of the products of this process was the ketone 83: 2-(2-(2,4-dinitrophenyl)hydrazono)cyclohexan-1-one, which is a yellow solid, with identical spectroscopic data to those reported above.

## Reaction of KOtBu with alcohols 61, 62.



A mixture of cis-4-(tert-butyl)cyclohexan-1-ol ( $74 \mathrm{mg}, 0.47 \mathrm{mmol}$ ), $t \mathrm{BuOK}$ ( 500 mg , $4.46 \mathrm{mmol})$ and benzene ( 8 mL ) was sealed in a pressure tube in a glovebox. It was heated to $170{ }^{\circ} \mathrm{C}$ for 16 h behind a shield. After cooling to room temperature, the reaction was quenched by water ( 20 mL ). The mixture was extracted with ether ( 15 mL ) and hexane ( 15 mL ). The combined organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered through a short plug of silica, and concentrated to afford a white solid (74 mg ). ${ }^{1} \mathrm{H}$ NMR showed that it was a mixture of the following compounds:



A mixture of trans-4-(tert-butyl)cyclohexan-1-ol ( $74 \mathrm{mg}, 0.47 \mathrm{mmol}$ ), $t \mathrm{BuOK}$ ( 500 $\mathrm{mg}, 4.46 \mathrm{mmol})$ and benzene ( 8 mL ) was sealed in a pressure tube in a glovebox. It was heated to $170^{\circ} \mathrm{C}$ for 16 h behind a shield. After cooling to room temperature, the reaction was quenched by water ( 20 mL ). The mixture was extracted with ether ( 15 mL ) and hexane ( 15 mL ). The combined organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered through a short plug of silica, and concentrated to afford a white solid ( 72 mg ).
${ }^{1} \mathrm{H}$ NMR showed that it was a mixture of the following compounds:


## Formation of potassium enolate derived from ketone75


$\mathrm{KH}(\sim 30 \%$ in mineral oil, $0.200 \mathrm{~g}, 1.5 \mathrm{mmol})$ in a flask was washed with dry hexane $(50 \mathrm{~mL})$ and dried under argon gas. This flask was then taken into a glove-box and dry THF ( 5 mL ) was added. A solution of 4-(tert-butyl)cyclohexan-1-one 75 (0.154 $\mathrm{g}, 1 \mathrm{mmol}$ ) in dry THF ( 5 mL ) was added slowly into this flask. The resulting reaction mixture was stirred for 1 h at room temperature in glove box, which resulted in formation of the enolate ( 1 mmol ) in 10 mL THF solution. This enolate solution was used later in coupling reactions.
Part of this preformed enolate solution was quickly quenched with $\mathrm{D}_{2} \mathrm{O}(5 \mathrm{~mL})$ in glove box, which was then removed from the glove-box and extracted with diethyl ether ( $3 \times 10 \mathrm{~mL}$ ). The combined ether layers were then washed with brine ( 10 mL ) and dried over anhydrous sodium sulfate. The crude product was obtained after evaporation of solvent under reduced pressure using a rotary evaporator. The crude product was then adsorbed onto silica and purified by column chromatography ( $5 \%$ diethyl ether in hexane), providing the corresponding monodeuterated isotopomer of the starting material, i.e. $\mathbf{7 5 - \mathbf { d } ^ { 1 }}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 0.93\left(9 \mathrm{H}, \mathrm{s},\left(\mathrm{CH}_{3}\right)_{3}\right), 1.40-1.53\left(3 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{CHCH}_{2}\right)$, 2.07-2.12 ( $2 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{CHCH}_{2}$ ), 2.29-2.43 ( $3 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{COCHD}$ ).
${ }^{2} \mathrm{H}$ NMR ( $61.4 \mathrm{MHz}, \mathrm{CHCl}_{3}$, with $\mathrm{CDCl}_{3}$ as internal standard): $\delta 2.32$
For comparison; ${ }^{1} \mathrm{H}$ NMR of the starting material is provided along with ${ }^{1} \mathrm{H}$ NMR and ${ }^{2} \mathrm{H}$ NMR of dueterated product from the above reaction.

Coupling reactions using preformed potassium enolate of ketone 75 as an additive:

General reaction procedure: 2 mL of the above preformed enolate additive in THF (it is equivalent to 0.2 mmol of additive) was added to a flask in glove box and then,

THF was removed under vacuum in the glove box. Dry benzene ( 10 mL ) was added into this flask. The resulting suspension of additive in benzene was transferred to a pressure tube containing substrate ( 1 mmol ) and $\mathrm{KO}^{t} \mathrm{Bu}(3 \mathrm{mmol})$. The tube was then sealed properly before removing from the glove box and reaction was carried out as stated below. Later, reaction was stopped and pressure tube was cooled to room temperature. Reaction contents were quenched with water ( 10 mL ) and extracted with diethyl ether ( $3 \times 10 \mathrm{~mL}$ ). The combined ether layers were then washed with brine ( 10 mL ) and dried over anhydrous sodium sulfate. The crude product was obtained after evaporation of solvent under reduced pressure using a rotary evaporator. The crude product was then adsorbed onto silica and purified by column chromatography, providing the corresponding reduced products or recovered starting materials in yields as stated.


2-Iodo- $m$-xylene 33 ( $0.232 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with "preformed enolate" $(0.2$ $\mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under the general reaction procedure as mentioned above, and afforded mixture of 2,6-dimethylbiphenyl and biphenyl ( 0.004 g in $1: 1.17$ ratio respectively) along with starting material 33 (0.112 $\mathrm{g}, 48 \%)$.


4-Iodotoluene 70 ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with "preformed enolate" ( 0.2 mmol ), $\mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under the general reaction procedure as mentioned above, and afforded 4-methyl-1,1'-biphenyl 71 ( $0.064 \mathrm{~g}, 38 \%$ ) as a white solid along with starting material $70(0.099 \mathrm{~g}, 45 \%)$.

Synthesis of 2,2'-(ethane-1,2-diyl)bis(isoindoline-1,3-dione) 94:


A mixture of potassium phthalimide $93(30.8 \mathrm{~g}, 166.3 \mathrm{mmol})$ and 1,2-dibromoethane $(13.0 \mathrm{~g}, 69.1 \mathrm{mmol})$ in DMF $(200 \mathrm{~mL})$ was heated to $95-100{ }^{\circ} \mathrm{C}$ for 3.5 days. After it was cooled to room temperature, the mixture was poured into water (1.2 L), and the solid was collected by filtration. The solid was washed with water. The wet solid was dissolved by dichloromethane ( 450 mL ). The organic layer was washed with 2 N $\mathrm{NaOH}(100 \mathrm{~mL})$, and dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The product 94 was a white solid ( $17.68 \mathrm{~g}, 80 \%$ ), which was used in the next step without purification. ${ }^{6}$

## Ethylenediamine dihydrochloride 95:

2,2'-(ethane-1,2-diyl)bis(isoindoline-1,3-dione) $94(25.14 \mathrm{~g}, 78.56 \mathrm{mmol})$ was added to a solution of $\mathrm{KOH}(45.0 \mathrm{~g}, 85 \%)$ in water $(70 \mathrm{~mL})$. The mixture was stirred at room temperature for overnight, and a clear solution was obtained. The volatiles were distilled at atmospheric pressure until the residue was dry. The process was repeated three times (adding 80 mL of water, distillation at atmospheric pressure). The
distillate was acidified by concentrated hydrochloric acid to $\mathrm{pH}<2$. Water was removed by rotary evaporator, and the residue was dried under vacuum while heated. The product 95 was obtained as a white solid $(10.39 \mathrm{~g}, 99 \%)$ and used directly in the next step. ${ }^{7}$

## Synthesis of N,N'-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide) 96:

The mixture of ethylenediamine dihydrochloride 95 ( $7.89 \mathrm{~g}, 68.65 \mathrm{mmol}$ ) and toluenesulfonyl chloride ( $25.5 \mathrm{~g}, 133.7 \mathrm{mmol}$ ) in pyridine ( 150 mL ) was heated to reflux overnight. The mixture was cooled to room temperature, poured into water $(800 \mathrm{~mL})$. The solid was collected by filtration, washed with water and diethyl ether, and dried under vacuum while heated. The product 96 was obtained as an off-white solid, $(21.3 \mathrm{~g}, 97 \%)$. It was used in the next reaction without further purification. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO-d $)_{6}$ ) $\delta 2.39\left(6 \mathrm{H}, \mathrm{s}, \mathrm{CH}_{3}\right), 2.72\left(4 \mathrm{H}, \mathrm{m}, \mathrm{CH}_{2} \mathrm{CH}_{2}\right), 7.38(4 \mathrm{H}$, d, $J 8.2 \mathrm{~Hz}, \mathrm{ArH}$ ), 7.58 ( $2 \mathrm{H}, \mathrm{s}, \mathrm{NH}$ ), $7.61(4 \mathrm{H}, \mathrm{d}, J 8.2 \mathrm{~Hz}, \mathrm{ArH})$.

## Synthesis of $\mathbf{N}, \mathbf{N}^{\prime}$-(ethane-1,2-diyl)bis(N,4-dimethylbenzenesulfonamide) 97:

A mixture of $\mathrm{N}, \mathrm{N}^{\prime}$-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide) 96 ( 6.26 g , 17.01 mmol ) and potassium carbonate ( $7.0 \mathrm{~g}, 50.72 \mathrm{mmol}$ ) in DMF ( 50 mL ) was stirred in an ice-water cooling bath. MeI ( $3.2 \mathrm{~mL}, 51 \mathrm{mmol}, 3.0$ eq.) was added, and the mixture was stirred in the cooling bath overnight, while the temperature of the reaction rose naturally to room temperature. The mixture was poured into water (250 mL ). The solid was collected by filtration, washed with water, and dissolved in dichloromethane. The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The product 97 was obtained as an off-white solid $(6.6 \mathrm{~g}, 98 \%) .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right): \delta 2.46(6 \mathrm{H}, \mathrm{s}), 2.84\left(6 \mathrm{H}, \mathrm{s}, \mathrm{CH}_{3}\right), 3.24\left(4 \mathrm{H}, \mathrm{s}, \mathrm{CH}_{2}\right), 7.35(4 \mathrm{H}, \mathrm{d}, J=8.0 \mathrm{~Hz}$, ArH), $7.70(4 \mathrm{H}, \mathrm{d}, J=8 \mathrm{~Hz}, \mathrm{ArH})$.

## The synthesis of $N, N^{\prime}$-dimethylethane-1,2-diamine dihydrochloride 98:

A mixture of $\mathrm{N}, \mathrm{N}^{\prime}$-(ethane-1,2-diyl)bis( $\mathrm{N}, 4-$ dimethylbenzenesulfonamide) 97 ( 6.6 g , $16.67 \mathrm{mmol})$, hydrobromic acid ( $40 \mathrm{~mL}, 48 \% \mathrm{HBr}$ ) and acetic acid ( 20 mL ) was heated undr reflux for 2 h . The solvent was removed by distillation at atmospheric pressure, and the residual solvent was then removed under vacuum while the flask was heated. The residue was dissolved in water $(40 \mathrm{~mL})$ and the solution was basified
by adding solid $\mathrm{NaOH}(2.5 \mathrm{~g})$. A distillation set up was installed and water was distilled under atmospheric pressure until complete. Then more water ( 30 mL ) was added, and the distillation was repeated twice. The combined distillate ( $\sim 100 \mathrm{~mL}$ ) was acidified with concentrated hydrochloric acid to $\mathrm{pH}<2$. Water was then on a rotary evaporator under vacuum. The resulting solid was dried under vacuum while being heated. The product $\mathbf{9 8}$ was obtained as a white solid $(2.61 \mathrm{~g}, 97 \%)$.

## The synthesis of $N, N^{\prime}$-dimethylethane-1,2-diamine 90:

N,N'-dimethylethane-1,2-diamine dihydrochloride ( $4.2 \mathrm{~g}, 20.09 \mathrm{mmol}$ ) was placed in a Schlenk flask and cooled in an acetone-dry ice bath. $\mathrm{NaH}(2.0 \mathrm{~g}, 83.3 \mathrm{mmol})$ was added followed by installation of a dry ice condenser. $\mathrm{NH}_{3}(80 \mathrm{~mL})$ was condensed into the mixture. The mixture was stirred in the cooling bath for 1 h , then the cooling bath was removed, and the ammonia was reflux for 3 h . The ammonia was evaporated naturally overnight. A distillation set up with an air condenser was installed, with the receiving flask submerged into an acetone dry ice bath. The mixture was heated gently, with occasional heating of the distillation head and condenser with hot air. The product 90 was obtained as a colourless liquid ( $1.02 \mathrm{~g}, 44 \%$ ). [Found: ( $\mathrm{CI}^{+}$corona) $(\mathrm{M}+\mathrm{H})^{+}$89.1067. $\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{~N}_{2}(\mathrm{M}+\mathrm{H})$ requires 89.1073]; $\mathrm{v}_{\max }$ (neat) $/ \mathrm{cm}^{-1} 3273$, 2934, 2887, 2841, 2789, 1472, 1446, 1148, 1103, 748; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 1.16$ ( $2 \mathrm{H}, \mathrm{s}$ ), $2.38(6 \mathrm{H}, \mathrm{s}), 2.63(4 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 35.9,50.8 ; \mathrm{m} / \mathrm{z}$ $\left(\mathrm{ESI}^{+}\right) 177\left[(2 \mathrm{M}+\mathrm{H})^{+}, 22 \%\right], 119(19), 89\left[(\mathrm{M}+\mathrm{H})^{+}, 100 \%\right], 87(14)$.

## The tetradeutero series:



## Synthesis of 2,2'-(ethane-1,2-diyl-d $\mathbf{d}_{4}$ )bis(isoindoline-1,3-dione $\mathbf{d}_{4} \mathbf{- 9 4}$ ):

A mixture of potassium phthalimide $(30.0 \mathrm{~g}, 162.16 \mathrm{mmol})$ and 1,2-dibromoethane- $\mathrm{d}_{4}$ $(12.9 \mathrm{~g}, 67.18 \mathrm{mmol})$ in DMF $(200 \mathrm{~mL})$ was heated to $95-100{ }^{\circ} \mathrm{C}$ for 4.5 days. After the mixture was cooled to room temperature, it was poured into water $(1 \mathrm{~L})$. The solid was collected by filtration, and washed with water. The wet solid was dissolved in
dichloromethane ( 450 mL ). The organic layer was washed with $10 \% \mathrm{NaOH}$ (100 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The product, $\mathrm{d}_{4}-94$ was obtained as a white solid ( $18.97 \mathrm{~g}, 87 \%$ ). The product was used in next reaction without further purification. mp 234-236 ${ }^{\circ} \mathrm{C}$; [Found: $\left(\mathrm{ESI}^{\dagger}\right)(\mathrm{M}+\mathrm{H})^{+}$325.1116. $\mathrm{C}_{18} \mathrm{H}_{9} \mathrm{D}_{4} \mathrm{~N}_{2} \mathrm{O}_{4}(\mathrm{M}+\mathrm{H})$ requires 325.1121]; $v_{\max }$ (neat) $/ \mathrm{cm}^{-1} 1766,1703,1390,1286,1070,922,716{ }^{2} \mathrm{H}$ NMR ( $76 \mathrm{MHz}, \mathrm{CHCl}_{3}$, with $\mathrm{CDCl}_{3}$ as internal standard): $\delta 4.0 ;{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, $\mathrm{CDCl}_{3}$ ): $\delta 7.68-7.72(4 \mathrm{H}, \mathrm{m}), 7.77-7.78(4 \mathrm{H}, \mathrm{m}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ $122.8,131.5,133.5,167.7 ; m / z\left(\mathrm{ESI}^{+}\right) 666\left[\left(2 \mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 22 \%\right], 342\left[\left(\mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 90\right]$, $325\left[(\mathrm{M}+\mathrm{H})^{+}, 100\right]$. The ${ }^{13} \mathrm{C}$ peaks bonded to deuterium were not observed under routine acquisition conditions.


Synthesis of $\mathbf{N}, \mathbf{N}^{\prime}$-(ethane-1,2-diyl-d $\mathbf{d}_{4}$ bis(4-methylbenzenesulfonamide $\mathbf{d}_{4}-\mathbf{9 6}$ ):
To a solution of $\mathrm{KOH}(66 \mathrm{~g}, 85 \%)$ in water $(100 \mathrm{~mL})$ was added 2,2'-(ethane-1,2-diyl$\left.\mathrm{d}_{4}\right)$ bis(isoindoline-1,3-dione) $(37.79 \mathrm{~g}, 116.63 \mathrm{mmol})$. The suspension was stirred at room temperature for 39 h . A distillation set up was installed, and the water was distilled under atmospheric pressure until it was dry. More water ( 150 mL ) was added and distillation was repeated twice. The combined distillate was acidified with concentrated hydrochloric acid until $\mathrm{pH}<2$. Water was removed by rotary evaporator, and the product, $\mathbf{d}_{4}-\mathbf{9 5}$, was obtained as a white solid, $15.9 \mathrm{~g}, 99 \%$.

The mixture of ethane-d $\mathrm{d}_{4}$-1,2-diamine dihydrochloride ( $15.9 \mathrm{~g}, 116.06 \mathrm{mmol}$ ) and toluenesulfonyl chloride ( $50.0 \mathrm{~g}, 262.26 \mathrm{mmol}$ ) in pyridine ( 300 mL ) was heated to reflux for 15 h . Two thirds of the pyridine was removed by distillation. The residue was diluted with water, and the solid was collected by filtration, washed with water and dried under vacuum while being heated. The product, $\mathbf{d}_{4}-\mathbf{9 6}$, was obtained as an off-white solid ( $41.88 \mathrm{~g}, 97 \%$ ) and used in following reactions without further purification. mp 159-162 ${ }^{\circ} \mathrm{C}$; [Found: ( $\mathrm{ESI}^{+}$) $(\mathrm{M}+\mathrm{H})^{+}$373.1186. $\mathrm{C}_{16} \mathrm{H}_{17} \mathrm{D}_{4} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}_{2}$ $(\mathrm{M}+\mathrm{H})$ requires 373.1188]; $v_{\max }$ (neat) $/ \mathrm{cm}^{-1} 3287,1599,1393,1319,1159,1088$, 1001, 818, 808, 783, 667; ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 2.39(6 \mathrm{H}, \mathrm{s}), 7.38(4 \mathrm{H}, \mathrm{d}, J$
$=8.0 \mathrm{~Hz}), 7.57(2 \mathrm{H}, \mathrm{s}), 7.61(4 \mathrm{H}, \mathrm{d}, J=8.0 \mathrm{~Hz}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta$ $20.9,126.4,129.6,137.4,142.7 ; m / z\left(\mathrm{ESI}^{+}\right) 762\left[\left(2 \mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 55 \%\right], 390\left[\left(\mathrm{M}+\mathrm{NH}_{4}\right)^{+}\right.$, 100\%], $373\left[(\mathrm{M}+\mathrm{H})^{+}, 51\right]$.


## Synthesis of $\mathbf{N}, \mathbf{N}^{\prime}$-(ethane-1,2-diyl-d $\mathbf{d}_{4}$ bis(N,4-dimethylbenzenesulfonamide) $\mathbf{d}_{4}$ -

 97:To a solution of $\mathrm{N}, \mathrm{N}^{\prime}$-(ethane-1,2-diyl- $\mathrm{d}_{4}$ )bis(4-methylbenzenesulfonamide, $\mathbf{d}_{4}-\mathbf{9 6}$ ) $(8.0 \mathrm{~g}, 21.51 \mathrm{mmol})$ in DMF ( 50 mL ) was added potassium carbonate $(8.9 \mathrm{~g}, 64.49$ $\mathrm{mmol})$. The mixture was stirred in an ice water bath followed by the addition of iodomethane ( $7.7 \mathrm{~g}, 54.23 \mathrm{mmol}$ ). The mixture was stirred in the cooling bath overnight while the temperature of the reaction was allowed to rise to ambient temperature. The mixture was poured into water ( 200 mL ). The solid was collected by filtration, washed with water and dissolved in dichloromethane ( 90 mL ). The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The product, $\mathrm{d}_{4}-97$, was obtained as an off-white solid, $(8.5 \mathrm{~g}, 98 \%)$. It was used in next reaction without further purification. [Found: $\left(\mathrm{ESI}^{+}\right)(\mathrm{M}+\mathrm{H})^{+}$401.1490. $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{D}_{4} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}_{2}(\mathrm{M}+\mathrm{H})$ requires 401.1501]; $v_{\max }$ (neat) $/ \mathrm{cm}^{-1} 1595,1454,1336,1232,1188,1155,970,869$, 815, 717, $700{ }^{2} \mathrm{H}$ NMR ( $76 \mathrm{MHz}, \mathrm{CHCl}_{3}$, with $\mathrm{CDCl}_{3}$ as internal standard): $3.20 ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 2.44(6 \mathrm{H}, \mathrm{s}), 2.81(6 \mathrm{H}, \mathrm{s}), 7.34(4 \mathrm{H}, \mathrm{d}, J=8.5 \mathrm{~Hz}), 7.67$ $(4 \mathrm{H}, \mathrm{d}, J=8.5 \mathrm{~Hz}) ;{ }^{13} \mathrm{C}$ NMR ( $125 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 21.5,35.8,127.4,129.8,134.4$, 143.6; $\mathrm{m} / \mathrm{z}\left(\mathrm{ESI}^{+}\right) 818\left[\left(2 \mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 54 \%\right], 418\left[\left(\mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 52 \%\right], 400\left[(\mathrm{M}+\mathrm{H})^{+}\right.$, 100], 216 (12).


## The synthesis of $\mathbf{N}, \mathbf{N}^{\prime}$-dimethylethane-d $\mathbf{d}_{\mathbf{4}} \mathbf{- 1 , 2 - d i a m i n e , ~} \mathbf{1 0 0}$ :

The mixture of $\mathrm{N}, \mathrm{N}^{\prime}$-(ethane-1,2-diyl- $\mathrm{d}_{4}$ )bis( $\mathrm{N}, 4$-dimethylbenzenesulfonamide, $\mathbf{d}_{4}-97$ ) $(8.4 \mathrm{~g}, 21.0 \mathrm{mmol})$ in hydrobromic acid ( $50 \mathrm{~mL}, 48 \% \mathrm{HBr}$ ) and AcOH ( 25 mL ) was heated to reflux for 3 h . Normal distillation was set up to remove the volatiles. The residue was dried under vacuum while heated. Then the residue was dissolved in water ( 30 mL ), and the solution was basified by adding solid $\mathrm{NaOH}(3.0 \mathrm{~g})$. The solution was distilled under atmospheric pressure to dry. Water ( 30 mL ) was added and the distillation was repeated twice. The combined distillate was acidified with concentrated hydrochloric acid to $\mathrm{pH}<2$. The water was removed by rotary evaporator, and the white solid obtained was dried under vacuum while bring heated. The product, $\mathbf{d}_{4}-\mathbf{9 8},(3.06 \mathrm{~g}, 88 \%)$ was used in next step without further purification. The solid obtained ( $2.94 \mathrm{~g}, 17.81 \mathrm{mmol}$ ) was put into a Schlenk flask and cooled in an acetone dry ice bath. $\mathrm{NaH}(1.28 \mathrm{~g}, 53.33 \mathrm{mmol})$ was added. $\mathrm{NH}_{3}(80 \mathrm{~mL})$ was condensed into the mixture, and the mixture was stirred in the cooling bath for 2 h . The cooling bath was removed, and the ammonia was allowed to evaporate overnight. A distillation set up was installed with an air condenser. The receiving flask was emerged in an acetone dry ice bath. The mixture was heated gently with occasional warming of the whole distillation path with hot air. The product, 100, was obtained as a colourless liquid, ( $1.04 \mathrm{~g}, 63 \%$ ). [Found: $\left(\mathrm{CI}^{+}\right.$corona) $(\mathrm{M}+\mathrm{H})^{+} 93.1317 . \mathrm{C}_{4} \mathrm{H}_{9} \mathrm{D}_{4} \mathrm{~N}_{2}$ $(\mathrm{M}+\mathrm{H})$ requires 93.1324]; $v_{\max }$ (neat)/ $\mathrm{cm}^{-1} 3293,2968,2940,2851,2791,2187,2070$, 1659, 1552, 1474, 1450, 1366, 1238, 1147, 911, 808, 698; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , $\left.\mathrm{CDCl}_{3}\right): \delta 1.20(2 \mathrm{H}, \mathrm{s}), 2.28(6 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 35.7$, 49.7(quintet, $J_{\mathrm{C}-\mathrm{D}}=20 \mathrm{~Hz}$ ); $m / z\left(\mathrm{CI}^{+}\right.$corona) 177 (19), $121(71), 93\left[(\mathrm{M}+\mathrm{H})^{+}, 100 \%\right]$, 91 (15), 79 (16), 62 (22).

## The hexadeutero series:



The synthesis of $\mathbf{N}, \mathbf{N}^{\prime}$-(ethane-1,2-diyl)bis(4-methyl-N-(methyl-d $\mathbf{d}_{3}$ ) benzenesulfonamide, $\mathbf{d}_{6}-97$ ):
To the mixture of $\mathrm{N}, \mathrm{N}^{\prime}$-(ethane-1,2-diyl)bis(4-methylbenzenesulfonamide) ( 7.4 g , $20.11 \mathrm{mmol})$ and potassium carbonate $(60.87 \mathrm{mmol})$ in DMF $(50 \mathrm{~mL})$ stirred in an ice water bath was added $\mathrm{CD}_{3} \mathrm{I}(7.3 \mathrm{~g}, 50.34 \mathrm{mmol})$. The mixture was stirred in the ice water bath for 3 h , then at room temperature overnight. The mixture was poured into water ( 250 mL ). The solid was collected by filtration, washed with water, and dissolved in dichloromethane ( 100 mL ). The organic layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The product, $\mathbf{d}_{\mathbf{6}} \mathbf{- 9 7}$, was obtained as an off-white solid (7.97 $\mathrm{g}, 98 \%)$. The product was used in next reaction without further purification. $\mathrm{mp} 164-$ $168{ }^{\circ} \mathrm{C}$; [Found: ( $\mathrm{ESI}^{+}$) (M+H) ${ }^{+}$403.1622. $\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{D}_{6} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}_{2}(\mathrm{M}+\mathrm{H})$ requires 403.1627]; $v_{\max }$ (neat) $/ \mathrm{cm}^{-1} 1595,1339,1159,1090,833,816,714,694,642$; ${ }^{2} \mathrm{HNMR}\left(76 \mathrm{MHz}, \mathrm{CHCl}_{3}\right.$, with $\mathrm{CDCl}_{3}$ as internal standard): 2.80; ${ }^{1} \mathrm{H}$ NMR (400 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 2.46(6 \mathrm{H}, \mathrm{s}), 3.23(4 \mathrm{H}, \mathrm{s}), 7.67-7.71(4 \mathrm{H}, \mathrm{m}) ;{ }^{13} \mathrm{C}$ NMR ( 100 MHz , $\left.\mathrm{CDCl}_{3}\right): \delta 21.01,48.37,126.89,129.29,133.90,143.11 ; \mathrm{m} / \mathrm{z}\left(\mathrm{ESI}^{+}\right) 822\left[\left(2 \mathrm{M}+\mathrm{NH}_{4}\right)^{+}\right.$, $75 \%], 420\left[\left(\mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 53\right], 403\left[(\mathrm{M}+\mathrm{H})^{+}, 100\right], 215(9)$.


## Synthesis of $N, N^{\prime}$-bis $\left(\right.$ methyl-d $\left._{3}\right)$ ethane-1,2-diamine 99:

The mixture of $\mathrm{N}, \mathrm{N}^{\prime}$-(ethane-1,2-diyl)bis(4-methyl-N-(methyl- $\mathrm{d}_{3}$ ) benzenesulfonamide, $\mathbf{d}_{6}-97$ ) ( $7.86 \mathrm{~g}, 19.55 \mathrm{mmol}$ ) in hydrobromic acid ( $50 \mathrm{~mL}, 48 \% \mathrm{HBr}$ ) and AcOH ( 25 mL ) was heated to reflux for 2 h . Normal distillation was set up to remove the volatiles. The residue was dried under vacuum while being heated. The residue was dissolved in water, and the solution was basified by adding solid $\mathrm{NaOH}(3.0 \mathrm{~g})$. The solution ( $\sim 50 \mathrm{~mL}$ ) was distilled under atmospheric pressure to dryness. Water (30 mL ) was added and the distillation was repeated twice. The combined distillate was acidified with concentrated hydrochloric acid to $\mathrm{pH}<2$. The water was removed by rotary evaporator, and the solid obtained was dried under vacuum while being heated,
to obtain the product $\mathbf{d}_{\mathbf{6}} \mathbf{- 9 8}(3.2 \mathrm{~g}, 98 \%)$ as a white solid. The product was used in the next step without further purification.

The solid just obtained ( $3.1 \mathrm{~g}, 18.56 \mathrm{mmol}$ ) was put into a Schlenk flask and cooled in an acetone dry ice bath. $\mathrm{NaH}(1.34 \mathrm{~g}, 55.83 \mathrm{mmol})$ was added. $\mathrm{NH}_{3}(80 \mathrm{~mL})$ was condensed into the mixture, and the mixture was stirred in the cooling bath for 2 h . The cooling bath was removed, and the ammonia was allowed to evaporate overnight. A distillation set up was installed with an air condenser. The receiving flask was immersed in an acetone dry ice bath. The mixture was heated gently occasional warming of the whole distillation path with hot air. The product, 99 , was obtained as a colourless liquid, ( 0.988 g , 56\%). [Found: $\left(\mathrm{CI}^{+}\right.$corona) $(\mathrm{M}+\mathrm{H})^{+} 95.1443$. $\mathrm{C}_{4} \mathrm{H}_{7} \mathrm{D}_{6} \mathrm{~N}_{2}$ $(\mathrm{M}+\mathrm{H})$ requires 95.1450]; $v_{\max }$ (neat) $/ \mathrm{cm}^{-1} 3283,2936,2889,2820,2181,2050,1460$, $1435,1352,1236,1145,1026,908,731 ;{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 1.14(2 \mathrm{H}, \mathrm{s})$, $2.53(4 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 34.9$ (septet, $J_{\mathrm{C}-\mathrm{D}} 20 \mathrm{~Hz}$ ), $50.7 ; \mathrm{m} / \mathrm{z}\left(\mathrm{Cl}^{+}\right.$ corona) $117\left[(\mathrm{M}+\mathrm{Na})^{+}, 5 \%\right], 107(22), 95\left[(\mathrm{M}+\mathrm{H})^{+}, 100 \%\right], 89(15)$.

## The decadeutero series:



Synthesis of $\mathbf{N}^{2} \mathbf{N}^{\prime}$-(ethane-1,2-diyl-d $\mathbf{d}_{4}$ )bis(4-methyl-N-(methyl-d $\mathbf{d}_{3}$ )-benzenesulfonamide $\mathrm{d}_{10}-97$ ):

To a solution of $\mathrm{N}_{2} \mathrm{~N}^{\prime}$-(ethane-1,2-diyl- $\mathrm{d}_{4}$ )bis(4-methylbenzenesulfonamide, $\mathbf{d}_{4}-\mathbf{9 6}$ ) $(8.0 \mathrm{~g}, 21.51 \mathrm{mmol})$ in DMF $(50 \mathrm{~mL})$ was added potassium carbonate $(8.9 \mathrm{~g}, 64.49$ mmol ). The mixture was stirred in an ice water bath followed by the addition of iodomethane- $\mathrm{d}_{3}(7.8 \mathrm{~g}, 54.79 \mathrm{mmol})$. The mixture was stirred in the cooling bath overnight while the temperature was the reaction allowed to warm to ambient temperature. The mixture was poured into water ( 200 mL ). The solid was collected by filtration, washed with water and dissolved in dichloromethane ( 90 mL ). The organic
layer was dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated. The product, $\mathbf{d}_{10}-\mathbf{9 7}$, was obtained as off-white solid, ( $8.64 \mathrm{~g}, 99 \%$ ). It was used in the next reaction without further purification. [Found: $\left(\mathrm{ESI}^{+}\right)(\mathrm{M}+\mathrm{H})^{+}$407.1872. $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{D}_{10} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}_{2}(\mathrm{M}+\mathrm{H})$ requires 407.1878]; $v_{\max }$ (neat) $/ \mathrm{cm}^{-1} 1595,1337,1173,1151,816,714,692,640 ;{ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 2.43(6 \mathrm{H}, \mathrm{s}), 7.32(4 \mathrm{H}, \mathrm{d}, J 8.4 \mathrm{~Hz}), 7.67(4 \mathrm{H}, \mathrm{d}, J 8.4 \mathrm{~Hz})$; ${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 21.0,34.5$ (septet, $J_{\mathrm{C}-\mathrm{D}} 21 \mathrm{~Hz}$ ), 47.4 (quintet, $J_{\mathrm{C}-\mathrm{D}}$ $21 \mathrm{~Hz}), 126.85,129.3,133.9,143.1 ; \mathrm{m} / \mathrm{z}\left(\mathrm{ESI}^{+}\right) 830\left[\left(2 \mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 71 \%\right], 424$ $\left[\left(\mathrm{M}+\mathrm{NH}_{4}\right)^{+}, 52 \%\right], 407\left[(\mathrm{M}+\mathrm{H})^{+}, 100 \%\right], 219$ (9).

## The synthesis of $\mathbf{N}, \mathbf{N}^{\prime}$-bis $\left(\right.$ methyl $\left.^{2} \mathbf{d}_{3}\right)$ ethane- $\mathbf{d}_{4}$-1,2-diamine 101:



N,N'-(ethane-1,2-diyl-d $\mathbf{d}_{4}$ )bis(N,4-dimethylbenzenesulfonamide, $\mathbf{d}_{\mathbf{1 0}} \mathbf{- 9 7}$ ) ( $8.53 \mathrm{~g}, 21.01$ mmol ) in hydrobromic acid ( $50 \mathrm{~mL}, 48 \% \mathrm{HBr}$ ) and $\mathrm{AcOH}(25 \mathrm{~mL})$ was heated to reflux for 3 h . Normal distillation was set up to remove the volatiles. The residue was dried under vacuum while heated. Then the residue was dissolved in water ( 30 mL ), and the solution was basified by adding solid $\mathrm{NaOH}(3.0 \mathrm{~g})$. The solution was distilled under atmospheric pressure to dry. Water ( 30 mL ) was added and the distillation was repeated twice. The combined distillate was acidified with concentrated hydrochloric acid to $\mathrm{pH}<2$. The water was removed by rotary evaporator, and the white solid, $\mathbf{d}_{10}{ }^{-}$ 98, obtained was dried under vacuum while heated, ( $3.41 \mathrm{~g}, 95 \%$ ). The product was used in the next step without further purification.
The solid obtained ( $3.28 \mathrm{~g}, 19.18 \mathrm{mmol}$ ) was put into a Schlenk flask and cooled in an acetone dry ice bath. $\mathrm{NaH}(1.38 \mathrm{~g}, 57.5 \mathrm{mmol})$ was added. $\mathrm{NH}_{3}(80 \mathrm{~mL})$ was condensed into the mixture, and the mixture was stirred in the cooling bath for 2 h . The cooling bath was removed, and the ammonia was evaporated naturally overnight. A distillation set up was installed with an air condenser. The receiving flask was emerged in an acetone dry ice bath. The mixture was heated gently occasional warming of the whole distillation path with hot air. The product, 101, was obtained as
a colourless liquid ( $1.038 \mathrm{~g}, 55 \%$ ). [Found: $\left(\mathrm{CI}^{+}\right.$corona) $(\mathrm{M}+\mathrm{H})^{+}$99.1694. $\mathrm{C}_{4} \mathrm{H}_{3} \mathrm{D}_{10} \mathrm{~N}_{2}(\mathrm{M}+\mathrm{H})$ requires 99.1701]; $v_{\max }$ (neat) $/ \mathrm{cm}^{-1} 3285,2181,2048,1418,1151$, 1053, 1013, 970, 764, 689; ${ }^{1} \mathrm{H}$ NMR (400MHz, $\mathrm{CDCl}_{3}$ ): $1.20(2 \mathrm{H}, \mathrm{s}) ;{ }^{13} \mathrm{C}$ NMR ( 100 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta 34.8$, (septet, $J_{\mathrm{C}-\mathrm{D}}=20 \mathrm{~Hz}$ ), 49.6 (quintet, $J_{\mathrm{C}-\mathrm{D}}=20 \mathrm{~Hz}$ ); $m / z\left(\mathrm{Cl}^{+}\right.$ corona) 139 (12), $99\left[(\mathrm{M}+\mathrm{H})^{+}, 100 \%\right], 95$ (19).

## Comparative testing of diamines $90,99-101$ as mediators in the coupling reaction

 between iodoarene 33 and benzene.

General procedure:
A mixture of 2,6-dimethyl-1-iodobenzene $33(232 \mathrm{mg}, 1.0 \mathrm{mmol}$ ), potassium tertbutoxide ( $224 \mathrm{mg}, 2.0 \mathrm{mmol}$ ) and additive ( $0.1 \mathrm{mmol} ; 0.5 \mathrm{mmol}$ of the diamine was weighed and made into 25 mL solution of benzene in a volumetric flask, 5 mL of the solution was used for every reaction) in 10 mL benzene was sealed in a 15 mL pressure tube in a glove box. The tube was removed out of the glove box and heated to the specified temperature for 4 h behind a shield. After cooling to room temperature, the reaction was quenched by water ( 30 mL ). The mixture was extracted with diethyl ether $(15 \mathrm{~mL})$ + hexane $(15 \mathrm{~mL})$. The organic layer was dried over sodium sulfate. Filtration and concentration gave a residue, which was purified by careful chromatography, eluting with pure hexane. The products were: recovered starting material (2,6-dimethyl-1-iodobenzene), and a mixture of biphenyl and dimethylbiphenyl (see Table below)

Table 2. Deuterium-labelled and unlabelled additives for reaction with $\mathrm{KO} t \mathrm{Bu}$ and substrate 33.

| Additive | Temperature ( ${ }^{\circ} \mathrm{C}$ ) | Starting Material (mg) | Product (34 + 35) <br> $(\mathrm{mg})$ |
| :---: | :---: | :---: | :--- |
| $-\mathrm{NH} \mathbf{~ H N}-$ <br> $\mathbf{9 0}$ | 110 | 129 | 16 |


| $\mathrm{D}_{3} \mathrm{C}-\sqrt{\mathrm{NH}} \mathrm{HN}-\mathrm{CD}_{3}$ 99 | 110 | 170 | 10 |
| :---: | :---: | :---: | :---: |
|  | 110 | 209 | 0.5 |
|  | 110 | 215 | $<0.5$ |
| $\begin{gathered} -\mathrm{NH} \mathrm{HN}- \\ 90 \end{gathered}$ | 135 | 48 | 49 |
| $\mathrm{D}_{3} \mathrm{C}-\mathrm{NH} \mathrm{HN}-\mathrm{CD}_{3}$ | 135 | 65 | 47 |
|  | 135 | 128 | 28 |
|  | 135 | 180 | 10 |

## Coupling reactions of 4-iodotoluene using various additives (Figure 4 in paper):

General reaction procedure: Substrate (4-iodotoluene 70) and additive were added to a pressure tube. $\mathrm{KO}^{t} \mathrm{Bu}$ and benzene were added into the tube in glove box. The tube was then sealed properly before removing from the glove box and reaction was carried out at $130{ }^{\circ} \mathrm{C}$ for 3 h . Later, reaction was stopped and pressure tube was cooled to room temperature. Reaction contents were quenched with water ( 10 mL ) and extracted with diethyl ether ( $3 \times 10 \mathrm{~mL}$ ). The combined ether layers were then washed once again with water ( 10 mL ), brine ( 10 mL ) and dried over anhydrous
sodium sulfate. The crude product was obtained after evaporation of solvent under reduced pressure using a rotary evaporator. The crude product was then adsorbed onto silica and purified by column chromatography, providing the corresponding reduced products or recovered starting materials in yields as stated.

## Blank reaction (no additive)



4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with $\mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene ( 10 mL ) under general reaction procedure and afforded 4-methyl-1,1'biphenyl 71 ( $0.006 \mathrm{~g}, 4 \%$ ) as a white solid m.p. $46-48{ }^{\circ} \mathrm{C}$ (lit. ${ }^{9} 46-48{ }^{\circ} \mathrm{C}$ ), and recovered starting material 70 ( $0.194 \mathrm{~g}, 89 \%$ ). For 4-methyl-1,1'-biphenyl 71: [Found: $\left(\mathrm{Cl}^{+}\right.$corona) $(\mathrm{M}+\mathrm{H})^{+}$169.1012. $\mathrm{C}_{13} \mathrm{H}_{13}(\mathrm{M}+\mathrm{H})$ requires 169.1012]; ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 2.44\left(3 \mathrm{H}, \mathrm{s}, C H_{3}\right), 7.29(2 \mathrm{H}, \mathrm{d}, J=8.0 \mathrm{~Hz}, \mathrm{ArH}), 7.34-7.38(1 \mathrm{H}$, $\mathrm{m}, \mathrm{ArH}), 7.46(2 \mathrm{H}, \mathrm{t}, J=8.0 \mathrm{~Hz}, \mathrm{ArH}), 7.54(2 \mathrm{H}, \mathrm{d}, J=8.0 \mathrm{~Hz}, \mathrm{ArH}), 7.62(2 \mathrm{H}, \mathrm{d}, J$ $=8.4 \mathrm{~Hz}, \quad \mathrm{ArH}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 21.2\left(\mathrm{CH}_{3}\right), 127.07(\mathrm{CH}), 127.1$ (CH), $128.8(\mathrm{CH}), 129.6(\mathrm{CH}), 137.1(\mathrm{C}), 138.5(\mathrm{C}), 141.3(\mathrm{C}) ; m / z\left(\mathrm{CI}^{+}\right.$corona) 271 (83), $169\left[(\mathrm{M}+\mathrm{H})^{+}, 100 \%\right]$.

Additive: 2-(methylamino)acetic acid $\mathbf{8}$


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with 2-(methylamino)acetic acid $\mathbf{8}$ $(0.018 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1, 1'-biphenyl $71(0.1526 \mathrm{~g}, 91 \%)$ as a white solid.

## Additive: ( $L$ )-proline 9



4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with ( $L$ )-proline $9(0.023 \mathrm{~g}, 0.2$ $\mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.154 \mathrm{~g}, 92 \%)$ as a white solid.

## Additive: 2-amino-2-methylpropanoic acid 41



4-Iodotoluene 70 ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with 2-amino-2-methylpropanoic acid $41(0.021 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.014 \mathrm{~g}, 8 \%)$ as a white solid and recovered starting material ( $0.161 \mathrm{~g}, 74 \%$ ).

Additive: 2-(dimethylamino)acetic acid $\mathbf{4 2}$


4-Iodotoluene 70 ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with 2-(dimethylamino) acetic acid $\mathbf{4 2}$ $(0.021 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.020 \mathrm{~g}, 12 \%)$ as a white solid and recovered starting material ( $0.139 \mathrm{~g}, 64 \%$ ).

Additive: glycine 43


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with glycine $43(0.015 \mathrm{~g}, 0.2 \mathrm{mmol})$, $\mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.096 \mathrm{~g}, 57 \%)$ as a white solid and recovered starting material ( $0.0586 \mathrm{~g}, 27 \%$ ).

Repeated experiment: The above reaction was carried out for 5 h and afforded 4-methyl-1,1'-biphenyl $71(0.149 \mathrm{~g}, 89 \%)$ as a white solid.

Additive: 1,4-dipropylpiperazine-2,5-dione 44


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with 1,4-dipropylpiperazine-2,5dione $44(0.0396 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl 71 ( $0.148 \mathrm{~g}, 88 \%$ ) as a white solid.

## Additive: piperazine-2,5-dione 47



4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with piperazine-2,5-dione 47 ( 0.023 $\mathrm{g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.0206 \mathrm{~g}, 12 \%)$ as a white solid and recovered starting material ( $0.136 \mathrm{~g}, 62 \%$ ).

Additive: 2-(dimethylamino)- $N, N$-dimethylacetamide 51


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with 2-(dimethylamino)- $N, N$ dimethylacetamide $51(0.026 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl 71 $(0.092 \mathrm{~g}, 55 \%)$ as a white solid and recovered starting material ( $0.063 \mathrm{~g}, 29 \%$ ).

Repeated experiment: The above reaction was carried out for 5 h and afforded 4-methyl-1,1'-biphenyl ( $0.145 \mathrm{~g}, 86 \%$ ) as a white solid.

Additive: 1-methylpyrrolidin-2-one 52


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with 1-methylpyrrolidin-2-one $\mathbf{5 2}$ $(0.0198 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.130 \mathrm{~g}, 77 \%)$ as a white solid and recovered starting material ( $0.022 \mathrm{~g}, 10 \%$ ).

## Additive: 3,3-dimethylbutan-2-one 54



4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with 3,3-dimethylbutan-2-one $\mathbf{5 4}$ $(0.020 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.072 \mathrm{~g}, 43 \%)$ as a white solid and recovered starting material ( $0.091 \mathrm{~g}, 42 \%$ ).

## Additive: ethyl acetate $5 \mathbf{5}$



4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with ethyl acetate $55(0.0264 \mathrm{~g}, 0.3$ $\mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.144 \mathrm{~g}, 86 \%)$ as a white solid.

Additive: ethyl 2-ethoxyacetate 56


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with ethyl 2-ethoxyacetate 56 ( 0.0264 $\mathrm{g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.142 \mathrm{~g}, 84 \%)$ as a white solid.

## Additive: ethyl 2,2-diethoxyacetate 57



4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with ethyl 2,2-diethoxyacetate $\mathbf{5 7}$ $(0.035 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.147 \mathrm{~g}, 88 \%)$ as a white solid.

Additive: $\gamma$-butyrolactone 58


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with $\gamma$-butyrolactone 58 ( $0.026 \mathrm{~g}, 0.3$ $\mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.145 \mathrm{~g}, 86 \%)$ as a white solid.

## Additive: dibutylamine 64



4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with dibutylamine $\mathbf{6 4}(0.026 \mathrm{~g}, 0.2$ $\mathrm{mmol}), \mathrm{KO}^{\mathrm{t}} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.021 \mathrm{~g}, 13 \%)$ as a white solid and recovered starting material ( $0.152 \mathrm{~g}, 70 \%$ ).

Additive: $(1 R, 2 S)$-cyclohexane-1,2-diamine 72


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with ( $1 R, 2 S$ )-cyclohexane-1,2diamine $72(0.023 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$
under general reaction procedure and afforded 4-methyl-1,1'-biphenyl 71 ( 0.152 g , $90 \%$ ) as a white solid.

Additive: $(1 R, 2 R)$-cyclohexane-1,2-diamine 73


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with $(1 R, 2 R)$-cyclohexane-1,2diamine $73(0.023 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene ( 10 mL ) under general reaction procedure and afforded 4-methyl-1,1'-biphenyl 71 ( 0.150 g , $89 \%$ ) as a white solid.

## Additional examples:

Additive: 1,4-dioxane-2,5-dione AE 1


4-Iodotoluene $70(0.218 \mathrm{~g}, 1 \mathrm{mmol})$ was treated with 1,4-dioxane-2,5-dione AE 1 $(0.035 \mathrm{~g}, 0.3 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl 71 ( $0.122 \mathrm{~g}, 73 \%$ ) as a white solid and recovered starting material $70(0.032 \mathrm{~g}, 15 \%)$.

## Additive: $N, N$-dimethylacetamide AE 2



4-Iodotoluene 70 ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with $\mathrm{N}, \mathrm{N}$-dimethylacetamide AE 2 $(0.0174 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $71(0.024 \mathrm{~g}, 14 \%)$ as a white solid and recovered starting material 70 ( $0.173 \mathrm{~g}, 79 \%$ ).

## Additive: cyclohexanone AE 3



4-Iodotoluene 70 ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with cyclohexanone AE 3 ( 0.0196 g , $0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl ( $0.074 \mathrm{~g}, 44 \%$ ) as a white solid and recovered starting material $70(0.093 \mathrm{~g}, 43 \%)$.

## Additive: 2-methoxycyclohexanone AE 4



4-Iodotoluene ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with 2-methoxycyclohexanone ( 0.0256 $\mathrm{g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $(0.107 \mathrm{~g}, 64 \%)$ as a white solid and recovered starting material ( $0.058 \mathrm{~g}, 27 \%$ ).

## Additive: methyl 2-(dimethylamino)acetate AE 5



4-Iodotoluene ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with methyl 2-(dimethylamino)acetate $(0.0234 \mathrm{~g}, 0.2 \mathrm{mmol}), \mathrm{KO}^{t} \mathrm{Bu}(0.224 \mathrm{~g}, 2 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl ( $0.048 \mathrm{~g}, 29 \%$ ) as a white solid and recovered starting material ( $0.104 \mathrm{~g}, 48 \%$ ).

## Additive: acetic acid AE 6



4-Iodotoluene ( $0.218 \mathrm{~g}, 1 \mathrm{mmol}$ ) was treated with dibutylamine ( $0.012 \mathrm{~g}, 0.2 \mathrm{mmol}$ ), $\mathrm{KO}^{t} \mathrm{Bu}(0.336 \mathrm{~g}, 3 \mathrm{mmol})$ and benzene $(10 \mathrm{~mL})$ under general reaction procedure and afforded 4-methyl-1,1'-biphenyl $(0.016 \mathrm{~g}, 10 \%)$ as a white solid and recovered starting material ( $0.176 \mathrm{~g}, 81 \%$ ).
1.

All calculations were performed using Density Functional Theory (DFT) [10, 11] using the Gaussian 09 [12] software package. All minima (reactants, intermediates, products) and maxima (transition states) were optimised using the M062X [13] functional with a $6-311 \mathrm{G}(\mathrm{d}, \mathrm{p})$ [14-16] basis set. All reactant and product structures were optimised as their respective complexes. Solvation was modelled implicitly using the Conductor-like Polarisable Continuum Model (CPCM) [17,18] for a solvent of benzene. Frequency calculations were performed on all optimised structures in order to characterise minima (zero negative frequencies) and maxima (single imaginary frequency. All profiles are plotted using the Gibbs free energy values (electronic energy values are quoted in brackets for instances where transition states do not appear as maxima in the free energy plot). GaussView 5.0 .8 was used for the visualisation of structures.


Figure 1: Reaction Profile for the reduction of $\mathbf{7 5}$ by hydride transfer from $\mathbf{7 6}$


Figure 2: Reaction Profile for the loss of $\mathrm{H}_{2}$ from a complex of $\mathbf{7 6}$ and $\mathbf{6 1}$


Figure 3: Formation of 46


Figure 4: Visualisation of structure 46

Coordinates for optimised geometries of all species mentioned in the text in XYZ format.

Reaction complex of $\mathbf{7 5}$ and 76

|  |  |  |  |
| :--- | ---: | ---: | ---: |
| O | 0.124546 | 1.636340 | 0.785836 |
| O | -2.339316 | 3.044616 | -0.708130 |
| K | -0.042469 | 3.937630 | 0.107764 |
| H | 0.553972 | -0.278479 | 0.126497 |
| C | 1.038716 | 0.673535 | 0.469845 |
| C | 1.960813 | 1.098878 | -0.690119 |
| C | 1.926068 | 0.268952 | 1.659219 |
| C | 3.007268 | 0.042786 | -1.051243 |
| H | 2.467326 | 2.027136 | -0.383783 |
| H | 1.340194 | 1.341257 | -1.562032 |
| C | 2.985314 | -0.781173 | 1.306444 |
| H | 2.419253 | 1.181124 | 2.022602 |
| H | 1.281980 | -0.087912 | 2.469116 |
| C | 3.889855 | -0.307038 | 0.157661 |
| H | 3.614433 | 0.388040 | -1.892327 |
| H | 2.486473 | -0.862880 | -1.386324 |
| H | 3.579049 | -1.008029 | 2.195111 |
| H | 2.484842 | -1.712786 | 1.012150 |
| H | 4.363920 | 0.628364 | 0.495250 |
| C | -2.447559 | 1.862381 | -0.427027 |
| C | -2.054787 | 0.776191 | -1.392626 |
| C | -2.926832 | 1.405932 | 0.923151 |
| C | -3.042299 | -0.395906 | -1.392213 |
| H | -1.073457 | 0.440161 | -1.038178 |
| H | -1.933269 | 1.215228 | -2.384659 |
| C | -3.848078 | 0.179396 | 0.887818 |
| H | -1.982909 | 1.163737 | 1.431804 |
| H | -3.390401 | 2.251871 | 1.434352 |
| C | -3.262208 | -0.946834 | 0.024418 |
| H | -2.667962 | -1.168317 | -2.066668 |
| H | -4.002075 | -0.056107 | -1.798129 |
| H | -3.996385 | -0.155309 | 1.915391 |
| H | -4.832425 | 0.464486 | 0.498049 |
| H | -2.273462 | -1.190491 | 0.442928 |
| C | 5.059509 | -1.274994 | -0.182098 |
| C | 6.037160 | -0.587681 | -1.146719 |
| H | 6.892370 | -1.240162 | -1.345476 |
| H | 5.571926 | -0.356435 | -2.106725 |
| H | 6.417377 | 0.344348 | -0.716920 |
| C | 4.564421 | -2.575074 | -0.828607 |
| H | 3.827072 | -3.080587 | -0.199797 |
| H | 4.113185 | -2.392858 | -1.806705 |
| H | 5.403415 | -3.262076 | -0.973992 |
| C | 5.840355 | -1.628625 | 1.092424 |
|  |  |  |  |


| H | 6.763970 | -2.153946 | 0.833293 |
| :--- | ---: | ---: | ---: |
| H | 6.108914 | -0.725899 | 1.650547 |
| H | 5.265574 | -2.279876 | 1.753695 |
| C | -4.084374 | -2.266302 | 0.051702 |
| C | -5.405584 | -2.137738 | -0.717153 |
| H | -5.993206 | -3.052392 | -0.597857 |
| H | -6.009688 | -1.304937 | -0.347236 |
| H | -5.237440 | -1.990542 | -1.786692 |
| C | -3.254692 | -3.396592 | -0.574476 |
| H | -2.314063 | -3.533582 | -0.033000 |
| H | -3.809480 | -4.337990 | -0.531489 |
| H | -3.019236 | -3.203372 | -1.622962 |
| C | -4.394794 | -2.666820 | 1.501071 |
| H | -4.803082 | -3.680682 | 1.528521 |
| H | -3.489401 | -2.649565 | 2.115941 |
| H | -5.131858 | -2.002798 | 1.957703 |

Transition state complex 78

| O | -1.114147 | 2.973426 | 0.701116 |
| :--- | ---: | ---: | ---: |
| O | 1.118842 | 1.956491 | -0.846562 |
| K | 0.613069 | 4.344147 | -0.357910 |
| H | -0.568551 | 1.014669 | 0.111398 |
| C | -1.559602 | 1.790558 | 0.472822 |
| C | -2.080445 | 0.996280 | 1.673353 |
| C | -2.427100 | 1.607855 | -0.776351 |
| C | -2.441056 | -0.448454 | 1.334400 |
| H | -2.970724 | 1.529771 | 2.032744 |
| H | -1.333962 | 1.047762 | 2.471106 |
| C | -2.834544 | 0.159772 | -1.060129 |
| H | -3.321766 | 2.226904 | -0.625409 |
| H | -1.879833 | 2.032655 | -1.624590 |
| C | -3.442566 | -0.530657 | 0.171055 |
| H | -2.836895 | -0.942377 | 2.224779 |
| H | -1.526149 | -0.984937 | 1.055529 |
| H | -3.542489 | 0.152681 | -1.891410 |
| H | -1.955222 | -0.404403 | -1.388130 |
| H | -4.332217 | 0.049986 | 0.461270 |
| C | 0.773877 | 0.891806 | -0.248078 |
| C | 1.333739 | 0.651110 | 1.151399 |
| C | 0.747848 | -0.400037 | -1.062396 |
| C | 2.786916 | 0.181349 | 0.994243 |
| H | 0.752346 | -0.116397 | 1.675249 |
| H | 1.265490 | 1.583926 | 1.717540 |
| C | 2.201658 | -0.879288 | -1.210607 |
| H | 0.155569 | -1.172561 | -0.559739 |
| H | 0.306804 | -0.201343 | -2.042298 |
| C | 2.868565 | -1.109153 | 0.158406 |
| H | 3.229413 | 0.032261 | 1.981312 |


|  |  |  |  |
| :--- | ---: | ---: | ---: |
| H | 3.348786 | 0.978302 | 0.495417 |
| H | 2.214314 | -1.793815 | -1.807239 |
| H | 2.754228 | -0.113576 | -1.765135 |
| H | 2.267556 | -1.868628 | 0.683509 |
| C | -3.943584 | -1.978189 | -0.106875 |
| C | -4.772015 | -2.476680 | 1.086232 |
| H | -5.177653 | -3.470233 | 0.875035 |
| H | -4.176821 | -2.553293 | 1.998056 |
| H | -5.612638 | -1.804042 | 1.282022 |
| C | -2.780625 | -2.952417 | -0.340003 |
| H | -2.131084 | -2.619956 | -1.154499 |
| H | -2.169808 | -3.071184 | 0.558137 |
| H | -3.170472 | -3.938719 | -0.608637 |
| C | -4.855857 | -1.995746 | -1.342287 |
| H | -5.347915 | -2.968303 | -1.431428 |
| H | -5.633185 | -1.228718 | -1.264414 |
| H | -4.297236 | -1.823511 | -2.264433 |
| C | 4.305119 | -1.698138 | 0.062261 |
| C | 5.275728 | -0.739764 | -0.639339 |
| H | 6.269001 | -1.194528 | -0.698875 |
| H | 4.952659 | -0.514463 | -1.658469 |
| H | 5.374724 | 0.202305 | -0.094741 |
| C | 4.840931 | -1.997389 | 1.470680 |
| H | 4.134501 | -2.614192 | 2.035108 |
| H | 5.786303 | -2.542771 | 1.404012 |
| H | 5.030327 | -1.086102 | 2.041215 |
| C | 4.274825 | -3.023774 | -0.712729 |
| H | 5.247830 | -3.518439 | -0.646365 |
| H | 3.522585 | -3.702750 | -0.298746 |
| H | 4.055453 | -2.874378 | -1.771363 |

Reaction complex of $\mathbf{7 5}$ and $\mathbf{7 4}$

| O | -1.469400 | 3.034511 | 0.582661 |
| :--- | ---: | ---: | ---: |
| O | 0.894034 | 1.296847 | -0.777671 |
| K | 0.748918 | 3.671251 | -0.693308 |
| H | -0.339956 | 0.281218 | 0.534903 |
| C | -2.153118 | 2.045883 | 0.384527 |
| C | -3.049476 | 1.503238 | 1.472588 |
| C | -2.211891 | 1.409788 | -0.982435 |
| C | -3.319963 | 0.002966 | 1.358403 |
| H | -3.996907 | 2.049803 | 1.368666 |
| H | -2.622709 | 1.783067 | 2.437423 |
| C | -2.693214 | -0.047339 | -1.043330 |
| H | -2.884627 | 2.052207 | -1.566355 |
| H | -1.198343 | 1.492748 | -1.394524 |
| C | -3.813208 | -0.370504 | -0.046067 |
| H | -4.042075 | -0.282428 | 2.126061 |
| H | -2.394233 | -0.542521 | 1.570177 |


|  |  | -3.015123 | -0.248289 |
| :--- | ---: | ---: | ---: |
| H | -2.066197 |  |  |
| H | -1.839991 | -0.703248 | -0.845682 |
| H | -4.672078 | 0.276777 | -0.284517 |
| C | 0.708520 | 0.305683 | 0.137857 |
| C | 1.615776 | 0.475131 | 1.378491 |
| C | 0.983433 | -1.092919 | -0.453368 |
| C | 3.087692 | 0.344051 | 0.985576 |
| H | 1.366953 | -0.274332 | 2.142510 |
| H | 1.426423 | 1.462917 | 1.816411 |
| C | 2.456727 | -1.238822 | -0.843248 |
| H | 0.712113 | -1.876139 | 0.269659 |
| H | 0.353716 | -1.228205 | -1.339876 |
| C | 3.383328 | -1.032023 | 0.366518 |
| H | 3.730184 | 0.530187 | 1.851011 |
| H | 3.299247 | 1.118659 | 0.241630 |
| H | 2.620124 | -2.221422 | -1.292043 |
| H | 2.674597 | -0.481613 | -1.603569 |
| H | 3.108744 | -1.795055 | 1.113597 |
| C | -4.331044 | -1.834882 | -0.140991 |
| C | -5.638878 | -1.968038 | 0.652396 |
| H | -6.027570 | -2.986725 | 0.568469 |
| H | -5.501562 | -1.757676 | 1.714909 |
| H | -6.399566 | -1.284553 | 0.263192 |
| C | -3.308707 | -2.835965 | 0.413240 |
| H | -2.334158 | -2.729976 | -0.071333 |
| H | -3.169195 | -2.713357 | 1.490034 |
| H | -3.658830 | -3.857286 | 0.238961 |
| C | -4.635486 | -2.194892 | -1.601754 |
| H | -5.166405 | -3.149470 | -1.647791 |
| H | -5.267725 | -1.433611 | -2.070238 |
| H | -3.723661 | -2.295359 | -2.193853 |
| C | 4.891793 | -1.261147 | 0.058325 |
| C | 5.473446 | -0.140674 | -0.813320 |
| H | 6.505768 | -0.378450 | -1.088233 |
| H | 4.901221 | -0.015349 | -1.736318 |
| H | 5.481616 | 0.814685 | -0.283610 |
| C | 5.685143 | -1.327562 | 1.371574 |
| H | 5.307228 | -2.129944 | 2.012683 |
| H | 6.740725 | -1.529544 | 1.166340 |
| H | 5.631648 | -0.391319 | 1.930215 |
| C | 5.090001 | -2.599072 | -0.669349 |
| H | 6.154785 | -2.844460 | -0.720769 |
| H | 4.579880 | -3.411379 | -0.141407 |
| H | 4.707968 | -2.564896 | -1.691402 |
|  |  |  |  |

Reaction complex A

|  |  |  |  |
| :--- | ---: | ---: | :---: |
| O | 0.796754 | 1.938250 | 0.369204 |
| O | -1.600731 | 1.529199 | 0.179665 |
| K | -0.529463 | 3.956044 | 0.253157 |
| H | 1.233060 | -0.014667 | 0.864486 |
| C | 1.697021 | 0.890669 | 0.415071 |
| C | 2.184443 | 0.483043 | -0.980640 |
| C | 2.912598 | 1.235629 | 1.280541 |
| C | 3.205677 | -0.655273 | -0.923982 |
| H | 2.630930 | 1.369625 | -1.449738 |
| H | 1.319750 | 0.197799 | -1.590085 |
| C | 3.956836 | 0.116089 | 1.330499 |
| H | 3.365774 | 2.144070 | 0.861466 |
| H | 2.566948 | 1.485196 | 2.288562 |
| C | 4.431683 | -0.276828 | -0.077568 |
| H | 3.504070 | -0.940894 | -1.935817 |
| H | 2.723583 | -1.533453 | -0.476363 |
| H | 4.800674 | 0.439434 | 1.944259 |
| H | 3.521371 | -0.761634 | 1.825045 |
| H | 4.872567 | 0.627447 | -0.525902 |
| C | -1.835361 | 0.886461 | -1.052326 |
| C | -3.259329 | 1.187087 | -1.512277 |
| C | -1.642914 | -0.627330 | -0.920075 |
| C | -4.300022 | 0.576916 | -0.568740 |
| H | -3.402042 | 0.781816 | -2.521264 |
| H | -3.396661 | 2.271660 | -1.574628 |
| C | -2.680743 | -1.227470 | 0.030177 |
| H | -1.726937 | -1.092507 | -1.910327 |
| H | -0.631351 | -0.824791 | -0.550097 |
| C | -4.115804 | -0.943806 | -0.442300 |
| H | -5.298172 | 0.815869 | -0.941974 |
| H | -4.194734 | 1.043023 | 0.416707 |
| H | -2.506499 | -2.301346 | 0.131663 |
| H | -2.533596 | -0.776864 | 1.016410 |
| H | -4.220317 | -1.363278 | -1.456136 |
| C | 5.554864 | -1.354227 | -0.098922 |
| C | 6.158435 | -1.439332 | -1.508663 |
| H | 6.980869 | -2.160356 | -1.524916 |
| H | 5.425043 | -1.761663 | -2.250506 |
| H | 6.555328 | -0.468264 | -1.820058 |
| C | 5.030338 | -2.740783 | 0.295876 |
| H | 4.537604 | -2.721343 | 1.271652 |
| H | 4.319389 | -3.126091 | -0.438606 |
| H | 5.861720 | -3.449368 | 0.356721 |
| C | 6.683369 | -0.964314 | 0.865909 |
| H | 7.545627 | -1.620966 | 0.719114 |
| H | 7.009465 | 0.066463 | 0.692817 |
| C | -5.373464 | -1.053237 | 1.909113 |
|  |  | -1.646757 | 0.420988 |


| C | -5.054211 | -1.317133 | 1.911582 |
| :--- | ---: | ---: | ---: |
| H | -5.882342 | -1.758445 | 2.474180 |
| H | -4.123621 | -1.717132 | 2.320237 |
| H | -5.068111 | -0.238289 | 2.087204 |
| C | -6.604010 | -1.221541 | -0.040577 |
| H | -6.708651 | -1.328579 | -1.125343 |
| H | -7.362409 | -1.849643 | 0.435199 |
| H | -6.822417 | -0.184482 | 0.222546 |
| C | -5.098405 | -3.168086 | 0.237783 |
| H | -5.890422 | -3.671129 | 0.800067 |
| H | -5.209824 | -3.439553 | -0.816542 |
| H | -4.143670 | -3.561184 | 0.591978 |
| H | -0.540496 | 1.552244 | 0.312014 |
| H | -1.125307 | 1.261994 | -1.808214 |

Transition state complex $\mathbf{T S} \mathbf{A} \rightarrow \mathbf{B}$

| O | -2.108613 | 3.313211 | 0.144710 |
| :--- | ---: | ---: | ---: |
| O | 0.796040 | 1.093299 | 0.529430 |
| K | 0.294609 | 3.367787 | -0.586946 |
| H | -0.983305 | 1.174637 | -1.072515 |
| C | -2.531409 | 2.157216 | 0.063604 |
| C | -2.395390 | 1.219545 | 1.245090 |
| C | -3.588682 | 1.792200 | -0.956791 |
| C | -2.614106 | -0.263011 | 0.946364 |
| H | -3.168545 | 1.561703 | 1.949297 |
| H | -1.429216 | 1.403063 | 1.718785 |
| C | -3.750401 | 0.293902 | -1.205838 |
| H | -4.523736 | 2.196556 | -0.540521 |
| H | -3.384814 | 2.341145 | -1.877060 |
| C | -3.875922 | -0.501693 | 0.102759 |
| H | -2.679074 | -0.794533 | 1.897877 |
| H | -1.742369 | -0.648575 | 0.409679 |
| H | -4.624527 | 0.136109 | -1.841973 |
| H | -2.870568 | -0.052949 | -1.752183 |
| H | -4.728351 | -0.091514 | 0.667697 |
| C | 1.038402 | -0.104398 | 1.247797 |
| C | 2.287040 | 0.097260 | 2.098292 |
| C | 1.231473 | -1.284869 | 0.293629 |
| C | 3.545363 | 0.255009 | 1.239371 |
| H | 2.401694 | -0.769283 | 2.759558 |
| H | 2.147189 | 0.976330 | 2.733984 |
| C | 2.485172 | -1.109412 | -0.565905 |
| H | 1.307577 | -2.205776 | 0.883918 |
| H | 0.348338 | -1.380151 | -0.346417 |
| C | 3.744819 | -0.943793 | 0.298573 |
| H | 4.406727 | 0.375015 | 1.899602 |
| H | 3.456607 | 1.173151 | 0.649020 |


|  |  | 2.580524 | -1.963903 |
| :--- | ---: | ---: | ---: |
| H | -1.239279 |  |  |
| H | 2.351558 | -0.218410 | -1.187910 |
| H | 3.824445 | -1.839754 | 0.934987 |
| C | -4.196879 | -2.007038 | -0.125693 |
| C | -4.163682 | -2.765333 | 1.209756 |
| H | -4.572036 | -3.771262 | 1.078856 |
| H | -3.146457 | -2.869544 | 1.592638 |
| H | -4.764632 | -2.252699 | 1.967921 |
| C | -3.198807 | -2.664850 | -1.087724 |
| H | -3.283277 | -2.255899 | -2.096913 |
| H | -2.167228 | -2.530834 | -0.750567 |
| H | -3.393628 | -3.739680 | -1.146363 |
| C | -5.612483 | -2.150965 | -0.703208 |
| H | -5.856566 | -3.208371 | -0.839173 |
| H | -6.353822 | -1.718823 | -0.024061 |
| H | -5.713680 | -1.663775 | -1.674870 |
| C | 5.064499 | -0.890257 | -0.523002 |
| C | 5.053358 | 0.239420 | -1.560828 |
| H | 6.016622 | 0.278356 | -2.078180 |
| H | 4.278635 | 0.086022 | -2.315755 |
| H | 4.890245 | 1.213935 | -1.093058 |
| C | 6.260620 | -0.681368 | 0.416970 |
| H | 6.239752 | -1.399019 | 1.243402 |
| H | 7.197239 | -0.822647 | -0.129341 |
| H | 6.276064 | 0.325238 | 0.839691 |
| C | 5.273648 | -2.225404 | -1.252622 |
| H | 6.240310 | -2.227435 | -1.764076 |
| H | 5.264397 | -3.060754 | -0.545741 |
| H | 4.504889 | -2.406312 | -2.006079 |
| H | 0.032789 | 0.950946 | -0.137614 |
| H | 0.183454 | -0.313298 | 1.908006 |

Reaction complex B

|  | -2.317666 | 3.161982 | 0.073587 |
| :--- | :---: | :---: | :---: |
| O | -2.649667 | 1.099444 | 0.370401 |
| K | 0.052534 | 3.179042 | -0.990773 |
| H | -0.443980 | 0.768934 | -1.741963 |
| C | -2.930070 | 2.148667 | 0.353801 |
| C | -2.470811 | 1.193592 | 1.424270 |
| C | -4.199194 | 1.754122 | -0.356023 |
| C | -2.445138 | -0.259751 | 0.921762 |
| H | -3.188404 | 1.277086 | 2.250677 |
| H | -1.487525 | 1.507968 | 1.775788 |
| C | -4.078044 | 0.311592 | -0.873411 |
| H | -5.021901 | 1.816239 | 0.366436 |
| H | -4.388608 | 2.464452 | -1.161200 |
| C | -3.764264 | -0.678673 | 0.258100 |
| H | -2.213756 | -0.903371 | 1.771854 |


| H | -1.631410 | -0.352887 | 0.196317 |
| :--- | ---: | ---: | ---: |
| H | -5.000973 | 0.045979 | -1.392349 |
| H | -3.265536 | 0.279936 | -1.606084 |
| H | -4.559303 | -0.595628 | 1.015705 |
| C | 0.981091 | 0.033983 | 1.242944 |
| C | 2.221134 | 0.433911 | 2.038645 |
| C | 1.246854 | -1.262317 | 0.476265 |
| C | 3.447854 | 0.546751 | 1.131853 |
| H | 2.397527 | -0.316848 | 2.817677 |
| H | 2.029536 | 1.386887 | 2.540936 |
| C | 2.486055 | -1.162811 | -0.417432 |
| H | 1.385826 | -2.068111 | 1.207061 |
| H | 0.369923 | -1.519670 | -0.126267 |
| C | 3.733272 | -0.769103 | 0.390617 |
| H | 4.311023 | 0.856737 | 1.725815 |
| H | 3.256755 | 1.334695 | 0.396613 |
| H | 2.634737 | -2.124970 | -0.911801 |
| H | 2.299848 | -0.421596 | -1.202419 |
| H | 3.880068 | -1.551414 | 1.152460 |
| C | -3.768940 | -2.158339 | -0.225382 |
| C | -3.215064 | -3.078497 | 0.871547 |
| H | -3.392834 | -4.123596 | 0.604246 |
| H | -2.137978 | -2.949131 | 1.002012 |
| H | -3.704084 | -2.887831 | 1.832448 |
| C | -2.926399 | -2.345362 | -1.494852 |
| H | -3.388613 | -1.863720 | -2.359677 |
| H | -1.920046 | -1.932776 | -1.381552 |
| H | -2.831299 | -3.411321 | -1.720326 |
| C | -5.212150 | -2.594592 | -0.515581 |
| H | -5.228016 | -3.629386 | -0.869025 |
| H | -5.824879 | -2.538024 | 0.389261 |
| H | -5.681163 | -1.978255 | -1.285462 |
| C | 5.045487 | -0.734568 | -0.443728 |
| C | 5.073488 | 0.448946 | -1.419898 |
| H | 5.961569 | 0.387104 | -2.055849 |
| H | 4.196106 | 0.452038 | -2.072138 |
| H | 5.111539 | 1.403998 | -0.890641 |
| C | 6.253831 | -0.628557 | 0.497967 |
| H | 6.276113 | -1.471901 | 1.194846 |
| H | 7.183220 | -0.644017 | -0.078490 |
| H | 6.244390 | 0.295040 | 1.079761 |
| C | 5.196385 | -2.035665 | -1.244878 |
| H | 6.197617 | -2.093709 | -1.680766 |
| H | 5.056665 | -2.910129 | -0.601046 |
| H | 4.476062 | -2.096448 | -2.063191 |
| H | 0.187455 | 0.770337 | -0.488289 |
| H | 0.147908 | -0.133876 | 1.941904 |
|  |  |  |  |

Transition state complex TS B $\rightarrow \mathbf{C}$

|  |  |  |  |
| :--- | :---: | :---: | :---: |
| O | -2.292456 | 3.151188 | -0.081356 |
| K | 0.606689 | 1.113477 | 0.387504 |
| H | 0.170350 | 3.168768 | -0.886177 |
| C | -2.308373 | 0.664725 | -1.613801 |
| C | -2.467596 | 2.164297 | 1.253750 |
| C | -4.19297721 | 1.368073 |  |
| C | -2.439273 | -0.750153 | -0.431942 |
| H | -3.189339 | 1.367949 | 0.913740 |
| H | -1.479612 | 1.568863 | 1.704771 |
| C | -4.060010 | 0.295623 | -0.913227 |
| H | -5.012688 | 1.821482 | 0.292407 |
| H | -4.391508 | 2.437698 | -1.254463 |
| C | -3.745934 | -0.662715 | 0.245034 |
| H | -2.218919 | -0.829678 | 1.787941 |
| H | -1.608647 | -0.328525 | 0.211479 |
| H | -4.977665 | 0.010445 | -1.431259 |
| H | -3.245277 | 0.249088 | -1.643475 |
| H | -4.551390 | -0.569006 | 0.990087 |
| C | 0.944344 | 0.081110 | 1.265003 |
| C | 2.206531 | 0.455296 | 2.051487 |
| C | 1.192703 | -1.244656 | 0.530825 |
| C | 3.421297 | 0.549221 | 1.127395 |
| H | 2.386699 | -0.296362 | 2.830412 |
| H | 2.037675 | 1.413381 | 2.553099 |
| C | 2.418387 | -1.172768 | -0.383941 |
| H | 1.339886 | -2.037148 | 1.275606 |
| H | 0.307535 | -1.511833 | -0.055151 |
| C | 3.683515 | -0.776604 | 0.395224 |
| H | 4.298224 | 0.858633 | 1.701998 |
| H | 3.221310 | 1.330503 | 0.387094 |
| H | 2.554219 | -2.143337 | -0.866718 |
| H | 2.224991 | -0.440274 | -1.174788 |
| H | 3.840166 | -1.550925 | 1.163453 |
| C | -3.728762 | -2.154660 | -0.199242 |
| C | -3.182874 | -3.038843 | 0.930945 |
| H | -3.344084 | -4.092673 | 0.688716 |
| H | -2.110016 | -2.892482 | 1.076531 |
| H | -3.690639 | -2.828473 | 1.877850 |
| C | -2.862647 | -2.366171 | -1.448778 |
| H | -3.313800 | -1.911343 | -2.333901 |
| H | -1.861616 | -1.943186 | -1.325722 |
| H | -2.753590 | -3.436386 | -1.645621 |
| C | -5.162047 | -2.614290 | -0.501308 |
| H | -5.161811 | -3.659376 | -0.823655 |
| H | -5.790923 | -2.537202 | 0.390851 |
| H | -5.624188 | -2.026300 | -1.297193 |
| C | 4.979472 | -0.762851 | -0.465096 |
|  |  |  |  |


| C | 4.991624 | 0.400260 | -1.465857 |
| ---: | ---: | ---: | ---: |
| H | 5.869337 | 0.325802 | -2.115003 |
| H | 4.103530 | 0.390329 | -2.103396 |
| H | 5.037621 | 1.365598 | -0.956119 |
| C | 6.207282 | -0.639518 | 0.448907 |
| H | 6.239403 | -1.464326 | 1.167333 |
| H | 7.125190 | -0.674859 | -0.145163 |
| H | 6.213204 | 0.298957 | 1.006227 |
| C | 5.112569 | -2.080539 | -1.242185 |
| H | 6.104479 | -2.149736 | -1.697682 |
| H | 4.985145 | -2.940756 | -0.577018 |
| H | 4.374814 | -2.157897 | -2.043383 |
| H | 0.110257 | 0.755326 | -0.690147 |
| H | 0.128068 | -0.083150 | 1.992343 |

Reaction complex $\mathbf{C}$

| O | -2.263486 | 3.118919 | -0.297480 |
| :--- | ---: | ---: | ---: |
| O | 0.632605 | 1.121989 | 0.433480 |
| K | 0.327623 | 3.128942 | -0.714786 |
| H | -0.640468 | 0.480158 | -2.203089 |
| C | -2.901056 | 2.186930 | 0.156732 |
| C | -2.402285 | 1.314798 | 1.276067 |
| C | -4.235676 | 1.786085 | -0.418205 |
| C | -2.429562 | -0.169205 | 0.867323 |
| H | -3.069919 | 1.473655 | 2.132270 |
| H | -1.379013 | 1.600035 | 1.526371 |
| C | -4.147170 | 0.323220 | -0.886334 |
| H | -4.996190 | 1.872100 | 0.365873 |
| H | -4.491507 | 2.461040 | -1.235355 |
| C | -3.766497 | -0.620049 | 0.263844 |
| H | -2.187271 | -0.759336 | 1.751572 |
| H | -1.613624 | -0.317459 | 0.154141 |
| H | -5.099258 | 0.038223 | -1.337904 |
| H | -3.386121 | 0.259281 | -1.671503 |
| H | -4.534781 | -0.516192 | 1.045737 |
| C | 0.937529 | 0.075166 | 1.257804 |
| C | 2.208701 | 0.347544 | 2.092160 |
| C | 1.171477 | -1.235068 | 0.474633 |
| C | 3.433907 | 0.471138 | 1.185707 |
| H | 2.366664 | -0.457284 | 2.823111 |
| H | 2.062213 | 1.277411 | 2.651904 |
| C | 2.397129 | -1.125772 | -0.435905 |
| H | 1.309150 | -2.072435 | 1.173059 |
| H | 0.282084 | -1.456545 | -0.126378 |
| C | 3.668916 | -0.810730 | 0.369828 |
| H | 4.316891 | 0.724081 | 1.779206 |
| H | 3.250995 | 1.301279 | 0.495923 |
| H | 2.518145 | -2.055649 | -0.997418 |


| H | 2.214487 | -0.322764 | -1.158480 |
| :---: | :---: | :---: | :---: |
| H | 3.803185 | -1.636124 | 1.088139 |
| C | -3.771873 | -2.118701 | -0.158629 |
| C | -3.203068 | -2.987851 | 0.971992 |
| H | -3.370287 | -4.044846 | 0.748158 |
| H | -2.127465 | -2.840384 | 1.093958 |
| H | -3.691194 | -2.763221 | 1.925813 |
| C | -2.937608 | -2.358416 | -1.424617 |
| H | -3.391587 | -1.892565 | -2.302676 |
| H | -1.920782 | -1.970672 | -1.317926 |
| H | -2.865490 | -3.431836 | -1.620859 |
| C | -5.214472 | -2.574310 | -0.419722 |
| H | -5.229797 | -3.631221 | -0.700243 |
| H | -5.827450 | -2.455594 | 0.478822 |
| H | -5.684547 | -2.014199 | -1.230876 |
| C | 4.970259 | -0.774125 | -0.482365 |
| C | 5.006742 | 0.439761 | -1.420064 |
| H | 5.892483 | 0.392609 | -2.061056 |
| H | 4.126499 | 0.468568 | -2.067934 |
| H | 5.051306 | 1.376099 | -0.859028 |
| C | 6.195725 | -0.719973 | 0.442041 |
| H | 6.205876 | -1.578592 | 1.120516 |
| H | 7.116367 | -0.746423 | -0.148494 |
| H | 6.216879 | 0.190271 | 1.043890 |
| C | 5.087403 | -2.050288 | -1.328274 |
| H | 6.080524 | -2.111715 | -1.782659 |
| H | 4.941709 | -2.942640 | -0.710794 |
| H | 4.352383 | -2.072333 | -2.135324 |
| H | -0.310088 | 0.528044 | -1.529767 |
| H | 0.120076 | -0.130916 | 1.988135 |

Reaction complex between $\mathrm{KO}^{\mathrm{t}} \mathrm{Bu}$ and 44

| C | -0.359036 | -1.842008 | -1.367561 |
| :---: | :---: | :---: | :---: |
| C | 1.125861 | -1.755923 | -1.071301 |
| C | 0.618561 | -0.304470 | 0.873859 |
| C | -0.851818 | -0.561397 | 0.683089 |
| H | -0.504599 | -1.381631 | -2.350895 |
| H | -0.592791 | -2.905608 | -1.466074 |
| H | 0.859901 | -0.603371 | 1.898769 |
| H | 0.701538 | 0.793621 | 0.776715 |
| N | 1.519531 | -0.972157 | -0.050975 |
| N | -1.257311 | -1.230715 | -0.404220 |
| O | -1.641354 | -0.111513 | 1.517508 |
| O | 1.896947 | -2.372903 | -1.789047 |
| C | -2.687529 | -1.419668 | -0.634801 |
| H | -2.835428 | -1.505478 | -1.715078 |
| C | 2.947017 | -0.864202 | 0.237923 |
| H | 3.482876 | -0.847690 | -0.712610 |


|  |  | 3.107741 | 0.095440 |
| :--- | ---: | ---: | ---: |
| H | 0.737430 |  |  |
| C | 3.453352 | -2.015087 | 1.104400 |
| H | 3.272715 | -2.950191 | 0.568266 |
| H | 2.872761 | -2.052474 | 2.031833 |
| C | 4.938336 | -1.861836 | 1.420114 |
| H | 5.298419 | -2.687168 | 2.036082 |
| H | 5.529921 | -1.845230 | 0.501500 |
| H | 5.130626 | -0.930393 | 1.958960 |
| C | -3.236868 | -2.649690 | 0.083152 |
| H | -3.078814 | -2.516018 | 1.156368 |
| H | -2.667037 | -3.532707 | -0.222376 |
| C | -4.719121 | -2.852284 | -0.217009 |
| H | -5.113174 | -3.722309 | 0.309899 |
| H | -5.301495 | -1.980279 | 0.091258 |
| H | -4.884854 | -3.004173 | -1.286647 |
| H | -3.204166 | -0.522425 | -0.291069 |
| O | -0.117437 | 2.600866 | 0.260955 |
| C | 0.353023 | 2.866686 | -1.000662 |
| C | -0.180115 | 1.823723 | -2.007794 |
| H | 0.140859 | 2.017421 | -3.037130 |
| H | 0.180778 | 0.832843 | -1.715795 |
| H | -1.274278 | 1.812024 | -1.973884 |
| C | -0.096521 | 4.266900 | -1.464644 |
| H | -1.189648 | 4.316388 | -1.458961 |
| H | 0.280796 | 5.016380 | -0.762682 |
| H | 0.258924 | 4.518524 | -2.469659 |
| C | 1.895298 | 2.815123 | -1.035396 |
| H | 2.295617 | 3.516452 | -0.297660 |
| H | 2.233556 | 1.807789 | -0.768991 |
| H | 2.307828 | 3.064527 | -2.019047 |
| K | -1.550106 | 2.411002 | 2.112226 |

Transition state complex TS $\mathbf{4 4} \boldsymbol{\rightarrow 4 5}$

| C | 1.154091 | -2.226366 | 0.698625 |
| :--- | ---: | ---: | ---: |
| C | -0.360582 | -2.352883 | 0.695039 |
| C | -0.412521 | -0.395183 | -0.821068 |
| C | 1.017049 | -0.175794 | -0.622395 |
| H | 1.473729 | -2.451141 | 1.717574 |
| H | 1.553497 | -3.016193 | 0.048588 |
| H | -0.625390 | -0.525224 | -1.887215 |
| H | -0.921314 | 0.800945 | -0.432916 |
| N | -1.032006 | -1.443126 | -0.025972 |
| N | 1.660668 | -0.917096 | 0.318627 |
| O | 1.604597 | 0.747697 | -1.221094 |
| O | -0.886090 | -3.255805 | 1.335452 |
| C | 3.058385 | -0.632319 | 0.617437 |
| H | 3.252743 | -0.966576 | 1.641596 |
| C | -2.489694 | -1.479202 | -0.019692 |


| H | -2.816897 | -1.848248 | 0.954871 |
| :--- | ---: | ---: | ---: |
| H | -2.834908 | -0.448008 | -0.140019 |
| C | -3.053006 | -2.373597 | -1.121819 |
| H | -2.671125 | -3.386574 | -0.967911 |
| H | -2.680775 | -2.028776 | -2.091961 |
| C | -4.578799 | -2.374442 | -1.114638 |
| H | -4.980625 | -3.017953 | -1.898991 |
| H | -4.961146 | -2.735266 | -0.156311 |
| H | -4.970679 | -1.366028 | -1.271773 |
| C | 4.033983 | -1.298388 | -0.351874 |
| H | 3.804649 | -0.944752 | -1.360444 |
| H | 3.879937 | -2.381888 | -0.341841 |
| C | 5.481164 | -0.976943 | 0.010490 |
| H | 6.178757 | -1.441641 | -0.688003 |
| H | 5.655846 | 0.101899 | -0.008565 |
| H | 5.721889 | -1.336449 | 1.014361 |
| H | 3.189279 | 0.450114 | 0.582064 |
| O | -1.346982 | 1.960515 | -0.143789 |
| C | -1.089042 | 2.331721 | 1.184423 |
| C | -1.005012 | 1.096668 | 2.096653 |
| H | -0.888904 | 1.389155 | 3.143990 |
| H | -1.915659 | 0.499020 | 2.000562 |
| H | -0.153361 | 0.467974 | 1.821118 |
| C | 0.247486 | 3.090697 | 1.266229 |
| H | 1.051567 | 2.463180 | 0.864654 |
| H | 0.194038 | 4.018593 | 0.684187 |
| H | 0.506451 | 3.362005 | 2.293627 |
| C | -2.223293 | 3.240115 | 1.668024 |
| H | -2.301687 | 4.113173 | 1.014212 |
| H | -3.170006 | 2.696221 | 1.624693 |
| H | -2.062038 | 3.584843 | 2.694006 |
| K | 0.180950 | 2.737126 | -1.988415 |

Reaction complex of ${ }^{\mathrm{t}} \mathrm{BuOH}$ and 45

| C | -0.552115 | -2.371946 | -0.682795 |
| :--- | ---: | ---: | ---: |
| C | 0.947958 | -2.146979 | -0.769731 |
| C | 0.546835 | -0.498961 | 0.989887 |
| C | -0.823278 | -0.452394 | 0.755003 |
| H | -0.875300 | -2.762538 | -1.648179 |
| H | -0.735219 | -3.147841 | 0.078737 |
| H | 0.933230 | -0.331358 | 1.987595 |
| H | 0.724909 | 1.358637 | 0.310747 |
| N | 1.409696 | -1.220500 | 0.093044 |
| N | -1.265517 | -1.137211 | -0.392139 |
| O | -1.663322 | 0.211864 | 1.441096 |
| O | 1.649161 | -2.764888 | -1.564268 |
| C | -2.697434 | -1.161850 | -0.652825 |
| H | -2.840182 | -1.408288 | -1.711181 |


| C | 2.823513 | -0.873759 | 0.065878 |
| :--- | ---: | ---: | ---: |
| H | 3.196541 | -1.065115 | -0.942880 |
| H | 2.906219 | 0.198537 | 0.271628 |
| C | 3.641316 | -1.675406 | 1.076044 |
| H | 3.540071 | -2.736401 | 0.831170 |
| H | 3.219245 | -1.533173 | 2.076049 |
| C | 5.110391 | -1.263531 | 1.058949 |
| H | 5.696592 | -1.845869 | 1.771708 |
| H | 5.543565 | -1.413579 | 0.066582 |
| H | 5.222685 | -0.206457 | 1.314978 |
| C | -3.483699 | -2.141175 | 0.220727 |
| H | -3.273959 | -1.903040 | 1.266817 |
| H | -3.135574 | -3.162826 | 0.038620 |
| C | -4.981679 | -2.051958 | -0.057478 |
| H | -5.546716 | -2.754264 | 0.557841 |
| H | -5.355485 | -1.046143 | 0.152391 |
| H | -5.199221 | -2.275634 | -1.105695 |
| H | -3.082824 | -0.154437 | -0.488545 |
| O | 0.742002 | 2.328051 | 0.109500 |
| C | 0.346741 | 2.509628 | -1.259020 |
| C | -1.179982 | 2.475113 | -1.346610 |
| H | -1.517359 | 2.572660 | -2.381267 |
| H | -1.555997 | 1.528708 | -0.948087 |
| H | -1.614643 | 3.302307 | -0.775201 |
| C | 0.883896 | 3.870919 | -1.678768 |
| H | 0.490018 | 4.651099 | -1.022294 |
| H | 1.973623 | 3.880113 | -1.611713 |
| H | 0.592077 | 4.102009 | -2.705786 |
| C | 0.946782 | 1.394797 | -2.112335 |
| H | 2.033448 | 1.375823 | -1.996559 |
| H | 0.542020 | 0.426004 | -1.805223 |
| H | 0.711409 | 1.548886 | -3.167863 |
| K | -0.978981 | 2.496366 | 2.113005 |

Reaction complex of $\mathrm{KO}^{t} \mathrm{Bu}$ and 45

| C | 0.004850 | -0.499053 | -1.436824 |
| :--- | ---: | ---: | ---: |
| C | -0.093299 | 1.001237 | -1.311489 |
| C | -2.003241 | 0.688086 | 0.191088 |
| C | -1.941696 | -0.711700 | 0.060934 |
| H | 0.125881 | -0.707098 | -2.507429 |
| H | 0.942237 | -0.776628 | -0.920338 |
| H | -2.152269 | 1.050894 | 1.204028 |
| N | -1.066447 | 1.500653 | -0.556778 |
| N | -1.139911 | -1.244274 | -0.936093 |
| O | -2.671082 | -1.493765 | 0.745339 |
| O | 0.748900 | 1.702434 | -1.908156 |
| C | -1.005056 | -2.688647 | -1.035622 |
| H | -0.686635 | -2.920364 | -2.059821 |


| C | -1.149123 | 2.944747 | -0.386324 |
| :---: | :---: | :---: | :---: |
| H | -0.821956 | 3.420684 | -1.31267 |
| H | -2.200974 | 3.190563 | -0.21 |
| C | -0.290142 | 3.437233 | 0.77701 |
| H | 0.752161 | 3.183326 | 0.562 |
| H | -0.569739 | 2.895166 | 1.685782 |
| C | -0.439972 | 4.940772 | 0.987621 |
| H | 0.185477 | 5.290483 | 1.810543 |
| H | -0.150857 | 5.491336 | 0.08842 |
| H | -1.476347 | 5.201692 | 1.21937 |
| C | -0.007778 | -3.283000 | $-0.03751$ |
| H | -0.399996 | -3.106756 | 0.96832 |
| H | 0.948670 | -2.752410 | -0.10615 |
| C | 0.196650 | -4.776977 | -0.27143 |
| H | 0.891126 | -5.200885 | 0.45653 |
| H | -0.748666 | -5.321474 | -0.19054 |
| H | 0.604794 | -4.964062 | -1.26899 |
| H | -1.988876 | -3.133104 | -0.88011 |
| K | -4.767195 | -0.180683 | 0.44284 |
| K | 3.166569 | 0.745206 | -1.820220 |
| O | 2.764656 | -0.721882 | 0.04237 |
| C | 2.651649 | -0.541058 | 1.398257 |
| C | 1.203384 | -0.169126 | 1.788212 |
| H | 0.520164 | -0.971628 | 1.49478 |
| H | 1.085123 | 0.010177 | 2.863249 |
| H | 0.902976 | 0.736606 | 1.250521 |
| C | 3.576964 | 0.604327 | 1.870299 |
| H | 4.613170 | 0.365944 | 1.609201 |
| H | 3.296747 | 1.530433 | 1.354306 |
| H | 3.523584 | 0.786465 | 2.949476 |
| C | 3.044683 | -1.823951 | 2.160334 |
| H | 2.375654 | -2.638634 | 1.866668 |
| H | 4.064996 | -2.107361 | 1.885699 |
| H | 2.992925 | -1.705600 | 3. |

Transition state complex TS $\mathbf{4 5} \boldsymbol{\rightarrow} \mathbf{4 6}$

| C | 0.236673 | -0.596085 | -1.208403 |
| :--- | ---: | ---: | ---: |
| C | 0.064660 | 0.857404 | -1.224587 |
| C | -1.993155 | 0.617636 | 0.114329 |
| C | -1.866930 | -0.800223 | 0.087871 |
| H | 0.436776 | -0.916019 | -2.240965 |
| H | 1.477985 | -0.762180 | -0.382617 |
| H | -2.221600 | 0.986426 | 1.114028 |
| N | -0.946013 | 1.405973 | -0.525014 |
| N | -0.900987 | -1.365955 | -0.691052 |
| O | -2.691058 | -1.547672 | 0.709939 |
| O | 0.906076 | 1.577282 | -1.834344 |
| C | -0.775613 | -2.806817 | -0.741821 |


| H | -0.337365 | -3.071964 | -1.712892 |
| :--- | ---: | ---: | ---: |
| C | -1.091325 | 2.846394 | -0.462538 |
| H | -0.513011 | 3.285300 | -1.276365 |
| H | -2.152271 | 3.078658 | -0.616508 |
| C | -0.626494 | 3.432718 | 0.871863 |
| H | 0.437195 | 3.207693 | 0.996558 |
| H | -1.152252 | 2.934767 | 1.692653 |
| C | -0.861691 | 4.939192 | 0.935832 |
| H | -0.510165 | 5.360561 | 1.879478 |
| H | -0.336514 | 5.449448 | 0.123651 |
| H | -1.925890 | 5.172087 | 0.840133 |
| C | 0.082714 | -3.389163 | 0.382841 |
| H | -0.416360 | -3.163100 | 1.329807 |
| H | 1.049448 | -2.877288 | 0.391877 |
| C | 0.270866 | -4.895643 | 0.227891 |
| H | 0.866427 | -5.312036 | 1.042827 |
| H | -0.692773 | -5.413542 | 0.220199 |
| H | 0.780844 | -5.131090 | -0.710945 |
| H | -1.776964 | -3.239061 | -0.692956 |
| K | -4.714822 | -0.263553 | 0.000127 |
| K | 3.136032 | 0.382104 | -2.002924 |
| O | 2.505565 | -0.832960 | 0.155578 |
| C | 2.518223 | -0.130606 | 1.379628 |
| C | 1.123600 | -0.126807 | 2.020377 |
| H | 0.753044 | -1.150427 | 2.116178 |
| H | 1.155483 | 0.331012 | 3.013779 |
| H | 0.413626 | 0.432836 | 1.405923 |
| C | 2.961010 | 1.320848 | 1.134205 |
| H | 3.985372 | 1.342707 | 0.743822 |
| H | 2.290049 | 1.792023 | 0.407091 |
| H | 2.942559 | 1.916047 | 2.051760 |
| C | 3.511901 | -0.825564 | 2.310974 |
| H | 3.181444 | -1.849825 | 2.500704 |
| H | 4.497948 | -0.865899 | 1.840267 |
| H | 3.601673 | -0.302640 | 3.267955 |
|  |  |  |  |

## Reaction complex of ${ }^{\mathrm{t}} \mathrm{BuOH}$ and 46

| C | -0.252466 | 0.649602 | -1.306813 |
| :--- | ---: | ---: | ---: |
| C | -0.043013 | -0.770209 | -1.307306 |
| C | 1.938193 | -0.468059 | 0.118933 |
| C | 1.768599 | 0.945586 | 0.086766 |
| H | -0.456132 | 1.002271 | -2.323209 |
| H | -1.742943 | 0.699778 | -0.201980 |
| H | 2.209902 | -0.800102 | 1.119732 |
| N | 0.885931 | -1.301074 | -0.460434 |
| N | 0.776578 | 1.479521 | -0.679709 |
| O | 2.566842 | 1.721232 | 0.710349 |
| O | -0.773698 | -1.531936 | -2.014077 |


| C | 0.562184 | 2.909441 | -0.677 |
| :---: | :---: | :---: | :---: |
| H | 0.099554 | 3.184931 | -1.633463 |
| C | 1.140316 | -2.724660 | -0.471909 |
| H | 0.400624 | -3.187554 | -1.12 |
| H | 2.141119 | -2.900537 | -0.898642 |
| C | 1.074595 | -3.366250 | 0.914817 |
| H | 0.091117 | -3.161566 | 1.349908 |
| H | 1.815845 | -2.908017 | 1.576093 |
| C | 1.316552 | -4.871972 | 0.838988 |
| H | 1.264873 | -5.338698 | 1.824525 |
| H | 0.571619 | -5.352861 | 0.199054 |
| H | 2.302642 | -5.086813 | 0.4174 |
| C | -0.315374 | 3.390590 | 0.479944 |
| H | 0.207539 | 3.149186 | 1.410048 |
| H | -1.251479 | 2.824535 | 0.477390 |
| C | -0.593312 | 4.888836 | 0.398546 |
| H | -1.196728 | 5.232268 | 1.241324 |
| H | 0.339439 | 5.460290 | 0.400463 |
| H | -1.131985 | 5.137578 | -0.520559 |
| H | 1.534410 | 3.402856 | -0.617490 |
| K | 4.624917 | 0.490908 | -0.016867 |
| K | -3.023659 | -0.427511 | -2.095979 |
| O | -2.639724 | 0.650168 | 0.283040 |
| C | -2.511460 | -0.177378 | 1.440137 |
| C | -1.183574 | 0.109918 | 2.140612 |
| H | -1.123895 | 1.167436 | 2.408989 |
| H | -1.094067 | -0.488666 | 3.05159 |
| H | -0.343156 | -0.130925 | 1.483729 |
| C | -2.580928 | -1.650520 | 1.023273 |
| H | -3.553956 | -1.866561 | 0.567340 |
| H | -1.788929 | -1.883746 | 0.30401 |
| H | -2.465309 | -2.311430 | 1.886582 |
| C | -3.684364 | 0.169760 | 2.350098 |
| H | -3.630498 | 1.220878 | 2.641959 |
| H | -4.629769 | 0.005013 | 1.826696 |
| H | -3.674343 | -0.447021 | 3.252 |

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$\begin{array}{lllllllllll}200 & 180 & 160 & 140 & 120 & 100 & 80 & 60 & 40 & 20 & \text { ppm }\end{array}$






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$\begin{array}{lllllllllllllllll} & 7.0 & 7.5 & 7.0 & 6.5 & 6.0 & 5.5 & 5.0 & 4.5 & 4.0 & 3.5 & 3.0 & 2.5 & 2.0 & 1.5 & 1.0 & \mathrm{ppm}\end{array}$
















