Electronic Supplementary Material (ESI) for ChemComm.
This journal is © The Royal Society of Chemistry 2019

BINOPtimal: A Web Tool for Optimal Chiral Phosphoric Acid Catalyst Selection

*Jolene P. Reid, Kristaps Ermanis and Jonathan M. Goodman**

Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

Supporting Information

List of contents:

- Full list of authors in the Gaussian09 reference. Page S2.
- Website details. Page S2
- Computational methods. Pages S2-S3
- Comparison of methods and transition state structures. Pages S4-S7
- Cartesian coordinates, energies, number and values of imaginary frequencies of all the transition state structures. Pages S8-S42
- Summary of reactions. Pages S42-S47
- Summary of imine and nucleophile types recognized. Page S48
- Complete imine-nucleophile steric relationship table. Pages S48-S49
- References. Pages S50-S51

Full list of authors in the Gaussian09 reference

M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

Website details

The structures are drawn in a molecular editor integrated in the website[1] – both the imine and nucleophile are entered in their active form. A list of recognized imines and nucleophiles can be found on page **S48** and a table of literature precedented combinations can found on page **S49**. As JMSE will always convert neighbouring opposite charges to a bond, triple bonds should be used to input diazo compounds. The application logic was coded in Python 2.7,[2] using RDKit for the chemoinformatic functionality.[3] The result from the Python application is returned as text and images, which are integrated in a dynamic webpage and served by Apache webserver.[4] The site is available at **http://www-mmm.ch.cam.ac.uk**. The full code can be found at github. https://github.com/KristapsE/BINOPtimal

Computational methods

Transition states were located first, by a conformational search in MacroModel (version 9.9)[5] using the OPLS-2005 force field.[6-8] Selected conformers within 10 kJ mol^{-1} of the minimum were optimized using the ONIOM method implemented in Gaussian 09 (revision D.01).[9] The B3LYP density functional,[10-11] and split-valence polarized 6-31G** basis set,[12-13] were used for the high-layer, and the force field UFF,[14] was used for the low-layer. The reactants and the phosphoric acid moiety of the catalyst were included in the high-layer, and the remaining regions of the catalyst

were treated as the low-layer. This method has previously been shown to give excellent results when used to describe reactions catalyzed by chiral phosphoric acids.[15-21] The position of the partition within the catalyst was chosen as the phosphoric acid binds directly to the reagents, whereas the remaining catalyst acts as steric bulk and can be adequately described by molecular mechanics. Single point energy calculations were performed on the resulting structures using M06-2X density functional,[22] and the 6-31G** basis set, as implemented in Gaussian 09 (revision D.01). This energy was used to correct the gas-phase energy derived from the ONIOM calculations. Free energies in solution were derived from structures optimized in the gas phase at the ONIOM (B3LYP/6-31G**:UFF), level of theory by means of a single point calculation using M06-2X/6-31G** with the polarizable continuum model (IEFPCM) as implemented in the Gaussian 09 (revision D.01), using *m*-xylene.[23] These values were used to correct the Gibbs free energy derived from the ONIOM calculations. To further validate the results key transition states from this process were re-optimized using the B3LYP functional and 6-31G* basis set. The free energies obtained from this process were corrected by a single point calculation in the same manner as above. Structures are illustrated using CYLview.[24]

Transition state structures and methods comparison

The mechanism of this class of reactions is well established and computations of the full catalyst systems have led to the development of the model depicted below.[25] This is based on a projection of the catalyst such that both the BINOL oxygens are in the plane of the paper. The free oxygens are above and below, each having bulky substituents on either side. The catalyst binds to the substrate via the catalyst hydroxyl group and there is a second interaction from the phosphoryl oxygen to the nucleophile proton. The imine can orient itself with respect to the catalyst in one of two ways. Noting that the C_2 symmetry of the phosphate anion allows us to draw the imine at the front of the diagram without loss of generality, the *N*-substituent, can be directed away from the front 3,3′ group, which we call *Type I*, or toward the 3,3′ groups, which we call *Type II*. Additionally, the imine can exist as either the *E* or *Z* stereoisomer; we define *E* or *Z* based on steric size. Combining these considerations, four unique TSs, **TS1-4**, for these reactions are formulated.

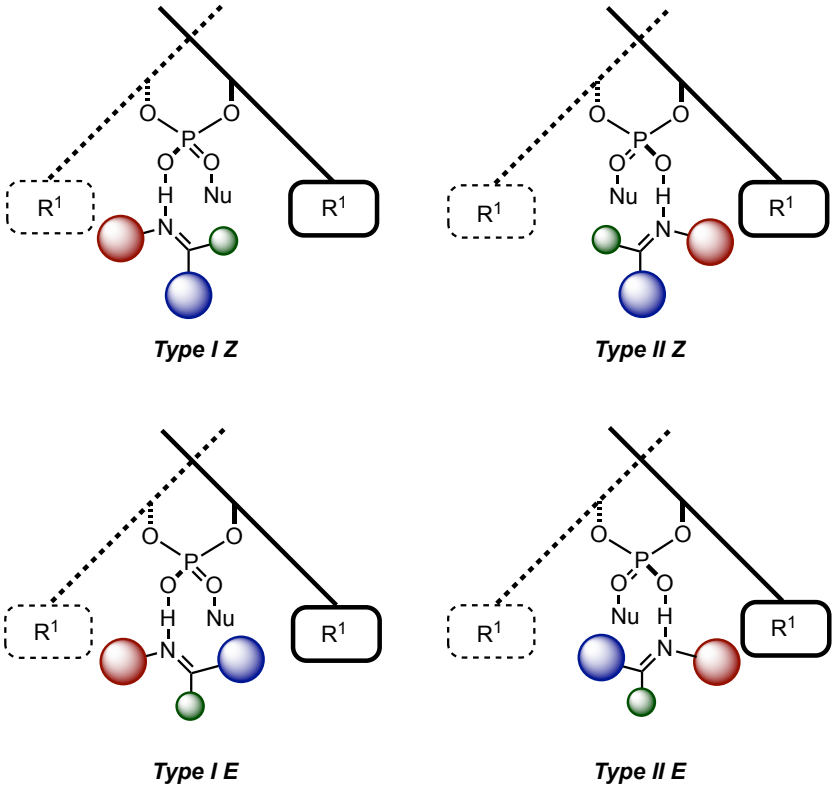
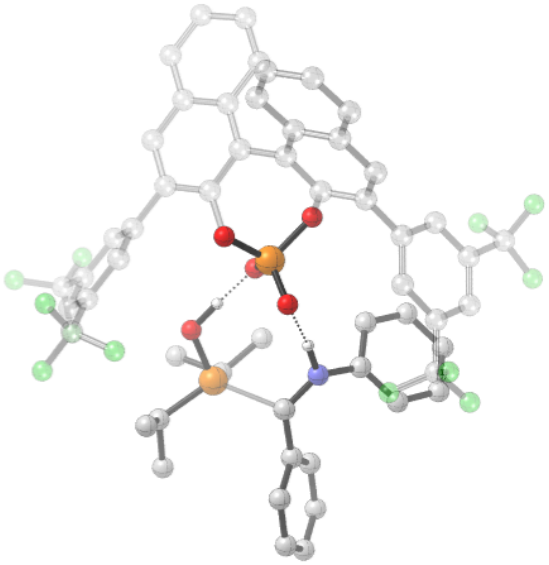
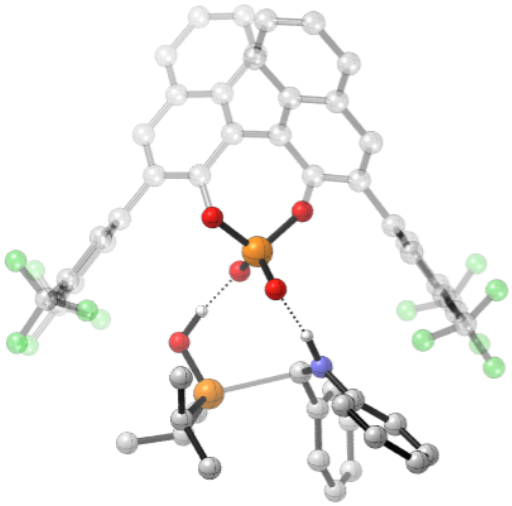


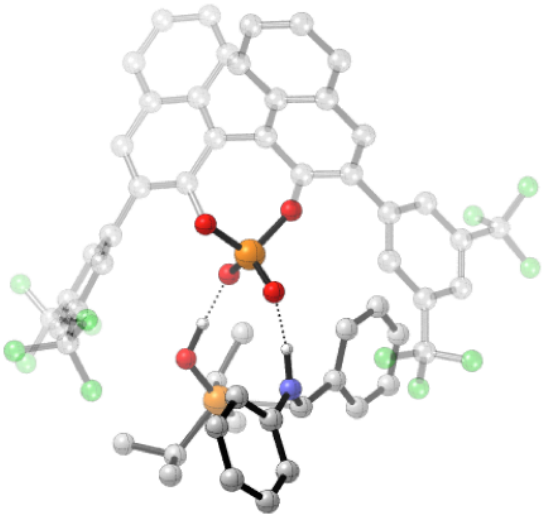
Figure 1. Transition state models for the prediction of stereoselectivity.



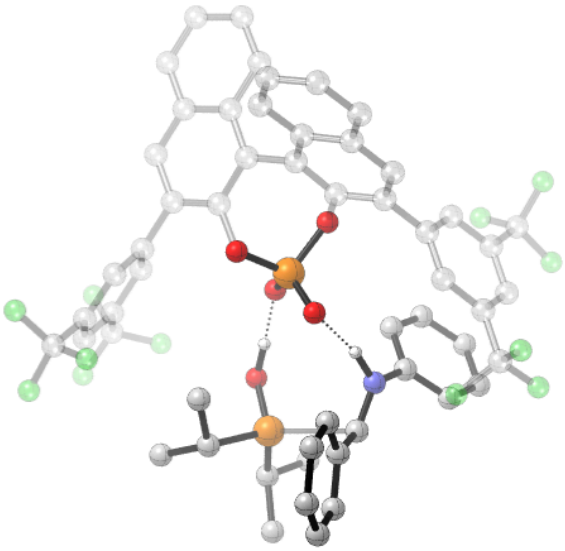
TS2-*Z*: $\Delta\Delta G^{\ddagger}$= +4.1, $\Delta\Delta G^{\ddagger}_{sol}$ = +3.7



TS1-*Z*: $\Delta\Delta G^{\ddagger}$= +4.3, $\Delta\Delta G^{\ddagger}_{sol}$ = +4.1

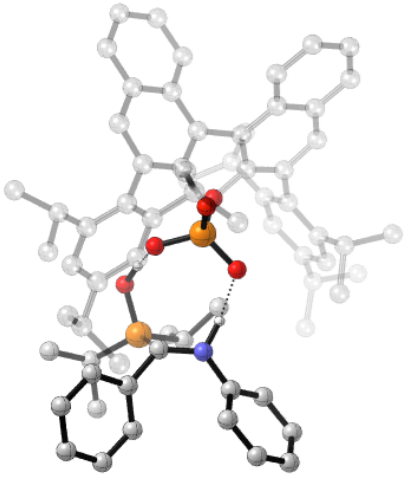


TS1-*E*: $\Delta\Delta G^{\ddagger}$= 0, $\Delta\Delta G^{\ddagger}_{sol}$ = 0

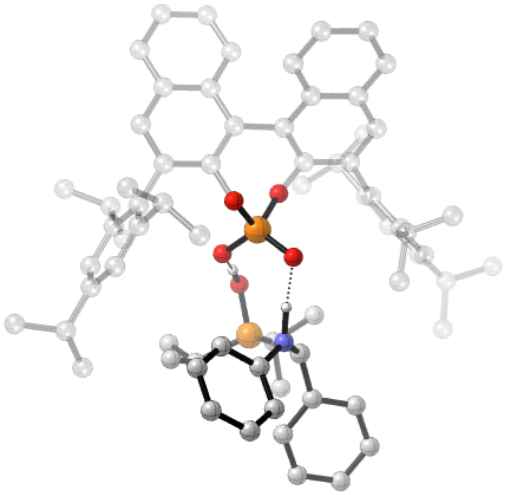


TS2-*E*: $\Delta\Delta G^{\ddagger}$= +1.7, $\Delta\Delta G^{\ddagger}_{sol}$ = +1.2

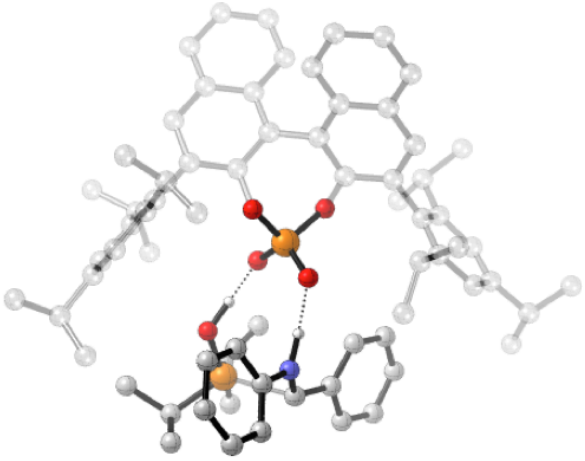
Figure 2. Competing TS for the 3,5-$CF_3C_6H_4$ derived phosphoric acid catalysed phosphorylation of imines. ONIOM (B3LYP/6-31G**:UFF), single-point energy M06-2X/6-31G**. Grayed-out regions were treated with UFF, and the full-colour regions were treated B3LYP/6-31G**. All energies in kcal mol^{-1}.



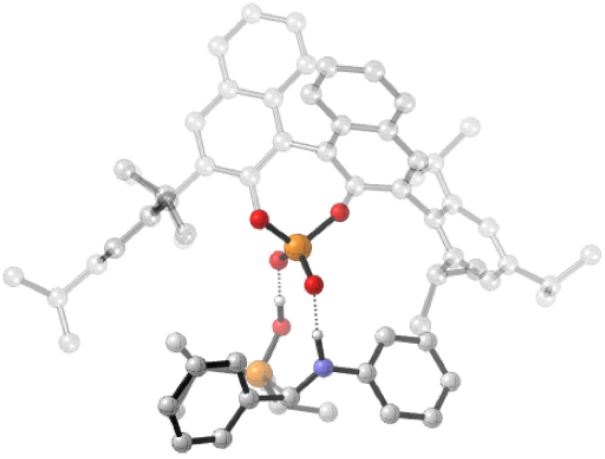
TS4-*Z*: $\Delta\Delta G^{\ddagger}$= +2.9, $\Delta\Delta G^{\ddagger}_{sol}$ = +2.7



TS3-*Z*: $\Delta\Delta G^{\ddagger}$= +4.6, $\Delta\Delta G^{\ddagger}_{sol}$ = +4.4



TS3-*E*: $\Delta\Delta G^{\ddagger}$= 0, $\Delta\Delta G^{\ddagger}_{sol}$ = 0



TS4-*E*: $\Delta\Delta G^{\ddagger}$= +3.5, $\Delta\Delta G^{\ddagger}_{sol}$ = +3.1

Figure 3. Competing TS for the TRIP derived phosphoric acid catalysed phosphorylation of imines. ONIOM (B3LYP/6-31G**:UFF), single-point energy M06-2X/6-31G**. Grayed-out regions were treated with UFF, and the full-colour regions were treated B3LYP/6-31G**. All energies in kcal mol^{-1}.

In order to test the ONIOM method, we re-optimized **TS1-TS4** using the B3LYP functional and 6-31G* basis set and then carried out single-point energy evaluations using the M06-2X/6-31G** with the polarizable continuum model (IEFPCM) for *m*-xylene. The corrected free energies between the two methods are compared in Table 1. The qualitative patterns with both catalysts remain the same. Superposition of the pairs of transition states optimized by the different methods show the structural differences quantified through RMSD. These values are obtained from Maestro[26] and superimposed using the ASL feature. These calculations indicate the energy difference between **TS1-*E*** and **TS2-*E*** is overestimated by the ONIOM method (77% ee vs 50% ee). This could be due to the UFF component of the optimization, which overestimates short-range repulsion effects.[17,27] Although the absolute values are larger as compared to our DFT optimized structures, both methods agree that TRIP should lead to higher levels of enantioselectivity.

	ONIOM M06-2X/6-31G**//B3LYP/6-31G**:UFF		**DFT** M06-2X/6-31G**//B3LYP/6-31G*		
$\Delta\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}_{sol}$	$\Delta\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}_{sol}$	RMSD
TS1-*E*	0	0	0	0	0.3470
TS1-*Z*	+4.3	+4.1	+6.8	+6.5	0.4828
TS2-*E*	+1.7	+1.2	+0.8	+0.6	1.6937
TS2-*Z*	+4.1	+3.7	+7.1	+6.6	0.2615
TS3-*E*	0	0	0	0	0.4426
TS3-*Z*	+4.6	+4.4	+4.6	+4.4	0.3148
TS4-*E*	+3.5	+3.1	+2.1	+2.0	1.1971
TS4-*Z*	+2.9	+2.7	+3.4	+4.5	0.3574

Table 1. Comparison of the relative energies and structures derived from both computational methods. All energies in kcal mol^{-1}.

TS1–*E*

(B3LYP/6-31G**:UFF) Energy = -1855.062520

(B3LYP/6-31G**:UFF) Free Energy = -1854.243434

M06-2X/6-31G** Derived free energy = -4431.381328

M06-2X/6-31G** Derived free energy in solution = -4431.389783

Number of Imaginary Frequencies = 1 (-93.16)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	2.08170	3.28790	0.50010	H	2.73200	7.14590	-2.61910
C	4.50590	2.25330	1.49540	H	2.90250	5.22700	-1.11670
C	3.67550	1.44590	0.71380	P	0.25120	0.66140	0.16090
C	2.45360	1.94820	0.23450	C	4.81790	-2.59910	-0.05840
H	5.44280	1.85110	1.86570	C	5.31380	-1.56850	-0.87860
C	-1.67630	4.64950	-1.10870	C	4.93090	-0.24310	-0.61920
C	-1.62360	3.51790	-0.28320	C	4.07310	0.05280	0.44640
C	-0.37930	3.09290	0.22150	C	3.60380	-0.97750	1.27070
C	0.80370	3.79560	-0.08370	C	3.95790	-2.31270	1.01470
H	-2.63280	4.98520	-1.49400	H	5.09110	-3.62910	-0.25100
C	4.11840	3.55470	1.83590	H	5.29830	0.55890	-1.24910
C	2.88820	4.07840	1.36030	H	2.96310	-0.73030	2.10740
C	2.49400	5.36740	1.78110	C	-5.13630	1.15080	0.42650
C	3.32070	6.12830	2.61070	C	-4.29850	1.48260	1.50270
C	4.54280	5.61690	3.04540	C	-3.17080	2.28890	1.27200
C	4.94000	4.33450	2.66570	C	-2.85870	2.73220	-0.02410
H	1.54580	5.79330	1.48280	C	-3.70550	2.38450	-1.08880
H	3.01010	7.11780	2.92070	C	-4.85010	1.60330	-0.87300
H	5.17890	6.21140	3.68840	H	-6.00790	0.53490	0.61020
H	5.88530	3.94820	3.02850	H	-2.53060	2.57370	2.09700
C	0.75180	4.89430	-0.97840	H	-3.46470	2.70650	-2.09530
C	-0.50640	5.33180	-1.46720	O	-0.30090	1.96460	0.99630
C	-0.57720	6.43440	-2.33420	O	1.65820	1.15510	-0.55930
C	0.58700	7.08930	-2.73750	C	-4.62570	0.95910	2.87960
C	1.83070	6.64470	-2.29020	F	-4.64060	-0.42360	2.85410
C	1.91820	5.55270	-1.42410	F	-3.69790	1.37060	3.82100
H	-1.53250	6.78290	-2.70890	F	-5.87390	1.41630	3.26130
H	0.52590	7.93580	-3.40910	C	-5.73720	1.26150	-2.04440

F	-6.18290	2.42790	-2.63930	C	-1.07120	-4.57640	2.62400
F	-5.01460	0.53200	-2.97050	C	-1.67220	-4.86190	3.84930
F	-6.83890	0.51840	-1.65700	H	-2.54550	-4.05590	5.64840
C	6.23640	-1.85530	-2.03710	H	-2.18400	-1.69080	4.96070
F	7.43500	-1.19300	-1.84420	H	-1.11220	-1.17580	2.77400
F	6.49570	-3.20900	-2.16470	H	-0.71090	-5.38690	1.99810
F	5.65790	-1.40610	-3.21030	H	-1.80270	-5.89710	4.15090
C	3.43080	-3.44430	1.86230	H	-0.90100	-4.57830	-0.01770
F	2.75280	-4.34450	1.06060	P	-2.52640	-2.63220	-1.23090
F	4.48900	-4.09310	2.47160	C	-2.67510	-2.38640	-3.08870
F	2.56490	-2.99200	2.84330	H	-3.58790	-1.79100	-3.21450
O	-0.67010	0.31880	-0.99440	C	-2.84400	-3.72580	-3.82210
O	0.52990	-0.39100	1.20640	H	-1.97630	-4.37590	-3.66730
H	0.11040	-1.92770	0.97530	H	-3.73970	-4.27040	-3.50790
C	-0.42050	-3.61260	-0.12850	H	-2.92880	-3.55010	-4.90030
N	-0.28220	-2.90690	0.99890	C	-1.49780	-1.57410	-3.65260
C	2.35760	-3.45120	-3.38320	H	-1.70540	-1.31370	-4.69720
C	1.51010	-4.55040	-3.21860	H	-1.32710	-0.65010	-3.09560
C	0.60910	-4.57920	-2.15800	H	-0.56950	-2.15150	-3.63250
C	0.55150	-3.51950	-1.23660	C	-4.16700	-3.39570	-0.73930
C	1.42980	-2.43620	-1.38960	H	-4.18300	-4.38040	-1.22610
C	2.31080	-2.39940	-2.46720	C	-4.22460	-3.59880	0.78240
H	3.05260	-3.41820	-4.21690	H	-4.13450	-2.64230	1.30420
H	1.54980	-5.38110	-3.91670	H	-5.18320	-4.04920	1.06260
H	-0.05780	-5.42990	-2.03880	H	-3.42910	-4.25340	1.14740
H	1.43450	-1.62890	-0.67030	C	-5.37200	-2.56930	-1.21660
H	2.95600	-1.53610	-2.58800	H	-5.31100	-1.55460	-0.81770
C	-2.08260	-3.82880	4.69310	H	-5.43860	-2.50680	-2.30600
C	-1.87750	-2.50180	4.30670	H	-6.30170	-3.02310	-0.85470
C	-1.28520	-2.20090	3.08330	O	-2.67150	-1.16250	-0.57560
C	-0.89350	-3.24280	2.22800	H	-1.86300	-0.53450	-0.72030

B3LYP/6-31G* Energy = -4433.622657

B3LYP/6-31G* Free Energy = -4432.854603

M06-2X/6-31G** Derived free energy = -4431.467621

M06-2X/6-31G** Derived free energy in solution = -4431.476759

Number of Imaginary Frequencies = 1 (-91.25)

B3LYP/6-31G* Geometry

C	2.36660	3.18550	0.41230	C	4.22640	-0.16430	0.42070
C	4.80530	2.08050	1.31800	C	3.68420	-1.15300	1.25190
C	3.90640	1.27670	0.65110	C	4.04720	-2.49070	1.08400
C	2.67970	1.84710	0.20620	H	5.21500	-3.90490	-0.05040
H	5.75020	1.66060	1.65400	H	5.54510	0.21370	-1.23900
C	-1.38120	4.72880	-1.06390	H	2.96870	-0.87640	2.01730
C	-1.36330	3.58160	-0.29580	C	-5.04410	1.50780	0.54290
C	-0.09670	3.10040	0.14960	C	-4.08820	1.67650	1.54750
C	1.09880	3.73790	-0.14550	C	-2.89660	2.34990	1.29420
H	-2.33340	5.13810	-1.39190	C	-2.62450	2.86160	0.01390
C	4.50850	3.43040	1.62950	C	-3.58180	2.67870	-0.99020
C	3.26100	3.98950	1.20090	C	-4.77980	2.01130	-0.72620
C	2.95160	5.31610	1.61310	H	-5.96580	0.97550	0.74370
C	3.83930	6.05440	2.36400	H	-2.16610	2.46310	2.08450
C	5.08860	5.51210	2.74710	H	-3.37610	3.03080	-1.99590
C	5.40970	4.22360	2.38960	O	-0.06420	1.94710	0.91530
H	1.99460	5.74470	1.34000	O	1.82340	1.04060	-0.51980
H	3.57370	7.06230	2.67120	C	-4.37580	1.14290	2.92440
H	5.78190	6.10810	3.33390	F	-5.02440	-0.04500	2.87400
H	6.35580	3.78360	2.69590	F	-3.24370	0.95280	3.64290
C	1.07420	4.87990	-1.01920	F	-5.15930	1.98090	3.64090
C	-0.19170	5.38840	-1.45760	C	-5.74790	1.80510	-1.85820
C	-0.23330	6.52770	-2.30640	F	-6.10330	2.97540	-2.43420
C	0.92500	7.12700	-2.74250	F	-5.20650	1.04270	-2.84120
C	2.17750	6.60050	-2.34860	F	-6.88260	1.18860	-1.45950
C	2.25100	5.50990	-1.51020	C	6.33120	-2.28110	-1.92420
H	-1.20380	6.90690	-2.61780	F	7.26370	-1.34550	-2.20340
H	0.88200	7.99230	-3.39800	F	6.97400	-3.44800	-1.70770
H	3.09240	7.05790	-2.71550	F	5.59240	-2.44350	-3.05370
H	3.21940	5.11440	-1.22760	C	3.42280	-3.53920	1.96680
P	0.38230	0.55160	0.13770	F	2.18600	-3.88530	1.53240
C	4.93590	-2.86600	0.07690	F	4.15690	-4.67410	1.99980
C	5.46210	-1.88540	-0.76290	F	3.28350	-3.10710	3.23700
C	5.11900	-0.54220	-0.58750	O	-0.53480	0.26010	-1.02320

O	0.59980	-0.48810	1.20410	H	-2.60740	-5.62300	4.19990
H	-0.13450	-2.07820	0.94460	H	-1.54400	-4.54510	0.02740
C	-0.91830	-3.67340	-0.12560	P	-2.83430	-2.47080	-1.29060
N	-0.69500	-2.95150	0.98120	C	-2.90650	-2.18090	-3.14420
C	1.92170	-4.21940	-3.28110	H	-3.71100	-1.44370	-3.26930
C	0.84340	-5.09520	-3.12520	C	-3.26430	-3.46940	-3.90250
C	-0.07150	-4.88920	-2.09720	H	-2.50040	-4.24160	-3.75530
C	0.07460	-3.80800	-1.21020	H	-4.23280	-3.88470	-3.60390
C	1.16940	-2.94370	-1.36330	H	-3.31300	-3.26230	-4.97830
C	2.08190	-3.15030	-2.39750	C	-1.60360	-1.55960	-3.67720
H	2.63990	-4.37470	-4.08130	H	-1.74940	-1.26050	-4.72290
H	0.72030	-5.93900	-3.79830	H	-1.30020	-0.67560	-3.11000
H	-0.90930	-5.57270	-1.97450	H	-0.77650	-2.27630	-3.64960
H	1.32070	-2.12180	-0.67400	C	-4.55930	-3.04830	-0.83430
H	2.92910	-2.48160	-2.50930	H	-4.60790	-4.07980	-1.21370
C	-2.76470	-3.51030	4.61010	C	-4.73250	-3.08580	0.69360
C	-2.44010	-2.22580	4.16770	H	-4.63830	-2.08670	1.12920
C	-1.75110	-2.04120	2.97090	H	-5.73030	-3.46950	0.93860
C	-1.38770	-3.15500	2.20200	H	-3.99960	-3.73390	1.18290
C	-1.68880	-4.44760	2.65450	C	-5.68610	-2.22930	-1.48710
C	-2.38220	-4.61850	3.85220	H	-5.62050	-1.17470	-1.21060
H	-3.30370	-3.64730	5.54310	H	-5.67850	-2.29250	-2.57900
H	-2.73700	-1.35540	4.74370	H	-6.65700	-2.60680	-1.14280
H	-1.49750	-1.04650	2.62210	O	-2.81160	-0.98740	-0.62090
H	-1.35050	-5.31520	2.09530	H	-1.93780	-0.49190	-0.75190

TS2–*E*

(B3LYP/6-31G**:UFF) Energy = -1855.062889

(B3LYP/6-31G**:UFF) Free Energy = -1854.244496

M06-2X/6-31G** Derived free energy = -4431.378681

M06-2X/6-31G** Derived free energy in solution = -4431.387820

Number of Imaginary Frequencies = 1 (-81.44)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	0.36960	3.71660	0.58090	C	2.56350	2.66570	0.79720
C	2.90340	3.57980	1.80000	C	1.28760	2.71310	0.21390

H	3.88740	3.53050	2.25370
C	-3.45780	3.63150	-1.38590
C	-3.02170	2.54220	-0.62490
C	-1.75430	2.57200	-0.02140
C	-0.94960	3.72930	-0.11190
H	-4.43290	3.59330	-1.85960
C	1.98160	4.54550	2.22590
C	0.69630	4.61540	1.62740
C	-0.22890	5.56290	2.11470
C	0.12840	6.44120	3.14010
C	1.40280	6.38310	3.70370
C	2.32570	5.43790	3.25380
H	-1.23210	5.62830	1.71550
H	-0.58770	7.16800	3.50160
H	1.67330	7.06660	4.49820
H	3.30610	5.39990	3.71380
C	-1.37160	4.81430	-0.92240
C	-2.64360	4.75910	-1.54900
C	-3.08160	5.83030	-2.34410
C	-2.26320	6.94370	-2.53830
C	-1.00030	6.99520	-1.94940
C	-0.55110	5.93980	-1.15270
H	-4.05380	5.80280	-2.82210
H	-2.60520	7.76460	-3.15520
H	-0.36400	7.85530	-2.11410
H	0.44170	6.01070	-0.72950
P	-0.10970	0.63350	-0.08170
C	5.41260	-0.27810	-0.43260
C	5.03640	0.74420	-1.32340
C	4.09100	1.69570	-0.91290
C	3.54180	1.64640	0.37420
C	3.93190	0.63240	1.25800
C	4.86130	-0.34140	0.86110
H	6.14120	-1.01550	-0.74140
H	3.79590	2.48910	-1.59020
H	3.50290	0.59480	2.25290
C	-5.58230	-0.85940	-0.22790
C	-5.32910	-0.04340	0.89080
C	-4.47560	1.06190	0.75280
C	-3.89250	1.36150	-0.48460
C	-4.15460	0.54670	-1.59250
C	-4.99310	-0.57170	-1.47350
H	-6.23720	-1.71470	-0.12990
H	-4.27580	1.69910	1.60670
H	-3.69870	0.77980	-2.54800
O	-1.30750	1.47840	0.68160
O	0.91960	1.76640	-0.70960
C	-5.96530	-0.31760	2.23120
F	-6.79610	0.73570	2.56660
F	-6.71200	-1.48310	2.21700
F	-4.98230	-0.43750	3.19680
C	-5.24370	-1.43240	-2.68700
F	-4.04200	-1.94030	-3.14670
F	-6.08960	-2.49050	-2.40230
F	-5.81860	-0.66520	-3.68380
C	5.65410	0.86640	-2.69480
F	4.65840	0.92460	-3.65230
F	6.40040	2.02890	-2.75600
F	6.48040	-0.20590	-2.98360
C	5.25840	-1.42030	1.83830
F	4.13360	-2.11180	2.24830
F	6.14710	-2.32100	1.27700
F	5.85570	-0.84080	2.94270
O	-0.63710	-0.11120	-1.28610
O	0.58550	-0.14760	1.01540
H	1.50160	-1.39050	0.50370
C	1.40740	-3.42200	0.73650
N	1.90090	-2.31800	0.18800
C	0.44310	-3.95790	4.86470
C	0.62260	-2.66450	4.36970
C	0.91460	-2.45030	3.02430
C	1.02600	-3.54800	2.15170
C	0.84680	-4.84790	2.65940
C	0.55620	-5.05280	4.00420

H	0.21800	-4.11350	5.91560	C	-1.15080	-6.49070	-0.59950
H	0.53470	-1.81150	5.03550	H	-0.14390	-6.59100	-0.17670
H	1.02830	-1.44030	2.64660	H	-1.86510	-6.50990	0.22940
H	0.93940	-5.70020	1.99100	H	-1.33210	-7.38030	-1.21280
H	0.42410	-6.06220	4.38170	C	-0.29600	-5.23590	-2.64120
C	4.02690	-2.46870	-3.44680	H	-0.48880	-6.10590	-3.27940
C	4.39940	-3.29180	-2.38300	H	-0.40140	-4.33250	-3.24570
C	3.69670	-3.24100	-1.18080	H	0.74580	-5.29690	-2.30440
C	2.61170	-2.36440	-1.04340	C	-2.45410	-3.61370	0.76160
C	2.23800	-1.52930	-2.10310	H	-2.19840	-4.31400	1.56860
C	2.94890	-1.59400	-3.30020	C	-2.51190	-2.19070	1.34420
H	4.57810	-2.50370	-4.38150	H	-2.74740	-1.46500	0.56160
H	5.24770	-3.96260	-2.48060	H	-3.29230	-2.13360	2.10930
H	4.00920	-3.84640	-0.33520	H	-1.56790	-1.88150	1.79820
H	1.38050	-0.87160	-2.00350	C	-3.80340	-4.00800	0.14450
H	2.64920	-0.95570	-4.12560	H	-4.61320	-3.81500	0.85790
H	1.69630	-4.34760	0.24930	H	-4.00280	-3.41580	-0.75280
P	-1.01110	-3.67750	-0.43630	H	-3.85070	-5.06650	-0.12740
C	-1.27250	-5.22190	-1.45550	O	-1.35930	-2.55350	-1.55710
H	-2.29200	-5.15190	-1.85500	H	-1.05350	-1.59740	-1.38540

B3LYP/6-31G* Energy = -4433.619975

B3LYP/6-31G* Free Energy = -4432.853323

M06-2X/6-31G** Derived free energy = -4431.466303

M06-2X/6-31G** Derived free energy in solution = -4431.475737

Number of Imaginary Frequencies = 1 (-96.37)

B3LYP/6-31G* Geometry

C	1.03720	3.68640	0.06350	C	-0.32460	3.69850	-0.54520
C	3.66660	3.64400	1.08980	H	-4.05070	3.91840	-1.69020
C	3.13540	2.49020	0.55340	C	2.90480	4.83100	1.21590
C	1.80600	2.52950	0.03980	C	1.55750	4.85100	0.73100
H	4.68250	3.63170	1.47670	C	0.78660	6.02390	0.96690
C	-3.00660	3.81430	-1.40790	C	1.33010	7.11860	1.60220
C	-2.63560	2.81990	-0.52260	C	2.67560	7.10860	2.03870
C	-1.26080	2.75880	-0.13890	C	3.44190	5.98230	1.85240

H	-0.24980	6.04890	0.65250	F	-5.12190	-0.97980	3.50290
H	0.71500	7.99750	1.77600	F	-3.42710	0.33890	3.87220
H	3.09290	7.98180	2.53250	C	-6.85570	0.19430	-1.16850
H	4.47050	5.94760	2.20370	F	-8.02010	0.04670	-0.50090
C	-0.70390	4.66230	-1.54190	F	-7.07670	1.04210	-2.19520
C	-2.07050	4.71780	-1.96550	F	-6.56970	-1.01590	-1.71800
C	-2.46370	5.67540	-2.93940	C	7.11220	-0.06660	-1.12730
C	-1.54260	6.52500	-3.50600	F	6.74300	-0.67050	-2.28760
C	-0.18400	6.44580	-3.11930	F	7.62430	1.13700	-1.46330
C	0.22400	5.54370	-2.16140	F	8.11540	-0.80710	-0.60840
H	-3.50830	5.71190	-3.23940	C	4.25840	-1.98520	2.52000
H	-1.85130	7.24690	-4.25690	F	2.93630	-2.22940	2.64820
H	0.54670	7.10070	-3.58610	F	4.85600	-3.15370	2.19150
H	1.27020	5.48930	-1.88330	F	4.71440	-1.64410	3.74830
P	0.05510	0.52420	0.03430	O	-0.64750	-0.08090	-1.15030
C	5.67780	-0.97900	0.71220	O	0.52190	-0.34560	1.17160
C	5.95150	0.05690	-0.17930	H	0.83800	-2.03140	0.64550
C	5.11150	1.17060	-0.25030	C	0.08690	-3.93600	0.38730
C	3.96580	1.24930	0.55010	N	1.03220	-2.99220	0.30250
C	3.67420	0.19050	1.42070	C	-2.93340	-4.11560	3.41350
C	4.53630	-0.90440	1.50880	C	-2.23020	-2.92450	3.22230
H	6.33450	-1.83800	0.77460	C	-1.23720	-2.83500	2.24670
H	5.34620	1.98120	-0.93240	C	-0.94880	-3.94820	1.43900
H	2.76950	0.21880	2.01770	C	-1.65440	-5.14670	1.64550
C	-5.73170	0.27550	1.06870	C	-2.63780	-5.23200	2.62600
C	-4.66750	0.67880	1.87660	H	-3.70810	-4.17410	4.17290
C	-3.64770	1.48200	1.36890	H	-2.46340	-2.05170	3.82330
C	-3.66280	1.89610	0.02590	H	-0.70330	-1.89880	2.11160
C	-4.72620	1.46860	-0.78370	H	-1.43130	-6.01380	1.02690
C	-5.75190	0.67690	-0.26570	H	-3.17310	-6.16550	2.77560
H	-6.52530	-0.34440	1.47030	C	4.56850	-3.47350	-1.94660
H	-2.83520	1.78370	2.01620	C	4.15730	-4.47920	-1.07040
H	-4.75000	1.74870	-1.83080	C	2.99220	-4.32390	-0.31910
O	-0.85550	1.73720	0.70330	C	2.22100	-3.16330	-0.46100
O	1.32330	1.39830	-0.58560	C	2.62850	-2.15320	-1.34170
C	-4.66490	0.28350	3.32990	C	3.80330	-2.31160	-2.07430
F	-5.45770	1.08900	4.07190	H	5.48650	-3.58410	-2.51640

H	4.75570	-5.37790	-0.94910	H	1.04380	-4.08950	-3.62110
H	2.70440	-5.07880	0.40700	H	1.12310	-5.46190	-2.50640
H	2.02100	-1.26380	-1.46400	C	-3.09690	-3.37510	-1.79810
H	4.12640	-1.52030	-2.74320	H	-3.53450	-4.34000	-1.50500
H	0.39690	-4.91280	0.03310	C	-3.47940	-2.32570	-0.73950
P	-1.23960	-3.64270	-1.77310	H	-2.97560	-1.37100	-0.92650
C	-0.91530	-4.91310	-3.10480	H	-4.55800	-2.14680	-0.77480
H	-1.38510	-4.51360	-4.01290	H	-3.22090	-2.65120	0.27150
C	-1.56080	-6.26310	-2.75520	C	-3.61910	-2.97510	-3.18870
H	-1.16070	-6.67080	-1.81780	H	-4.68310	-2.71820	-3.12230
H	-2.64930	-6.19650	-2.65510	H	-3.08440	-2.09660	-3.56410
H	-1.34690	-6.99490	-3.54300	H	-3.51450	-3.77910	-3.92480
C	0.59080	-5.05270	-3.37340	O	-0.58650	-2.32900	-2.47560
H	0.75500	-5.73760	-4.21440	H	-0.59440	-1.48120	-1.92570

TS1–*Z*

(B3LYP/6-31G**:UFF) Energy = -1855.054985

(B3LYP/6-31G**:UFF) Free Energy = -1854.235169

M06-2X/6-31G** Derived free energy = -4431.374416

M06-2X/6-31G** Derived free energy in solution = -4431.383255

Number of Imaginary Frequencies = 1 (-102.32)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	-0.80840	3.91930	-0.28710	C	-0.71120	5.17420	0.36600
C	1.70830	4.88450	0.52280	C	-1.85100	5.94660	0.67930
C	1.61340	3.61020	-0.05460	C	-1.71830	7.18900	1.30330
C	0.35110	3.13110	-0.45990	C	-0.45550	7.67570	1.63820
H	2.67880	5.26350	0.82370	C	0.68230	6.91570	1.36600
C	-4.58480	2.17380	-1.40380	H	-2.84950	5.59790	0.45410
C	-3.75860	1.54220	-0.46560	H	-2.59930	7.77510	1.53120
C	-2.51220	2.11110	-0.14620	H	-0.35890	8.63900	2.12220
C	-2.11650	3.34120	-0.71640	H	1.65310	7.30250	1.65270
H	-5.54390	1.73230	-1.65200	C	-2.92820	3.94320	-1.71100
C	0.56540	5.66230	0.74310	C	-4.17810	3.35570	-2.03590

C	-5.00260	3.95130	-3.00410
C	-4.58940	5.10830	-3.66570
C	-3.34910	5.67560	-3.37520
C	-2.51920	5.09820	-2.41170
H	-5.96300	3.51680	-3.25560
H	-5.22800	5.56030	-4.41360
H	-3.02710	6.56490	-3.90140
H	-1.55740	5.55790	-2.22870
P	-0.39650	0.74040	-0.05740
C	5.10440	1.11050	-0.27320
C	4.25760	1.21620	-1.39070
C	3.13130	2.05120	-1.32280
C	2.82840	2.75690	-0.14720
C	3.68480	2.63720	0.95950
C	4.82630	1.82460	0.90480
H	5.98120	0.47900	-0.32210
H	2.49580	2.15550	-2.19400
H	3.45780	3.16970	1.87590
C	-4.95490	-2.18430	1.28950
C	-4.96920	-2.03510	-0.10930
C	-4.58470	-0.80860	-0.67170
C	-4.18410	0.26010	0.14320
C	-4.18850	0.10200	1.53700
C	-4.57480	-1.11440	2.12020
H	-5.25450	-3.12530	1.73080
H	-4.58160	-0.69200	-1.74940
H	-3.90220	0.93250	2.17200
O	-1.66350	1.45830	0.71480
O	0.23970	1.89550	-1.04610
C	-5.39820	-3.15750	-1.02160
F	-5.71960	-4.30280	-0.31380
F	-6.50810	-2.76100	-1.74510
F	-4.37310	-3.45550	-1.90030
C	-4.59990	-1.23320	3.62470
F	-3.35860	-0.90750	4.13970
F	-5.53980	-0.35710	4.13590
F	-4.92230	-2.51570	4.03390
C	4.53360	0.45830	-2.66510
F	3.45110	-0.34810	-2.96220
F	4.72440	1.35460	-3.70080
F	5.65990	-0.33920	-2.55780
C	5.73340	1.75310	2.10830
F	6.26010	3.00700	2.35840
F	5.00740	1.34460	3.21210
F	6.77840	0.86660	1.91390
O	-0.88710	-0.32230	-1.02990
O	0.58290	0.34500	1.02210
H	1.65320	-0.77000	0.46320
C	1.56670	-2.31290	-0.82150
N	2.21920	-1.57810	0.09630
C	3.34230	-5.42380	-3.19300
C	2.78320	-4.29380	-3.78820
C	2.20340	-3.30100	-2.99620
C	2.19050	-3.41950	-1.59840
C	2.75030	-4.56380	-1.00950
C	3.31970	-5.55740	-1.80140
H	3.78740	-6.20070	-3.80720
H	2.78960	-4.18400	-4.86840
H	1.75740	-2.42760	-3.46300
H	2.73450	-4.67380	0.06950
H	3.74520	-6.43970	-1.33280
C	5.75620	-2.18330	2.31080
C	5.74680	-2.46130	0.94250
C	4.58800	-2.28540	0.18960
C	3.41260	-1.83940	0.81190
C	3.43130	-1.52450	2.17910
C	4.59640	-1.70570	2.92200
H	6.66450	-2.31770	2.88990
H	6.65320	-2.80050	0.44980
H	4.60050	-2.46580	-0.87770
H	2.53530	-1.12280	2.64130
H	4.59740	-1.46230	3.98020
H	0.82320	-1.72130	-1.35030
P	-0.45320	-3.47020	0.14070

C	-0.92360	-5.14850	-0.54960	H	-1.46870	-4.25560	2.18090
H	-0.07900	-5.81260	-0.32190	C	0.64680	-4.41070	2.56080
C	-1.06790	-5.04080	-2.07770	H	0.52380	-4.57540	3.63690
H	-1.85160	-4.32450	-2.33880	H	0.77910	-5.39360	2.09430
H	-0.14060	-4.72170	-2.55880	H	1.57160	-3.84050	2.42280
H	-1.34370	-6.01490	-2.49610	C	-0.78210	-2.29030	2.66910
C	-2.20730	-5.72270	0.07550	H	-0.88870	-2.42190	3.75200
H	-2.50240	-6.63340	-0.45800	H	0.03710	-1.59240	2.48290
H	-2.08030	-5.98900	1.12810	H	-1.69010	-1.81730	2.29060
H	-3.03070	-5.00700	-0.00090	O	-1.72860	-2.56910	-0.27350
C	-0.56840	-3.65560	2.00160	H	-1.45820	-1.61720	-0.56900

B3LYP/6-31G* Energy = -4433.615015

B3LYP/6-31G* Free Energy = -4432.845957

M06-2X/6-31G** Derived free energy = -4431.456715

M06-2X/6-31G** Derived free energy in solution = -4431.466368

Number of Imaginary Frequencies = 1 (-83.23)

B3LYP/6-31G* Geometry

C	-0.75860	4.02560	-0.10890	H	-2.26380	7.94110	1.88870
C	1.85650	4.88890	0.51680	H	0.06360	8.73590	2.30840
C	1.68330	3.63500	-0.03660	H	1.98390	7.31210	1.65930
C	0.35040	3.22380	-0.34030	C	-2.96800	4.22680	-1.40220
H	2.86100	5.24620	0.72890	C	-4.25920	3.68270	-1.70570
C	-4.64300	2.44120	-1.14130	C	-5.12270	4.38170	-2.59200
C	-3.79800	1.72060	-0.32270	C	-4.72500	5.55520	-3.18870
C	-2.52240	2.27960	-0.02050	C	-3.43520	6.07320	-2.92540
C	-2.10810	3.51600	-0.49530	C	-2.58140	5.42870	-2.05740
H	-5.62870	2.04540	-1.37320	H	-6.10300	3.95960	-2.80060
C	0.76250	5.73030	0.83270	H	-5.39050	6.07730	-3.87050
C	-0.57100	5.29170	0.54360	H	-3.11170	6.98650	-3.41740
C	-1.65000	6.12180	0.95550	H	-1.59320	5.83450	-1.87600
C	-1.42130	7.32930	1.57790	P	-0.41870	0.75240	0.04360
C	-0.10200	7.77830	1.82280	C	5.09310	1.06280	-0.63090
C	0.96460	6.99020	1.45920	C	4.08420	1.12770	-1.59560
H	-2.66730	5.78930	0.78460	C	2.98200	1.96200	-1.42460

C	2.85070	2.74350	-0.26340
C	3.86280	2.66610	0.70190
C	4.97460	1.84070	0.51630
H	5.93830	0.39790	-0.75860
H	2.20890	1.98930	-2.18090
H	3.76440	3.22610	1.62600
C	-4.99530	-2.15310	1.12160
C	-5.05800	-1.84860	-0.23350
C	-4.66850	-0.58880	-0.69570
C	-4.19570	0.38340	0.19200
C	-4.11370	0.06330	1.55710
C	-4.51570	-1.18970	2.01190
H	-5.29660	-3.13000	1.48110
H	-4.69370	-0.37360	-1.75880
H	-3.73520	0.79500	2.26020
O	-1.66880	1.54500	0.78450
O	0.16290	1.97970	-0.91040
C	-5.55150	-2.86860	-1.22180
F	-5.53190	-4.12310	-0.71230
F	-6.82380	-2.62280	-1.61100
F	-4.79770	-2.88000	-2.34610
C	-4.39150	-1.55780	3.46540
F	-3.35250	-2.40600	3.67690
F	-4.19460	-0.48410	4.25560
F	-5.49880	-2.19560	3.91180
C	4.21420	0.29770	-2.84390
F	3.01600	0.07130	-3.43330
F	5.00190	0.88810	-3.76980
F	4.76430	-0.91460	-2.58280
C	6.03650	1.80760	1.58310
F	6.71980	2.97600	1.63400
F	5.50220	1.62110	2.81190
F	6.94020	0.82620	1.37960
O	-0.91430	-0.28930	-0.93290
O	0.55430	0.36960	1.12320
H	1.59950	-0.87930	0.56050
C	1.56400	-2.41240	-0.72490
N	2.16790	-1.68820	0.22770
C	3.42240	-5.47390	-3.09550
C	3.00510	-4.27160	-3.66520
C	2.39910	-3.29350	-2.87410
C	2.21400	-3.50620	-1.49950
C	2.63930	-4.71790	-0.93440
C	3.23800	-5.69400	-1.72710
H	3.88690	-6.23830	-3.71210
H	3.14700	-4.09030	-4.72680
H	2.09360	-2.35080	-3.31760
H	2.49960	-4.89470	0.12750
H	3.55790	-6.62980	-1.27720
C	5.59380	-2.14010	2.64190
C	5.61790	-2.61750	1.32970
C	4.49940	-2.50010	0.50560
C	3.32720	-1.91890	1.01100
C	3.30850	-1.41360	2.32100
C	4.43830	-1.52670	3.12860
H	6.47530	-2.22490	3.27050
H	6.52370	-3.06620	0.93090
H	4.55200	-2.81600	-0.52780
H	2.41640	-0.90880	2.67990
H	4.41530	-1.12450	4.13710
H	0.82950	-1.82080	-1.26490
P	-0.50210	-3.61690	0.18870
C	-1.11380	-5.08710	-0.79980
H	-0.28080	-5.80390	-0.80110
C	-1.37450	-4.63470	-2.24840
H	-2.19290	-3.90860	-2.28410
H	-0.48860	-4.18250	-2.70650
H	-1.66160	-5.49730	-2.86140
C	-2.36520	-5.76190	-0.21350
H	-2.66680	-6.59780	-0.85740
H	-2.19780	-6.16550	0.78980
H	-3.20510	-5.06220	-0.16930
C	-0.60140	-4.12660	1.98530
H	-1.65980	-4.37570	2.14060

C	0.26640	-5.35320	2.30350	H	-0.49950	-3.19840	3.94090
H	0.13140	-5.64140	3.35280	H	0.81170	-2.70570	2.85880
H	0.01750	-6.22380	1.68760	H	-0.82020	-2.04430	2.64000
H	1.33230	-5.13210	2.16730	O	-1.73930	-2.56260	0.07140
C	-0.25660	-2.94260	2.90280	H	-1.47100	-1.67170	-0.32280

TS2–*Z*

(B3LYP/6-31G**:UFF) Energy = -1855.053118

(B3LYP/6-31G**:UFF) Free Energy = -1854.233843

M06-2X/6-31G** Derived free energy = -4431.374731

M06-2X/6-31G** Derived free energy in solution = -4431.383842

Number of Imaginary Frequencies = 1 (-101.64)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	1.40320	3.74430	0.36880	C	-1.75920	6.17190	-2.64270
C	3.92400	3.26010	1.53110	C	-0.73920	7.02940	-3.05670
C	3.33230	2.28730	0.72120	C	0.55770	6.85910	-2.57350
C	2.06590	2.51530	0.16270	C	0.84160	5.83830	-1.66340
H	4.89850	3.06830	1.96730	H	-2.75760	6.31260	-3.03990
C	-2.51380	4.26510	-1.34220	H	-0.95310	7.82270	-3.76130
C	-2.25720	3.20240	-0.46490	H	1.34800	7.51900	-2.90770
C	-0.95230	3.01870	0.03200	H	1.86320	5.72810	-1.32550
C	0.07140	3.93970	-0.27710	P	0.21890	0.77670	0.09580
H	-3.51760	4.41090	-1.72580	C	5.31280	-1.44500	0.08070
C	3.25610	4.46090	1.80310	C	5.42520	-0.42320	-0.88120
C	1.97670	4.70780	1.23910	C	4.76750	0.79740	-0.66400
C	1.30120	5.89720	1.58820	C	4.02220	1.00510	0.50200
C	1.89970	6.83170	2.43610	C	3.92470	-0.01290	1.45760
C	3.16970	6.59370	2.96020	C	4.56010	-1.24660	1.25330
C	3.84500	5.41250	2.65110	H	5.81640	-2.38890	-0.07890
H	0.30720	6.11110	1.21990	H	4.84280	1.59040	-1.39920
H	1.37390	7.74280	2.69120	H	3.34600	0.15340	2.35910
H	3.62760	7.32170	3.61740	C	-5.46460	0.57940	0.66280
H	4.82390	5.23860	3.08210	C	-5.26700	0.88860	-0.69230
C	-0.17950	4.97460	-1.21250	C	-4.20700	1.73830	-1.05600
C	-1.48940	5.13730	-1.73210	C	-3.35900	2.28420	-0.07830

C	-3.58090	1.97340	1.27280
C	-4.62420	1.11680	1.65270
H	-6.28290	-0.07420	0.93860
H	-4.03600	1.97930	-2.09760
H	-2.95040	2.41290	2.03690
O	-0.67270	1.94480	0.84020
O	1.48790	1.55030	-0.62290
C	-6.21810	0.32820	-1.72090
F	-5.82240	0.63950	-3.01030
F	-6.27840	-1.04750	-1.59980
F	-7.48030	0.85080	-1.50710
C	-4.82960	0.81250	3.11610
F	-3.66950	0.27530	3.64420
F	-5.12980	1.98230	3.78970
F	-5.86150	-0.08890	3.31360
C	6.25280	-0.59940	-2.13050
F	6.78810	-1.87300	-2.21780
F	5.46500	-0.37600	-3.24470
F	7.28990	0.31530	-2.12450
C	4.43350	-2.32060	2.30540
F	5.07010	-3.48990	1.92620
F	4.99780	-1.87350	3.48600
F	3.09680	-2.59920	2.52500
O	-0.52940	0.18030	-1.08730
O	0.66700	-0.14480	1.20440
H	0.82650	-1.62950	0.69820
C	-0.23830	-3.33690	0.79930
N	0.83190	-2.65050	0.39880
C	-0.67350	-7.61120	0.82970
C	-0.35220	-6.96920	-0.36980
C	-0.20310	-5.58540	-0.41100
C	-0.37550	-4.81780	0.75230
C	-0.70040	-5.47110	1.95130
C	-0.84570	-6.85860	1.99100
H	-0.79090	-8.69030	0.85580
H	-0.22120	-7.54890	-1.27850
H	0.03960	-5.09790	-1.34820
H	-0.83310	-4.88910	2.85920
H	-1.09430	-7.34710	2.92820
C	3.85060	-3.56360	-2.39850
C	3.03290	-2.44620	-2.57090
C	2.02560	-2.15700	-1.65060
C	1.82710	-3.00740	-0.55490
C	2.65840	-4.11870	-0.36610
C	3.66330	-4.39440	-1.29150
H	4.63860	-3.77900	-3.11370
H	3.17600	-1.79010	-3.42370
H	1.38520	-1.28910	-1.77520
H	2.52730	-4.74540	0.50870
H	4.31100	-5.25230	-1.13750
H	-0.73010	-2.85720	1.64010
P	-2.34290	-2.71310	-0.53370
C	-2.53380	-3.24600	-2.32720
H	-2.50960	-4.34370	-2.32150
C	-1.33830	-2.72190	-3.14060
H	-1.27310	-1.63080	-3.08270
H	-0.38490	-3.12350	-2.78600
H	-1.44820	-3.00090	-4.19440
C	-3.85810	-2.76120	-2.93690
H	-3.90450	-3.03350	-3.99760
H	-4.73120	-3.19920	-2.44510
H	-3.93300	-1.67240	-2.86340
C	-3.91400	-3.25710	0.31900
H	-4.70580	-2.70130	-0.19820
C	-4.19200	-4.76190	0.20510
H	-5.12470	-5.00740	0.72560
H	-4.30260	-5.08730	-0.83350
H	-3.39480	-5.35640	0.66210
C	-3.88620	-2.78210	1.78050
H	-4.87240	-2.90800	2.24080
H	-3.17160	-3.36140	2.37620
H	-3.61450	-1.72640	1.84310
O	-2.59250	-1.11820	-0.54840
H	-1.74730	-0.55140	-0.76490

B3LYP/6-31G* Energy = -4433.612318

B3LYP/6-31G* Free Energy = -4432.843574

M06-2X/6-31G** Derived free energy = -4431.456251

M06-2X/6-31G** Derived free energy in solution = -4431.466315

Number of Imaginary Frequencies = 1 (-78.42)

B3LYP/6-31G* Geometry

C	1.99060	3.57860	0.25190	H	2.65280	5.46720	-1.51050
C	4.47710	2.76330	1.32510	P	0.31190	0.73390	0.11490
C	3.69740	1.84680	0.65470	C	5.07390	-2.21840	0.28720
C	2.44570	2.27270	0.12990	C	5.32560	-1.29730	-0.72710
H	5.43940	2.45610	1.72700	C	4.87080	0.01960	-0.61910
C	-1.88790	4.63380	-1.31740	C	4.14960	0.43060	0.50530
C	-1.75700	3.56350	-0.45630	C	3.88290	-0.50100	1.51570
C	-0.44720	3.21770	-0.01210	C	4.34680	-1.81290	1.40630
C	0.67900	3.95310	-0.35130	H	5.42830	-3.23730	0.20200
H	-2.87790	4.93030	-1.65520	H	5.07300	0.72850	-1.41620
C	4.04010	4.09470	1.54000	H	3.29790	-0.20100	2.37770
C	2.77030	4.51020	1.02100	C	-5.27650	1.46950	0.86430
C	2.32330	5.82480	1.33320	C	-5.05180	1.69440	-0.49250
C	3.10120	6.68420	2.07720	C	-3.90720	2.36590	-0.92060
C	4.37160	6.28220	2.55270	C	-2.95360	2.81210	0.00370
C	4.82510	5.01070	2.29090	C	-3.17490	2.56640	1.36620
H	1.34840	6.14740	0.98740	C	-4.32990	1.90920	1.78870
H	2.73160	7.68000	2.30660	H	-6.16750	0.94990	1.19700
H	4.97700	6.97250	3.13350	H	-3.73350	2.51290	-1.98060
H	5.78980	4.67870	2.66730	H	-2.44710	2.89620	2.09790
C	0.54160	5.02400	-1.30000	O	-0.30970	2.10900	0.80520
C	-0.76580	5.36650	-1.77690	O	1.69290	1.34840	-0.56730
C	-0.91430	6.42850	-2.70940	C	-6.07130	1.22160	-1.49090
C	0.18110	7.11170	-3.18370	F	-5.54370	1.06560	-2.72630
C	1.47670	6.75090	-2.74500	F	-6.61090	0.03030	-1.13010
C	1.65250	5.73740	-1.82850	F	-7.10260	2.08920	-1.61190
H	-1.91510	6.68250	-3.05070	C	-4.52190	1.61450	3.25180
H	0.05640	7.91760	-3.90160	F	-3.91260	0.45700	3.61230
H	2.34330	7.27540	-3.13850	F	-4.00560	2.58490	4.03470

F	-5.82860	1.48260	3.57320	C	2.91160	-4.94090	-1.35160
C	6.10600	-1.69520	-1.95030	H	3.97410	-4.46240	-3.16760
F	6.31950	-3.02810	-2.01550	H	2.81840	-2.28400	-3.47410
F	5.46220	-1.33530	-3.08720	H	1.09090	-1.54640	-1.83840
F	7.31780	-1.09460	-1.98980	H	1.75580	-5.11600	0.46270
C	4.00710	-2.80110	2.48940	H	3.42860	-5.88450	-1.20000
F	4.80520	-3.89140	2.45330	H	-1.22360	-2.83530	1.58640
F	4.12180	-2.25440	3.71910	P	-2.81890	-2.45220	-0.60740
F	2.72950	-3.24610	2.38280	C	-3.08700	-2.90780	-2.41330
O	-0.52570	0.27050	-1.05410	H	-3.16960	-4.00380	-2.42950
O	0.61610	-0.21850	1.23910	C	-1.85340	-2.49290	-3.23300
H	0.50550	-1.83440	0.66540	H	-1.68470	-1.41220	-3.17200
C	-0.79090	-3.36620	0.74420	H	-0.93950	-2.98850	-2.88970
N	0.35530	-2.81910	0.34480	H	-1.99940	-2.75250	-4.28850
C	-1.80250	-7.53760	0.67110	C	-4.36570	-2.28820	-3.00090
C	-1.39340	-6.91730	-0.51370	H	-4.44670	-2.54630	-4.06440
C	-1.05700	-5.56640	-0.52190	H	-5.27350	-2.64540	-2.50480
C	-1.12790	-4.81090	0.66020	H	-4.34650	-1.19790	-2.91990
C	-1.54550	-5.44010	1.84350	C	-4.45080	-2.80490	0.23270
C	-1.87620	-6.79620	1.85000	H	-5.15960	-2.10540	-0.23020
H	-2.06530	-8.59170	0.67160	C	-4.93530	-4.24660	0.01340
H	-1.33970	-7.48820	-1.43640	H	-5.89590	-4.39350	0.52200
H	-0.74800	-5.09420	-1.44790	H	-5.08590	-4.48190	-1.04470
H	-1.60240	-4.86690	2.76530	H	-4.23170	-4.97770	0.42670
H	-2.19270	-7.26830	2.77560	C	-4.35530	-2.46910	1.73030
C	3.21700	-4.14310	-2.45760	H	-5.34560	-2.54870	2.19560
C	2.56730	-2.91980	-2.63080	H	-3.69610	-3.17240	2.25430
C	1.60370	-2.49600	-1.71360	H	-3.98680	-1.45500	1.90390
C	1.29570	-3.30640	-0.61390	O	-2.84890	-0.82240	-0.58130
C	1.96220	-4.52240	-0.42050	H	-1.94690	-0.39050	-0.74570

TS3–*E*

(B3LYP/6-31G**:UFF) Energy = -1855.033782

(B3LYP/6-31G**:UFF) Free Energy = -1853.714213

M06-2X/6-31G** Derived free energy = -3790.479530

M06-2X/6-31G** Derived free energy in solution = -3790.487462

Number of Imaginary Frequencies = 1 (-108.32)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	1.78290	3.01880	0.19530	O	0.43400	-0.63930	1.13830
C	4.23150	2.32230	1.38910	H	-0.22710	-2.12650	1.21480
C	3.52570	1.36710	0.65050	C	-0.65960	-4.03830	0.51630
C	2.28340	1.70150	0.07830	N	-0.73440	-3.03030	1.39580
H	5.19850	2.06360	1.80570	C	2.69620	-4.79700	-2.03370
C	-1.94020	4.23920	-1.55840	C	1.75830	-5.79730	-1.76550
C	-1.87570	3.09090	-0.75980	C	0.68730	-5.53130	-0.91830
C	-0.63050	2.64450	-0.28150	C	0.53970	-4.26830	-0.31900
C	0.53920	3.38230	-0.54550	C	1.51280	-3.28370	-0.55310
H	-2.90400	4.59520	-1.90260	C	2.57240	-3.55120	-1.41770
C	3.69360	3.59180	1.61580	H	3.52350	-4.99130	-2.70960
C	2.44820	3.94650	1.04030	H	1.85880	-6.77840	-2.21970
C	1.89970	5.21210	1.34520	H	-0.05400	-6.30360	-0.72660
C	2.59510	6.11270	2.15500	H	1.44280	-2.31230	-0.07710
C	3.83760	5.76690	2.68420	H	3.29710	-2.77220	-1.62100
C	4.38480	4.51090	2.42140	C	-3.63280	-2.68790	4.43630
H	0.92840	5.51140	0.97570	C	-3.10440	-3.94160	4.12570
H	2.16640	7.08170	2.37590	C	-2.13690	-4.07380	3.13000
H	4.37250	6.46920	3.31040	C	-1.70340	-2.94370	2.42350
H	5.34320	4.25350	2.85680	C	-2.21630	-1.67830	2.74930
C	0.48810	4.46400	-1.46060	C	-3.17600	-1.55960	3.75030
C	-0.76970	4.90030	-1.94940	H	-4.38560	-2.58950	5.21230
C	-0.84060	5.99670	-2.82340	H	-3.43470	-4.82240	4.66840
C	0.32490	6.64600	-3.23330	H	-1.70480	-5.04800	2.92310
C	1.56840	6.20660	-2.77920	H	-1.85470	-0.80960	2.21280
C	1.65490	5.12300	-1.90230	H	-3.57540	-0.57860	3.98830
H	-1.79630	6.34550	-3.19640	H	-1.21210	-4.93200	0.78260
H	0.26450	7.48730	-3.91150	P	-2.34970	-3.37310	-1.21070
H	2.47000	6.70630	-3.10940	C	-2.05250	-3.41740	-3.07000
H	2.63750	4.80010	-1.58430	H	-2.88810	-2.84360	-3.49330
P	0.19410	0.25320	-0.05350	C	-0.73750	-2.72980	-3.47520
O	-0.57650	1.56880	0.56640	H	0.12810	-3.32560	-3.17210
O	1.61940	0.77980	-0.69300	H	-0.70630	-2.63240	-4.56670
O	-0.57000	-0.30820	-1.23760	H	-0.62650	-1.73510	-3.03960

C	-2.10440	-4.85480	-3.61440
H	-1.32310	-5.47690	-3.16510
H	-3.06890	-5.34430	-3.45090
H	-1.92600	-4.84160	-4.69530
C	-4.11580	-3.99490	-1.05140
H	-4.15890	-4.88580	-1.68990
C	-4.43110	-4.42860	0.38750
H	-5.47390	-4.75700	0.46080
H	-3.79950	-5.26200	0.71020
H	-4.28570	-3.61100	1.09650
C	-5.12860	-2.95640	-1.56110
H	-5.03020	-2.02410	-1.00330
H	-4.98970	-2.72760	-2.62150
H	-6.14860	-3.33600	-1.43230
O	-2.51660	-1.82940	-0.78280
H	-1.70210	-1.20180	-0.94500
C	5.68520	-2.33840	0.34110
C	4.96690	-2.03280	1.50030
C	4.16690	-0.87980	1.58560
C	4.12950	0.02100	0.48300
C	4.82430	-0.30260	-0.71540
C	5.58210	-1.48750	-0.76640
H	5.03940	-2.69750	2.35120
H	6.11850	-1.73950	-1.67090
C	-5.41910	0.89850	0.35960
C	-4.71180	1.64030	1.31080
C	-3.58080	2.39630	0.95990
C	-3.12270	2.37160	-0.39010
C	-3.86520	1.65350	-1.37540
C	-5.00800	0.93660	-0.97590
H	-5.06010	1.64410	2.33450
H	-5.59420	0.40690	-1.71460
C	4.80480	0.60830	-1.94310
H	4.20260	1.51920	-1.75940
C	3.38430	-0.62290	2.87370
H	2.67580	0.22020	2.73380
C	6.57430	-3.56990	0.30440
H	6.56060	-4.06900	1.29920
C	-6.63710	0.08350	0.75670
H	-7.02120	-0.46800	-0.13050
C	-2.93050	3.27270	2.03420
H	-2.04900	3.81180	1.63540
C	-3.50710	1.68430	-2.86540
H	-2.52730	2.17310	-3.02910
C	-4.54790	2.49410	-3.64860
H	-4.64950	3.51150	-3.21600
H	-4.23170	2.59900	-4.70840
H	-5.54100	1.99690	-3.62300
C	-3.36230	0.28030	-3.46800
H	-4.32300	-0.27410	-3.46840
H	-3.00780	0.35360	-4.51840
H	-2.61220	-0.29790	-2.90230
C	-3.90000	4.36330	2.50720
H	-4.24990	4.96170	1.63870
H	-4.78230	3.92570	3.02020
H	-3.38630	5.04830	3.21530
C	-2.42860	2.43820	3.22160
H	-3.27180	1.99600	3.79180
H	-1.76890	1.61920	2.86960
H	-1.84120	3.07970	3.91270
C	-7.77080	0.99210	1.24550
H	-7.48320	1.52830	2.17480
H	-8.02220	1.73990	0.46310
H	-8.67940	0.38770	1.45310
C	-6.27980	-0.96760	1.81520
H	-6.03020	-0.49230	2.78720
H	-7.13640	-1.65730	1.97050
H	-5.40770	-1.56440	1.47860
C	2.52830	-1.83690	3.27350
H	1.99710	-2.24960	2.39270
H	3.15000	-2.64580	3.71180
H	1.77220	-1.53480	4.02940
C	4.32850	-0.23560	4.01810
H	5.03240	-1.06270	4.25140

H	4.91740	0.66410	3.74580	H	5.03780	-4.91810	-0.43040
H	3.74200	-0.00000	4.93170	C	4.15310	-0.09720	-3.13920
C	8.03390	-3.19310	0.02010	H	4.74960	-0.97510	-3.46520
H	8.38080	-2.43350	0.75310	H	3.13110	-0.43880	-2.86770
H	8.68300	-4.08940	0.11690	H	4.06640	0.60610	-3.99470
H	8.15200	-2.78410	-1.00560	C	6.21400	1.10360	-2.29270
C	6.06130	-4.59460	-0.71190	H	6.86790	0.26960	-2.62340
H	6.04090	-4.17010	-1.73800	H	6.16070	1.85090	-3.11310
H	6.71490	-5.49280	-0.71260	H	6.67390	1.59310	-1.40760

B3LYP/6-31G* Energy = -3793.115361

B3LYP/6-31G* Free Energy = -3791.866960

M06-2X/6-31G** Derived free energy = -3790.561782

M06-2X/6-31G** Derived free energy in solution = -3790.570949

Number of Imaginary Frequencies = 1 (-85.85)

B3LYP/6-31G* Geometry

C	1.54100	3.13740	0.24060	H	5.07830	4.58940	2.85180
C	4.07830	2.61130	1.33340	C	0.13750	4.58070	-1.32260
C	3.45200	1.61760	0.60740	C	-1.15720	4.93760	-1.81580
C	2.15080	1.89790	0.09300	C	-1.29870	6.07600	-2.65440
H	5.08300	2.43360	1.70770	C	-0.20380	6.82200	-3.02420
C	-2.27360	4.14110	-1.46050	C	1.08350	6.45050	-2.56970
C	-2.15210	2.97760	-0.72800	C	1.24970	5.36380	-1.73950
C	-0.84810	2.62400	-0.26590	H	-2.29260	6.33700	-3.01040
C	0.25970	3.43840	-0.45750	H	-0.32170	7.68620	-3.67240
H	-3.25960	4.45070	-1.79600	H	1.95110	7.02570	-2.88200
C	3.45440	3.84660	1.63260	H	2.24400	5.08870	-1.40690
C	2.15650	4.11700	1.09570	P	0.15670	0.18770	-0.07620
C	1.52350	5.33630	1.46790	O	-0.71000	1.47610	0.49760
C	2.15320	6.24270	2.29210	O	1.51570	0.92520	-0.66340
C	3.45400	5.98800	2.78700	O	-0.51730	-0.44900	-1.26780
C	4.08670	4.81060	2.46370	O	0.48190	-0.65760	1.13090
H	0.52360	5.54570	1.10670	H	0.01060	-2.29920	1.27360
H	1.64280	7.16140	2.56870	C	-0.29510	-4.23910	0.62280
H	3.94210	6.71540	3.43010	N	-0.39090	-3.23740	1.49950

C	2.97470	-4.85560	-2.05640	H	-5.24700	-4.65360	0.92840
C	2.08180	-5.89130	-1.76320	H	-3.54080	-4.78340	1.37930
C	1.02530	-5.66400	-0.88830	H	-4.23990	-3.19660	1.03530
C	0.84550	-4.40220	-0.29260	C	-4.98820	-3.74080	-1.63020
C	1.76140	-3.37520	-0.57020	H	-5.00040	-2.65670	-1.48180
C	2.81500	-3.60580	-1.45360	H	-4.84450	-3.94000	-2.69680
H	3.79600	-5.02520	-2.74700	H	-5.97340	-4.13560	-1.35190
H	2.21020	-6.87080	-2.21540	O	-2.45370	-2.13790	-0.80090
H	0.32360	-6.46530	-0.66580	H	-1.67700	-1.50210	-0.96150
H	1.65820	-2.39980	-0.10750	C	5.98590	-1.83910	0.03290
H	3.51360	-2.80240	-1.66330	C	5.32860	-1.61940	1.24380
C	-2.83260	-3.20550	4.93470	C	4.44170	-0.55250	1.43820
C	-2.31350	-4.41480	4.46950	C	4.20380	0.33920	0.36530
C	-1.50040	-4.44600	3.33710	C	4.81920	0.10880	-0.88910
C	-1.21730	-3.25660	2.65010	C	5.69500	-0.97460	-1.02760
C	-1.72110	-2.03730	3.12520	H	5.53070	-2.29270	2.07400
C	-2.52460	-2.02030	4.26240	H	6.18910	-1.12550	-1.98470
H	-3.46120	-3.18590	5.82030	C	-5.79390	0.81950	0.18410
H	-2.52520	-5.34000	4.99860	C	-5.08970	1.50440	1.17800
H	-1.06210	-5.38690	3.01770	C	-3.89710	2.18390	0.91410
H	-1.47170	-1.12210	2.59910	C	-3.37730	2.17460	-0.40370
H	-2.91410	-1.07140	4.61990	C	-4.07140	1.48770	-1.42770
H	-0.79230	-5.15700	0.91210	C	-5.26400	0.82670	-1.10590
P	-2.18640	-3.71590	-1.08800	H	-5.48970	1.52660	2.18910
C	-1.97510	-3.87260	-2.94960	H	-5.80470	0.30420	-1.89230
H	-2.82910	-3.32840	-3.37370	C	4.59890	1.03100	-2.08820
C	-0.68640	-3.18800	-3.43710	H	3.92520	1.83420	-1.77890
H	0.20350	-3.74650	-3.13100	C	3.79100	-0.38120	2.81190
H	-0.69150	-3.14730	-4.53360	H	3.04960	0.41850	2.73520
H	-0.58910	-2.16470	-3.06270	C	7.02620	-2.94580	-0.09290
C	-2.03700	-5.34170	-3.39780	H	6.99510	-3.52260	0.84180
H	-1.23460	-5.93230	-2.94000	C	-7.11680	0.12330	0.47840
H	-2.99340	-5.81850	-3.15700	H	-7.40550	-0.41780	-0.43360
H	-1.90440	-5.40280	-4.48480	C	-3.23920	2.96850	2.04980
C	-3.90310	-4.39400	-0.75660	H	-2.31310	3.40910	1.67190
H	-3.83820	-5.46450	-0.99720	C	-3.59050	1.46430	-2.88000
C	-4.24620	-4.24930	0.73490	H	-2.58280	1.88710	-2.90750

C	-4.48970	2.33530	-3.78100	C	3.03260	-1.64440	3.25890
H	-4.53330	3.37280	-3.43240	H	2.25920	-1.90380	2.53250
H	-4.11210	2.34060	-4.81090	H	3.70150	-2.50440	3.38450
H	-5.51690	1.95120	-3.80280	H	2.54240	-1.46420	4.22330
C	-3.48900	0.03810	-3.44960	C	4.82240	0.03580	3.87930
H	-4.47350	-0.43760	-3.53680	H	5.59150	-0.73480	4.01340
H	-3.04820	0.06760	-4.45360	H	5.33070	0.96760	3.60890
H	-2.86120	-0.58790	-2.81280	H	4.33060	0.18870	4.84760
C	-4.13320	4.13830	2.50780	C	8.44550	-2.35800	-0.22280
H	-4.37040	4.80530	1.67140	H	8.67580	-1.69280	0.61640
H	-5.08090	3.78140	2.92810	H	9.19720	-3.15660	-0.24360
H	-3.62620	4.72860	3.28090	H	8.54830	-1.77630	-1.14680
C	-2.85180	2.06780	3.23660	C	6.73320	-3.92510	-1.24320
H	-3.73160	1.59360	3.68920	H	6.76000	-3.42120	-2.21710
H	-2.16120	1.28310	2.91340	H	7.48250	-4.72570	-1.26700
H	-2.35530	2.65790	4.01640	H	5.74660	-4.38540	-1.12740
C	-8.23230	1.14330	0.78020	C	3.91190	0.29380	-3.25320
H	-8.00680	1.71730	1.68700	H	4.53230	-0.52810	-3.63180
H	-8.34960	1.85580	-0.04360	H	2.94800	-0.11710	-2.93740
H	-9.19310	0.63670	0.93450	H	3.73000	0.98280	-4.08690
C	-7.00100	-0.91330	1.61030	C	5.91000	1.70040	-2.54430
H	-6.73930	-0.43930	2.56360	H	6.64030	0.96390	-2.89970
H	-7.95440	-1.43660	1.75300	H	5.71590	2.39840	-3.36760
H	-6.23090	-1.65950	1.38750	H	6.37390	2.26130	-1.72510

TS4–*E*

(B3LYP/6-31G**:UFF) Energy = -1855.027236

(B3LYP/6-31G**:UFF) Free Energy = -1853.708507

M06-2X/6-31G** Derived free energy = -3790.473954

M06-2X/6-31G** Derived free energy in solution = -3790.482544

Number of Imaginary Frequencies = 1 (-105.69)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	-1.32090	3.08870	-0.35430	C	-3.30330	1.70970	-0.67820
C	-3.87340	2.72270	-1.45930	C	-1.98940	1.85730	-0.18970

H	-4.88750	2.60670	-1.82460
C	2.39270	4.01450	1.57210
C	2.27500	2.86710	0.77820
C	1.01940	2.49970	0.25940
C	-0.09060	3.34550	0.44420
H	3.36550	4.29880	1.95660
C	-3.14790	3.87360	-1.77800
C	-1.85560	4.06580	-1.23250
C	-1.13590	5.22790	-1.58570
C	-1.70220	6.18380	-2.43190
C	-2.98630	5.99710	-2.94310
C	-3.70800	4.84730	-2.62020
H	-0.13010	5.39890	-1.22520
H	-1.14170	7.07190	-2.69420
H	-3.42110	6.74240	-3.59660
H	-4.70130	4.71610	-3.03320
C	0.00400	4.43870	1.34320
C	1.26480	4.77520	1.89520
C	1.38310	5.87680	2.75750
C	0.25790	6.63060	3.09380
C	-0.99230	6.29140	2.57680
C	-1.12400	5.20380	1.71050
H	2.34410	6.14970	3.17730
H	0.35390	7.47550	3.76350
H	-1.86400	6.87180	2.85020
H	-2.11310	4.96010	1.34590
P	-0.05120	0.19490	-0.03750
O	0.92020	1.41380	-0.57270
O	-1.42910	0.87040	0.58480
O	0.58950	-0.50620	1.14010
O	-0.35980	-0.60230	-1.28510
H	-0.23060	-2.19510	-1.19490
C	0.85730	-3.97890	-1.25090
N	-0.25920	-3.25210	-1.15080
C	4.28690	-2.81010	-3.53520
C	4.10760	-4.13750	-3.13700
C	2.98420	-4.49140	-2.39590
C	2.02470	-3.52820	-2.03940
C	2.19910	-2.19850	-2.46010
C	3.33040	-1.85120	-3.19810
H	5.16530	-2.52670	-4.10730
H	4.83950	-4.89330	-3.40560
H	2.84780	-5.52390	-2.08230
H	1.46430	-1.43790	-2.21080
H	3.46430	-0.82150	-3.51150
C	-3.93390	-4.81520	0.18210
C	-3.42850	-3.62920	0.72080
C	-2.21400	-3.11290	0.28100
C	-1.48700	-3.79800	-0.70090
C	-1.99490	-4.97960	-1.25500
C	-3.21430	-5.48570	-0.80740
H	-4.88150	-5.21820	0.52380
H	-3.96710	-3.09730	1.49770
H	-1.81150	-2.20490	0.71280
H	-1.45500	-5.47630	-2.05560
H	-3.60940	-6.39770	-1.24510
H	0.71500	-5.05360	-1.21250
P	1.71970	-4.00230	1.13560
C	3.51340	-3.62090	1.52590
H	3.51670	-3.32660	2.58350
C	4.42780	-4.84010	1.32970
H	4.19070	-5.66330	2.00910
H	4.37470	-5.21710	0.30210
H	5.46930	-4.55230	1.51230
C	4.00260	-2.43450	0.68370
H	3.32190	-1.58060	0.72580
H	4.98320	-2.11320	1.04930
H	4.11440	-2.71930	-0.36380
C	1.31850	-5.49240	2.19910
H	1.96390	-6.29750	1.82270
C	1.62210	-5.24570	3.68670
H	1.32390	-6.11900	4.27820
H	2.68480	-5.06830	3.87340
H	1.06350	-4.37910	4.05040

C	-0.14780	-5.90770	2.00360
H	-0.37150	-6.78870	2.61530
H	-0.82350	-5.10310	2.30590
H	-0.37490	-6.15720	0.96340
O	0.83780	-2.87490	1.87050
H	0.75620	-1.91010	1.49320
C	-6.12130	-1.41820	0.21460
C	-5.47900	-1.38150	-1.02790
C	-4.50370	-0.41030	-1.32480
C	-4.14590	0.53920	-0.32470
C	-4.75640	0.47370	0.96050
C	-5.73760	-0.50460	1.20250
H	-5.78740	-2.08100	-1.79390
H	-6.24120	-0.52550	2.15830
C	5.86310	0.66190	-0.15300
C	5.34670	0.65750	1.14700
C	4.15870	1.33790	1.47090
C	3.49260	2.08290	0.45430
C	4.03810	2.13000	-0.86150
C	5.20220	1.39500	-1.14410
H	5.88070	0.11760	1.91790
H	5.62060	1.42180	-2.14090
C	-4.43710	1.47330	2.07440
H	-3.67690	2.21010	1.75400
C	-3.91940	-0.36370	-2.73900
H	-3.13660	0.41790	-2.81870
C	-7.29840	-2.35780	0.42880
H	-7.33560	-3.09610	-0.40340
C	7.15190	-0.08120	-0.46180
H	7.49090	-0.63030	0.44510
C	3.65790	1.29090	2.91860
H	2.68570	1.81200	3.02200
C	3.44510	3.00680	-1.96790
H	2.54790	3.55150	-1.61560
C	2.99440	2.16530	-3.16910
H	2.30310	1.36220	-2.83820
H	2.45480	2.80570	-3.89910
H	3.86100	1.70240	-3.68580
C	4.43860	4.09250	-2.40210
H	4.75870	4.68760	-1.52000
H	3.95570	4.78130	-3.12780
H	5.33700	3.65200	-2.88340
C	3.40040	-0.14420	3.39800
H	2.64350	-0.63060	2.75340
H	4.32790	-0.75320	3.39390
H	2.99920	-0.13190	4.43400
C	4.64130	2.00340	3.85590
H	5.60940	1.46180	3.90820
H	4.83040	3.03790	3.49960
H	4.21580	2.06350	4.88040
C	8.26990	0.89900	-0.83580
H	8.03400	1.43460	-1.77990
H	8.40830	1.64540	-0.02450
H	9.22710	0.35130	-0.96990
C	6.95040	-1.12750	-1.56590
H	6.68970	-0.65030	-2.53400
H	7.88210	-1.71600	-1.70540
H	6.14090	-1.83030	-1.28480
C	-3.22750	-1.67930	-3.11200
H	-2.42740	-1.89500	-2.38180
H	-3.93980	-2.53010	-3.13070
H	-2.75820	-1.59260	-4.11520
C	-5.00120	-0.01300	-3.76890
H	-5.76360	-0.81740	-3.84080
H	-5.50800	0.93370	-3.48780
H	-4.54160	0.12610	-4.77080
C	-8.61320	-1.57100	0.39390
H	-8.70400	-1.02410	-0.56910
H	-9.47690	-2.26440	0.48120
H	-8.65820	-0.83760	1.22760
C	-7.18880	-3.16310	1.73170
H	-7.29710	-2.51200	2.62400
H	-7.99120	-3.93070	1.76700
H	-6.21620	-3.68680	1.78750

C	-3.84600	0.76100	3.29740	C	-5.67290	2.29830	2.45690
H	-4.58760	0.08060	3.76650	H	-6.45600	1.66660	2.92570
H	-2.95510	0.16840	2.99730	H	-5.38890	3.09360	3.17890
H	-3.52610	1.50810	4.05480	H	-6.09650	2.78650	1.55310

B3LYP/6-31G* Energy = -3793.112673

B3LYP/6-31G* Free Energy = -3791.864116

M06-2X/6-31G** Derived free energy = -3790.558399

M06-2X/6-31G** Derived free energy in solution = -3790.567771

Number of Imaginary Frequencies = 1 (-76.17)

B3LYP/6-31G* Geometry

C	1.11370	3.24070	0.48840	C	0.35330	6.72160	-2.01690
C	3.71660	2.93450	1.50570	C	0.61680	5.59310	-1.27220
C	3.21110	1.95060	0.67880	H	-2.95910	6.24350	-2.65080
C	1.87230	2.11180	0.21190	H	-1.14390	7.87420	-3.08840
H	4.74520	2.85640	1.84700	H	1.15620	7.42140	-2.23310
C	-2.73080	3.93310	-1.29740	H	1.62280	5.41170	-0.91280
C	-2.50150	2.73200	-0.65580	P	0.10980	0.19220	-0.06990
C	-1.19000	2.49810	-0.14270	O	-0.94630	1.31410	0.53670
C	-0.18450	3.45500	-0.20970	O	1.34010	1.14740	-0.63010
H	-3.73070	4.14730	-1.66450	O	-0.46210	-0.49600	-1.28310
C	2.94170	4.03650	1.94340	O	0.57290	-0.64310	1.09940
C	1.61210	4.19560	1.44020	H	0.95880	-2.28970	0.69670
C	0.83640	5.28160	1.93340	C	0.23040	-4.17650	1.04960
C	1.35810	6.17030	2.84750	N	1.05670	-3.30750	0.47300
C	2.68620	6.02970	3.31510	C	-1.33650	-3.97370	5.01850
C	3.45790	4.98130	2.87100	C	-1.32340	-5.17670	4.30720
H	-0.18530	5.39970	1.59140	C	-0.82640	-5.20620	3.00800
H	0.74140	6.98560	3.21660	C	-0.33460	-4.03630	2.39900
H	3.08750	6.74240	4.03050	C	-0.34830	-2.82910	3.12070
H	4.47490	4.84990	3.23350	C	-0.84950	-2.80850	4.42140
C	-0.40740	4.64830	-0.98150	H	-1.72300	-3.94630	6.03360
C	-1.71130	4.89020	-1.51650	H	-1.69440	-6.08900	4.76570
C	-1.95710	6.07380	-2.26350	H	-0.81460	-6.14370	2.45620
C	-0.94870	6.97600	-2.50880	H	0.01100	-1.91210	2.66350

H	-0.85880	-1.87130	4.97040	C	5.49710	-1.07900	0.85280
C	3.39080	-4.39100	-2.86920	C	4.52620	-0.13970	1.22140
C	2.72690	-3.16230	-2.84140	C	4.10880	0.81950	0.26770
C	1.95710	-2.79310	-1.74010	C	4.65070	0.78850	-1.04030
C	1.85720	-3.66590	-0.64990	C	5.61440	-0.17540	-1.35390
C	2.54370	-4.88790	-0.65880	H	5.83040	-1.80720	1.58900
C	3.29880	-5.25100	-1.77290	H	6.03930	-0.17720	-2.35450
H	3.98180	-4.67360	-3.73570	C	-6.10060	0.36420	-0.28860
H	2.79570	-2.48520	-3.68760	C	-5.37970	0.39960	-1.48290
H	1.40300	-1.86020	-1.74330	C	-4.17100	1.09610	-1.61400
H	2.51500	-5.53510	0.21320	C	-3.66360	1.79300	-0.49180
H	3.82900	-6.19930	-1.77440	C	-4.35450	1.73720	0.74290
H	0.32360	-5.19550	0.69310	C	-5.55570	1.02360	0.81750
P	-1.91530	-3.97060	-0.54740	H	-5.78480	-0.11570	-2.35110
C	-3.56010	-3.37830	0.12030	H	-6.09230	1.00480	1.76340
H	-4.19090	-3.16080	-0.75210	C	4.26120	1.80200	-2.11700
C	-4.23160	-4.45790	0.98430	H	3.52830	2.49170	-1.69060
H	-4.47000	-5.36320	0.41450	C	3.97590	-0.17850	2.64850
H	-3.59700	-4.74490	1.83130	H	3.12620	0.50770	2.70030
H	-5.17150	-4.07330	1.39830	C	7.18850	-2.09180	-0.74090
C	-3.34920	-2.07020	0.89920	H	7.22710	-2.81570	0.08510
H	-2.86370	-1.30500	0.28620	C	-7.45550	-0.33080	-0.22000
H	-4.31320	-1.66150	1.21760	H	-7.62680	-0.79740	-1.20000
H	-2.74000	-2.23310	1.79430	C	-3.47150	1.10920	-2.97460
C	-2.32190	-5.43210	-1.64580	H	-2.47440	1.53650	-2.83520
H	-2.68090	-6.21160	-0.95830	C	-3.84920	2.45970	1.99160
C	-3.41460	-5.13180	-2.68470	H	-2.94870	3.01680	1.71930
H	-3.56840	-6.00640	-3.32940	C	-3.44400	1.46280	3.09400
H	-4.37550	-4.89340	-2.21800	H	-2.66400	0.78510	2.73370
H	-3.12410	-4.28850	-3.31880	H	-3.05480	1.99800	3.96900
C	-1.03660	-5.93480	-2.32530	H	-4.29930	0.86040	3.42410
H	-1.25250	-6.82110	-2.93410	C	-4.86750	3.49010	2.51630
H	-0.61700	-5.16470	-2.98010	H	-5.13070	4.21770	1.74040
H	-0.26370	-6.20950	-1.59840	H	-4.44920	4.03830	3.36910
O	-1.49720	-2.88520	-1.69500	H	-5.79470	3.01210	2.85410
H	-1.09840	-2.00520	-1.40860	C	-3.27180	-0.30320	-3.55420
C	6.06810	-1.10980	-0.41970	H	-2.72410	-0.94680	-2.86250

H	-4.22730	-0.78600	-3.79500	H	5.90180	-0.36990	3.67720
H	-2.69530	-0.24230	-4.48510	H	5.37890	1.30530	3.46080
C	-4.22890	1.99440	-3.98550	H	4.60290	0.28840	4.68720
H	-5.23710	1.60420	-4.17240	C	8.55190	-1.37250	-0.78570
H	-4.33290	3.02450	-3.62890	H	8.75260	-0.84610	0.15390
H	-3.69740	2.02160	-4.94460	H	9.36550	-2.08790	-0.95870
C	-8.59270	0.68350	0.01120	H	8.57710	-0.63190	-1.59410
H	-8.48850	1.17880	0.98390	C	6.94700	-2.88500	-2.03640
H	-8.59050	1.46100	-0.76030	H	6.93920	-2.22820	-2.91450
H	-9.56930	0.18440	-0.00770	H	7.74440	-3.62300	-2.18730
C	-7.50130	-1.45060	0.83530	H	5.98920	-3.41380	-2.00590
H	-7.33980	-1.05630	1.84570	C	3.58840	1.12360	-3.32550
H	-8.47790	-1.94990	0.82720	H	4.26780	0.41880	-3.82090
H	-6.73230	-2.20710	0.64380	H	2.69120	0.58020	-3.01450
C	3.44500	-1.57100	3.03390	H	3.29070	1.87480	-4.06720
H	2.68920	-1.90810	2.32110	C	5.46760	2.65450	-2.55750
H	4.24360	-2.32150	3.07050	H	6.24450	2.04380	-3.03290
H	2.98250	-1.53550	4.02780	H	5.15320	3.41480	-3.28290
C	5.02630	0.29110	3.67530	H	5.92330	3.16740	-1.70300

TS3–*Z*

(B3LYP/6-31G**:UFF) Energy = -1855.019171

(B3LYP/6-31G**:UFF) Free Energy = -1853.702051

M06-2X/6-31G** Derived free energy = -3790.472230

M06-2X/6-31G** Derived free energy in solution = -3790.480407

Number of Imaginary Frequencies = 1 (-107.89)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	-2.49220	-2.76130	-0.38830	C	-3.40140	-1.70300	0.15260
C	-0.74430	-4.84290	-1.11540	H	-5.80180	1.14900	1.30190
C	-0.23890	-3.71800	-0.45420	C	-2.08510	-4.89790	-1.51130
C	-1.10860	-2.66610	-0.11080	C	-2.96890	-3.84140	-1.17500
H	-0.07960	-5.66680	-1.34570	C	-4.29820	-3.89370	-1.64750
C	-5.13150	0.35480	0.99510	C	-4.74550	-4.98840	-2.39040
C	-3.96710	0.67490	0.28860	C	-3.87810	-6.04000	-2.68410
C	-3.11920	-0.35530	-0.15650	C	-2.55230	-5.99590	-2.25130

H	-4.99580	-3.08900	-1.45790
H	-5.76870	-5.01980	-2.74200
H	-4.23080	-6.88630	-3.25930
H	-1.88870	-6.81410	-2.50520
C	-4.50190	-2.00450	0.99810
C	-5.39050	-0.96570	1.37910
C	-6.51050	-1.25510	2.17480
C	-6.74000	-2.55730	2.61990
C	-5.84990	-3.57750	2.28690
C	-4.73550	-3.30740	1.48970
H	-7.19980	-0.47110	2.46570
H	-7.60180	-2.77300	3.23830
H	-6.02160	-4.58220	2.65120
H	-4.05770	-4.12200	1.27450
P	-0.59410	-0.20300	-0.32120
O	-2.07830	-0.05670	-0.99580
O	-0.62420	-1.58290	0.57710
O	-0.37990	0.92310	0.67170
O	0.36730	-0.32860	-1.47560
H	1.44470	0.78730	-1.42580
C	3.24930	1.19360	-0.61090
N	2.23450	1.50150	-1.42160
C	7.25520	2.73200	-0.82820
C	6.19830	3.62140	-0.61220
C	4.88850	3.15430	-0.53750
C	4.61510	1.78520	-0.67880
C	5.68130	0.90020	-0.89850
C	6.99330	1.36980	-0.97340
H	8.27500	3.10070	-0.88090
H	6.39630	4.68270	-0.49640
H	4.07550	3.85110	-0.36540
H	5.47790	-0.15960	-1.02250
H	7.80620	0.67060	-1.14400
C	1.19590	4.84990	-3.75890
C	0.26850	4.25080	-2.90540
C	0.63740	3.16950	-2.10750
C	1.94960	2.67340	-2.16930
C	2.87560	3.25660	-3.04520
C	2.49720	4.34870	-3.82470
H	0.90360	5.69270	-4.37780
H	-0.74840	4.62640	-2.85970
H	-0.07360	2.70600	-1.43120
H	3.87210	2.84150	-3.13470
H	3.21910	4.79460	-4.50260
H	3.22990	0.14160	-0.33970
P	2.74060	1.66280	1.83960
C	2.42170	3.43250	2.38800
H	3.37650	3.96210	2.26750
C	1.37850	4.08430	1.46350
H	1.72890	4.15810	0.43020
H	0.44430	3.51600	1.44720
H	1.15290	5.09760	1.81320
C	1.98190	3.50200	3.85960
H	2.77710	3.19660	4.54570
H	1.69850	4.52880	4.11760
H	1.11760	2.85560	4.03390
C	4.00520	0.98970	3.04130
H	3.53910	1.11100	4.02760
C	4.17440	-0.51450	2.78020
H	4.86640	-0.95690	3.50500
H	3.21790	-1.03490	2.85020
H	4.58380	-0.68920	1.78160
C	5.34380	1.73880	3.02030
H	6.01460	1.31950	3.77860
H	5.84400	1.64680	2.05190
H	5.22750	2.80460	3.24000
O	1.45580	0.82250	2.32800
H	0.66490	0.82020	1.64770
C	3.98460	-3.87040	0.42590
C	3.04620	-3.90710	1.46250
C	1.66260	-3.83880	1.20710
C	1.21420	-3.66170	-0.13370
C	2.17120	-3.54370	-1.18470
C	3.53710	-3.69050	-0.88680

H	3.39610	-4.04860	2.47680
H	4.26150	-3.67400	-1.68910
C	-2.84610	4.80530	-0.30290
C	-3.23990	4.01710	-1.38690
C	-3.62780	2.67550	-1.22050
C	-3.59750	2.10210	0.08390
C	-3.21140	2.90750	1.19980
C	-2.85790	4.25060	0.98060
H	-3.26310	4.46190	-2.37300
H	-2.59220	4.87800	1.81970
C	1.76870	-3.27680	-2.63610
H	0.68940	-3.02720	-2.70080
C	0.69510	-4.02250	2.37810
H	-0.35840	-3.98190	2.04120
C	5.45690	-4.10620	0.72390
H	5.61000	-4.14880	1.82550
C	-2.44020	6.25190	-0.52500
H	-2.45780	6.48060	-1.61410
C	-4.11580	1.90400	-2.44780
H	-4.36980	0.85750	-2.18870
C	-3.21150	2.38390	2.64110
H	-3.37570	1.28930	2.66770
C	-4.34700	3.02880	3.44580
H	-5.32050	2.86620	2.93800
H	-4.40450	2.57300	4.45740
H	-4.18450	4.12180	3.55870
C	-1.86650	2.60390	3.34910
H	-1.64740	3.68090	3.50150
H	-1.87910	2.11280	4.34570
H	-1.04760	2.15090	2.76280
C	-5.40680	2.51930	-3.00200
H	-6.18060	2.55750	-2.20540
H	-5.23390	3.54770	-3.38370
H	-5.79760	1.89680	-3.83520
C	-3.03250	1.83450	-3.53530
H	-2.07750	1.46100	-3.11040
H	-3.34960	1.13820	-4.34060
H	-2.84910	2.83050	-3.99000
C	-1.00830	6.51070	-0.03950
H	-0.93580	6.41920	1.06470
H	-0.30830	5.78620	-0.50530
H	-0.68930	7.53490	-0.32800
C	-3.42980	7.20910	0.14930
H	-3.41450	7.09000	1.25350
H	-3.16880	8.26060	-0.09610
H	-4.45950	7.01210	-0.21870
C	0.86610	-5.40210	3.02740
H	0.75890	-6.19810	2.25960
H	1.85910	-5.50250	3.51350
H	0.08250	-5.55800	3.79950
C	0.85740	-2.90290	3.41420
H	0.74890	-1.91170	2.92570
H	0.07150	-2.99090	4.19440
H	1.84930	-2.95220	3.91040
C	5.90930	-5.45630	0.15560
H	5.84120	-5.46510	-0.95330
H	6.96140	-5.66050	0.44810
H	5.27260	-6.27200	0.56030
C	6.34480	-2.97160	0.19480
H	7.39610	-3.13390	0.51480
H	6.32320	-2.92010	-0.91380
H	6.01220	-1.99920	0.60470
C	2.00240	-4.51770	-3.50750
H	3.08140	-4.77760	-3.55150
H	1.44750	-5.38800	-3.10260
H	1.64130	-4.32930	-4.54100
C	2.51970	-2.06830	-3.22090
H	3.57630	-2.31880	-3.45260
H	2.02960	-1.73680	-4.16110
H	2.51610	-1.22150	-2.50670

B3LYP/6-31G* Energy = -3793.107784

B3LYP/6-31G* Free Energy = -3791.859241

M06-2X/6-31G** Derived free energy = -3790.554520

M06-2X/6-31G** Derived free energy in solution = -3790.563974

Number of Imaginary Frequencies = 1 (-98.84)

B3LYP/6-31G* Geometry

C	-2.74760	-2.61090	-0.27700	H	-4.44430	-3.82290	1.36500
C	-1.21630	-4.84890	-1.05170	P	-0.53070	-0.19900	-0.13900
C	-0.58030	-3.79890	-0.42090	O	-2.02840	0.06440	-0.77310
C	-1.37780	-2.67540	-0.05180	O	-0.76270	-1.64040	0.63310
H	-0.64140	-5.73280	-1.31580	O	-0.22540	0.81810	0.93640
C	-5.11140	0.73630	1.05980	O	0.40910	-0.34140	-1.30590
C	-3.93880	0.97220	0.37220	H	1.70340	0.68190	-1.30930
C	-3.16270	-0.16130	-0.01350	C	3.57220	1.01340	-0.60820
C	-3.54210	-1.46910	0.26190	N	2.52890	1.32840	-1.38140
H	-5.73800	1.57910	1.34040	C	7.56170	2.56480	-0.98820
C	-2.58570	-4.80070	-1.41190	C	6.50230	3.45560	-0.78960
C	-3.36510	-3.65570	-1.05000	C	5.19840	2.98280	-0.66410
C	-4.71090	-3.59520	-1.50810	C	4.93290	1.60540	-0.73340
C	-5.26090	-4.62300	-2.24200	C	6.00280	0.71830	-0.92880
C	-4.50040	-5.77370	-2.55640	C	7.30840	1.19510	-1.05910
C	-3.18870	-5.85430	-2.15100	H	8.57740	2.93830	-1.08360
H	-5.30610	-2.71750	-1.28510	H	6.69300	4.52340	-0.72940
H	-6.28860	-4.54600	-2.58720	H	4.38510	3.68320	-0.50770
H	-4.94900	-6.58120	-3.12870	H	5.81060	-0.35000	-0.98830
H	-2.58310	-6.72130	-2.40490	H	8.12380	0.49410	-1.21320
C	-4.69770	-1.68680	1.09150	C	1.57180	4.70100	-3.72430
C	-5.50550	-0.56410	1.46190	C	0.67420	4.21090	-2.77400
C	-6.66820	-0.76770	2.25360	C	1.01550	3.11530	-1.98090
C	-7.00980	-2.02280	2.70000	C	2.26550	2.50250	-2.14390
C	-6.18840	-3.12840	2.37660	C	3.15770	2.97340	-3.11610
C	-5.06660	-2.96590	1.59400	C	2.81090	4.07840	-3.89230
H	-7.27530	0.09660	2.51330	H	1.30280	5.55360	-4.34150
H	-7.89680	-2.16580	3.31130	H	-0.30160	4.66950	-2.64650
H	-6.44150	-4.11560	2.75390	H	0.32250	2.73250	-1.23770

H	4.10110	2.46440	-3.27760
H	3.50510	4.43930	-4.64630
H	3.55440	-0.03210	-0.31510
P	3.16710	1.54680	1.86020
C	3.01460	3.34040	2.40100
H	3.99640	3.78750	2.19150
C	1.95460	4.06310	1.55320
H	2.19570	4.05140	0.48530
H	0.96810	3.60410	1.67410
H	1.87560	5.11130	1.86610
C	2.70300	3.46910	3.90110
H	3.50150	3.06330	4.53060
H	2.57660	4.52630	4.16590
H	1.77510	2.94390	4.14810
C	4.45640	0.81140	2.99850
H	3.99910	0.86670	3.99550
C	4.66650	-0.67240	2.65600
H	5.30990	-1.14320	3.40940
H	3.72100	-1.22130	2.62770
H	5.16400	-0.78650	1.68560
C	5.78430	1.58370	3.00790
H	6.48690	1.09690	3.69520
H	6.25230	1.59910	2.01800
H	5.66390	2.61910	3.34270
O	1.85100	0.79670	2.44620
H	1.04030	0.77500	1.82620
C	3.65780	-4.29870	0.32110
C	2.74180	-4.26330	1.37390
C	1.37100	-4.06200	1.17070
C	0.89380	-3.88110	-0.14840
C	1.80940	-3.87360	-1.23130
C	3.16750	-4.08910	-0.96990
H	3.10490	-4.42430	2.38700
H	3.85930	-4.10630	-1.80830
C	-2.81340	5.07230	-0.46640
C	-3.19300	4.20500	-1.49230
C	-3.54480	2.87000	-1.25620
C	-3.50990	2.37760	0.06880
C	-3.11990	3.23650	1.12810
C	-2.78310	4.56200	0.83370
H	-3.24000	4.58810	-2.51010
H	-2.49540	5.21760	1.65170
C	1.37970	-3.65150	-2.68350
H	0.31700	-3.39770	-2.68680
C	0.44110	-4.10370	2.38210
H	-0.57120	-3.86910	2.04470
C	5.12510	-4.61890	0.58060
H	5.27910	-4.57030	1.66750
C	-2.49310	6.53340	-0.75840
H	-2.49000	6.65090	-1.85140
C	-4.00800	2.01700	-2.43640
H	-4.21080	1.00790	-2.06810
C	-3.06950	2.78640	2.59010
H	-3.27940	1.71490	2.62400
C	-4.15140	3.49490	3.42970
H	-5.15410	3.32860	3.01960
H	-4.14120	3.12280	4.46140
H	-3.98550	4.57860	3.46440
C	-1.67610	2.97780	3.21740
H	-1.37450	4.03250	3.23330
H	-1.68110	2.62200	4.25540
H	-0.93000	2.40380	2.66220
C	-5.32950	2.55260	-3.02360
H	-6.11390	2.59840	-2.25970
H	-5.20690	3.56100	-3.43670
H	-5.68050	1.90130	-3.83340
C	-2.92720	1.88980	-3.52600
H	-2.00750	1.46270	-3.11630
H	-3.27810	1.23330	-4.33150
H	-2.68750	2.86170	-3.97480
C	-1.10260	6.95220	-0.24570
H	-1.04310	6.88660	0.84720
H	-0.31440	6.31490	-0.66100
H	-0.88590	7.99030	-0.52600

C	-3.58520	7.46700	-0.20020	H	6.50420	-6.30520	0.37030
H	-3.63600	7.40250	0.89330	H	4.81330	-6.78480	0.62600
H	-3.37910	8.51120	-0.46580	C	6.08950	-3.60840	-0.06480
H	-4.57180	7.20130	-0.59520	H	7.12790	-3.84360	0.19810
C	0.39110	-5.51710	2.99670	H	6.01610	-3.62280	-1.15880
H	0.07450	-6.26010	2.25600	H	5.87700	-2.58830	0.27500
H	1.37180	-5.82430	3.37960	C	1.55820	-4.92990	-3.52660
H	-0.31790	-5.54710	3.83310	H	2.61250	-5.22760	-3.58210
C	0.81620	-3.04980	3.44090	H	0.99930	-5.77390	-3.10720
H	0.82970	-2.04340	3.01140	H	1.20380	-4.76570	-4.55150
H	0.08640	-3.06030	4.25940	C	2.11530	-2.46440	-3.33330
H	1.80220	-3.24900	3.87900	H	3.19870	-2.63020	-3.38480
C	5.46310	-6.05490	0.13150	H	1.75700	-2.31980	-4.36000
H	5.32810	-6.16860	-0.95080	H	1.91950	-1.54630	-2.77480

TS4–*Z*

(B3LYP/6-31G**:UFF) Energy = -1855.020675

(B3LYP/6-31G**:UFF) Free Energy = -1853.706081

M06-2X/6-31G** Derived free energy = -3790.474900

M06-2X/6-31G** Derived free energy in solution = -3790.483143

Number of Imaginary Frequencies = 1 (-117.49)

ONIOM (B3LYP/6-31G**:UFF) Geometry

C	2.90210	2.27390	0.29290	C	5.00930	4.67890	2.25030
C	4.98920	0.61400	1.18950	C	6.06020	3.84870	2.63850
C	3.91070	0.05630	0.49500	C	6.05620	2.50040	2.27990
C	2.84280	0.87550	0.08670	H	3.14910	4.84240	1.22610
H	5.81510	-0.02150	1.48800	H	5.00930	5.72080	2.54370
C	-0.18840	4.86780	-1.20440	H	6.87500	4.24880	3.22800
C	-0.51280	3.75840	-0.41600	H	6.87440	1.86780	2.60370
C	0.50540	2.88470	0.00550	C	2.15870	4.19210	-1.22220
C	1.85050	3.13720	-0.32530	C	1.12680	5.07220	-1.63950
H	-0.96920	5.55820	-1.49870	C	1.42310	6.14490	-2.49550
C	4.99950	1.97260	1.52070	C	2.72510	6.33560	-2.96010
C	3.94320	2.81530	1.09170	C	3.73950	5.45650	-2.58160
C	3.95520	4.17050	1.48820	C	3.46290	4.38950	-1.72400

H	0.64560	6.82950	-2.81350
H	2.94620	7.16120	-3.62410
H	4.74470	5.60060	-2.95640
H	4.27230	3.71850	-1.46880
P	0.33400	0.37250	0.08330
O	0.19990	1.83020	0.82420
O	1.81690	0.32610	-0.63980
O	-0.63530	0.32250	-1.08680
O	0.21230	-0.65060	1.18090
H	-1.19620	-1.51470	1.26340
C	-2.78420	-1.69280	0.02910
N	-2.12450	-1.99570	1.16930
C	-7.02010	-2.22910	-0.49320
C	-6.24320	-3.32080	-0.09550
C	-4.86650	-3.18410	0.07220
C	-4.24190	-1.94780	-0.15690
C	-5.03090	-0.86210	-0.56440
C	-6.40950	-0.99760	-0.72770
H	-8.09270	-2.34120	-0.62010
H	-6.71150	-4.28380	0.08530
H	-4.27630	-4.03960	0.38030
H	-4.55910	0.09770	-0.73970
H	-7.00080	-0.14050	-1.03540
C	-2.95630	-4.79610	4.21820
C	-1.80210	-4.91690	3.44360
C	-1.54560	-4.00650	2.41810
C	-2.44430	-2.96300	2.16320
C	-3.59160	-2.82880	2.95730
C	-3.84800	-3.74960	3.97160
H	-3.15530	-5.50510	5.01610
H	-1.09680	-5.72000	3.63600
H	-0.64840	-4.09390	1.81470
H	-4.26490	-1.99720	2.78230
H	-4.73910	-3.63810	4.58230
H	-2.43170	-0.75140	-0.38510
P	-1.77830	-2.70550	-1.94320
C	-0.47860	-4.00680	-1.57360
H	-0.97300	-4.74400	-0.92560
C	0.05850	-4.70650	-2.83390
H	-0.69850	-5.30170	-3.35130
H	0.46100	-3.97090	-3.53780
H	0.87680	-5.38130	-2.56060
C	0.68450	-3.35430	-0.80300
H	1.35240	-4.13140	-0.42120
H	1.26530	-2.70960	-1.46760
H	0.37400	-2.73430	0.03860
C	-2.80960	-3.38800	-3.34480
H	-2.06810	-3.61070	-4.12280
C	-3.55750	-4.67950	-2.98380
H	-4.03710	-5.09120	-3.87880
H	-2.89510	-5.45300	-2.58270
H	-4.34380	-4.49190	-2.24780
C	-3.75170	-2.30570	-3.89530
H	-3.19710	-1.40230	-4.15920
H	-4.25200	-2.67500	-4.79760
H	-4.52640	-2.03830	-3.17060
O	-0.98640	-1.52820	-2.70760
H	-0.75350	-0.73340	-2.07930
C	4.29000	-4.16080	-0.31140
C	3.96500	-3.70950	0.97300
C	3.75230	-2.34560	1.24040
C	3.92860	-1.39840	0.19140
C	4.23610	-1.85140	-1.12330
C	4.39100	-3.23170	-1.35150
H	3.88410	-4.42940	1.77560
H	4.63090	-3.58590	-2.34550
C	-4.59270	2.99100	0.76920
C	-4.21450	2.87530	-0.57090
C	-2.88940	3.10160	-0.98410
C	-1.92540	3.51900	-0.01740
C	-2.32380	3.71130	1.33720
C	-3.64900	3.42260	1.70710
H	-4.96080	2.58580	-1.29880
H	-3.95550	3.54720	2.73660

C	4.44800	-0.88950	-2.29400	H	-7.80060	3.64870	1.93810
H	4.33470	0.16480	-1.97590	H	-6.71960	4.70260	0.95790
C	3.35640	-1.92990	2.65800	C	-6.03240	1.51890	2.22020
H	3.09700	-0.85160	2.69230	H	-5.58570	1.84360	3.18370
C	4.56850	-5.63110	-0.57660	H	-7.07840	1.19560	2.40850
H	4.80510	-5.77690	-1.65440	H	-5.46230	0.64450	1.84170
C	-6.01290	2.65410	1.18780	C	2.10350	-2.67760	3.14000
H	-6.58640	2.29560	0.30380	H	1.30430	-2.62400	2.37520
C	-2.54540	2.91390	-2.46450	H	2.31990	-3.74660	3.34710
H	-1.44670	2.92480	-2.61380	H	1.72200	-2.21470	4.07500
C	-1.37450	4.26390	2.40300	C	4.51890	-2.14420	3.63500
H	-0.36530	4.45000	1.98620	H	4.77880	-3.22090	3.71760
C	-1.18990	3.27190	3.56030	H	5.41640	-1.58800	3.29370
H	-0.88660	2.27710	3.17260	H	4.24240	-1.76850	4.64330
H	-0.39350	3.63370	4.24510	C	3.34510	-6.50310	-0.26890
H	-2.12540	3.15400	4.14630	H	2.48480	-6.18440	-0.89140
C	-1.86410	5.62240	2.92070	H	3.56490	-7.56490	-0.51070
H	-2.83220	5.52700	3.45620	H	3.06070	-6.43840	0.80240
H	-1.11730	6.05420	3.62090	C	5.79280	-6.10650	0.21510
H	-1.99140	6.32780	2.07160	H	5.60130	-6.07290	1.30870
C	-3.02890	1.56020	-3.01420	H	6.04620	-7.15090	-0.06650
H	-2.77210	0.73870	-2.32030	H	6.66880	-5.46330	-0.01630
H	-4.12790	1.54980	-3.17120	C	3.40320	-1.11930	-3.39410
H	-2.54250	1.35380	-3.99150	H	3.50920	-2.12640	-3.84930
C	-3.13090	4.05910	-3.29980	H	2.37930	-1.02220	-2.97530
H	-4.24110	4.05320	-3.25800	H	3.52070	-0.35810	-4.19460
H	-2.77090	5.03840	-2.92340	C	5.87210	-1.00000	-2.85410
H	-2.81430	3.95810	-4.35990	H	6.04880	-1.99010	-3.32400
C	-6.73940	3.89450	1.72020	H	6.03950	-0.21490	-3.62230
H	-6.26510	4.26860	2.65230	H	6.61240	-0.85030	-2.03910

B3LYP/6-31G* Energy = -3793.107107

B3LYP/6-31G* Free Energy = -3791.859181

M06-2X/6-31G** Derived free energy = -3790.556335

M06-2X/6-31G** Derived free energy in solution = -3790.565360

Number of Imaginary Frequencies = 1 (-108.69)

B3LYP/6-31G* Geometry

C	2.93260	2.32100	0.29790	H	-1.21860	-1.58310	1.25820
C	5.05230	0.67350	1.15790	C	-2.83370	-1.79730	0.06760
C	4.00780	0.09940	0.46210	N	-2.15460	-2.03690	1.21330
C	2.93080	0.94960	0.07090	C	-7.08000	-2.35010	-0.32200
H	5.89710	0.05340	1.44700	C	-6.29160	-3.42160	0.10750
C	-0.19590	4.92340	-1.11670	C	-4.91180	-3.27320	0.23330
C	-0.53240	3.77490	-0.43040	C	-4.29810	-2.04670	-0.06580
C	0.53020	2.90350	-0.04840	C	-5.09600	-0.97710	-0.50050
C	1.86750	3.18740	-0.28620	C	-6.47880	-1.12890	-0.62620
H	-0.97970	5.62280	-1.39590	H	-8.15540	-2.46970	-0.41970
C	5.05130	2.03740	1.54030	H	-6.75220	-4.37710	0.34310
C	3.97080	2.87890	1.12360	H	-4.30860	-4.11370	0.56060
C	3.96190	4.22580	1.58260	H	-4.63380	-0.02010	-0.72830
C	4.97680	4.71580	2.37470	H	-7.08220	-0.29000	-0.96140
C	6.06340	3.89100	2.74950	C	-3.04850	-4.52040	4.51400
C	6.09360	2.57820	2.34090	C	-1.88410	-4.72300	3.77230
H	3.13300	4.87030	1.31480	C	-1.60380	-3.91760	2.66760
H	4.93900	5.74580	2.71950	C	-2.49130	-2.89860	2.29890
H	6.86140	4.29220	3.36840	C	-3.64660	-2.67740	3.06130
H	6.91100	1.92470	2.63690	C	-3.92550	-3.49380	4.15600
C	2.18990	4.32590	-1.10480	H	-3.26510	-5.14860	5.37350
C	1.13740	5.21140	-1.50290	H	-1.18740	-5.50850	4.05220
C	1.44420	6.35320	-2.29130	H	-0.69420	-4.06780	2.09490
C	2.73200	6.60300	-2.70470	H	-4.30910	-1.85890	2.80230
C	3.76820	5.70830	-2.34850	H	-4.82320	-3.31440	4.74140
C	3.50580	4.60320	-1.56900	H	-2.47910	-0.89050	-0.41590
H	0.63320	7.02040	-2.57440	P	-1.90740	-2.99170	-1.84060
H	2.95360	7.47530	-3.31380	C	-0.77210	-4.40870	-1.37760
H	4.78110	5.89120	-2.69740	H	-1.35220	-5.02480	-0.67500
H	4.30990	3.92320	-1.31310	C	-0.32740	-5.27350	-2.57000
P	0.37310	0.28480	-0.02090	H	-1.15450	-5.80420	-3.05070
O	0.20700	1.76970	0.67600	H	0.17530	-4.66000	-3.32570
O	1.89560	0.38440	-0.65310	H	0.39170	-6.02700	-2.22520
O	-0.55200	0.16030	-1.21390	C	0.46400	-3.84300	-0.65280
O	0.28140	-0.71910	1.09480	H	1.04130	-4.66180	-0.21010

H	1.11850	-3.32240	-1.35830
H	0.22250	-3.13080	0.13880
C	-2.98170	-3.61470	-3.24000
H	-2.25410	-3.95010	-3.99150
C	-3.87800	-4.79870	-2.84740
H	-4.37980	-5.19080	-3.74020
H	-3.31720	-5.62530	-2.39760
H	-4.65430	-4.49170	-2.14090
C	-3.79240	-2.46130	-3.85190
H	-3.14310	-1.62990	-4.13940
H	-4.31440	-2.81330	-4.75030
H	-4.54830	-2.08650	-3.15340
O	-0.96950	-1.93970	-2.64270
H	-0.72420	-1.11070	-2.10150
C	4.49690	-4.09950	-0.47560
C	4.20760	-3.67840	0.82500
C	3.98820	-2.33360	1.14660
C	4.06930	-1.36100	0.11900
C	4.32480	-1.76790	-1.21160
C	4.53010	-3.12730	-1.47630
H	4.16430	-4.41590	1.62320
H	4.74790	-3.43680	-2.49640
C	-4.69860	3.12050	0.56740
C	-4.24340	3.00300	-0.74680
C	-2.89760	3.17990	-1.09880
C	-1.96400	3.49140	-0.08140
C	-2.40130	3.60680	1.26110
C	-3.75530	3.41870	1.55390
H	-4.96640	2.78250	-1.53010
H	-4.08280	3.52250	2.58530
C	4.43810	-0.77700	-2.36950
H	4.23370	0.22490	-1.98410
C	3.67610	-1.97690	2.60130
H	3.50960	-0.89830	2.65770
C	4.81510	-5.55500	-0.79660
H	4.94040	-5.62430	-1.88610
C	-6.18010	2.97860	0.89490
H	-6.67600	2.60100	-0.01110
C	-2.50830	3.05500	-2.57320
H	-1.41940	3.11400	-2.64150
C	-1.45740	3.97600	2.40530
H	-0.44720	4.07010	1.99920
C	-1.40660	2.88160	3.48810
H	-1.09950	1.92360	3.05870
H	-0.68440	3.15320	4.26760
H	-2.38110	2.74700	3.97360
C	-1.82110	5.34610	3.01180
H	-2.81790	5.33480	3.46900
H	-1.10090	5.62220	3.79150
H	-1.81360	6.13250	2.24850
C	-2.91100	1.69800	-3.17970
H	-2.42190	0.88190	-2.64220
H	-3.99700	1.54290	-3.15760
H	-2.59540	1.64890	-4.22910
C	-3.09170	4.21650	-3.40300
H	-4.18850	4.19830	-3.39970
H	-2.77770	5.19040	-3.01100
H	-2.75960	4.14820	-4.44600
C	-6.81010	4.34680	1.22330
H	-6.36240	4.77920	2.12610
H	-7.88880	4.24840	1.39750
H	-6.65890	5.05790	0.40390
C	-6.44860	1.96650	2.02300
H	-6.00370	2.29340	2.97000
H	-7.52680	1.85170	2.18860
H	-6.03460	0.98190	1.78050
C	2.37780	-2.64670	3.09130
H	1.52970	-2.31660	2.48530
H	2.44430	-3.74130	3.04980
H	2.18050	-2.36690	4.13360
C	4.85610	-2.30930	3.53540
H	5.06110	-3.38660	3.55880
H	5.77580	-1.80540	3.21690
H	4.63320	-1.99150	4.56110

C	3.67990	-6.51750	-0.40460	C	3.39710	-1.05610	-3.46990
H	2.74390	-6.24880	-0.90640	H	3.55480	-2.03600	-3.93690
H	3.93230	-7.54770	-0.68390	H	2.38110	-1.02880	-3.06470
H	3.49710	-6.50320	0.67650	H	3.46790	-0.29860	-4.25990
C	6.14650	-5.98970	-0.15270	C	5.86700	-0.74830	-2.94810
H	6.08610	-5.95280	0.94160	H	6.14770	-1.71590	-3.38110
H	6.40140	-7.01720	-0.44020	H	5.94370	0.00570	-3.74100
H	6.96710	-5.33370	-0.46270	H	6.60300	-0.50340	-2.17390

Summary of tested reactions

Transfer hydrogenations of imines

1. M. Rueping, M. Stoeckel, E. Sugiono and T. Theissmann, *Tetrahedron* 2010, **66**, 6565.

2. J. Zhou, Q.-F. Zhang, W. H. Zhao and Q.-F. Jiang, *Org. Biomol. Chem.* 2016, **14**, 6937.

3. A. Aillerie, C. Gosset, C. Dumont, V. Skrzypczak, P. Champetter, S. Pellegrini, T. Bousquet and L. Pélinski, *RSC Adv.* 2016, **6**, 54185.

4. M. Rueping, C. Brinkmann, P. Antonchick and I. Atodiresei, *Org. Lett.* 2010, **12**, 4604.

5. M. Rueping, F. Tato and F. R. Schoepke, *Chem. Eur. J.* 2010, **16**, 2688.

6. C. Metallinos, F. B. Barrett and S. Xu, *Synlett* 2008, **5**, 720.

7. M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem. Int. Ed.* 2006, **45**, 6751. (BINOPtimal does not recognize benzoxazinones)

8. M. Rueping and A. P. Antonchick, *Angew. Chem. Int. Ed.* 2007, **46**, 4562.

9. M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem. Int. Ed.* 2006, **45**, 3683.

10. M. Rueping and A. P. Antonchick, *Angew. Chem. Int. Ed.* 2008, **47**, 5836.

11. R.-N. Guo, Z.-P. Chen, X.-F. Cai, Y.-G. Zhou, *Synthesis* 2014, 2751.

12. X.-F. Cai, M.-W. Chen, Z.-S. Ye, R.-N. Guo, L. Shi, Y.-Q. Li and Y.-G. Zhou, *Chem. Asian J.* 2013, **8**, 1381.

13. X.-F. Cai, R.-N. Guo, G.-S. Feng, B. Wu and Y.-G. Zhou, *Org. Lett.* 2014, **16**, 2680.

14. Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.* 2009, **131**, 9182.

15. Q. Kang, Z.-A. Zhao and S.-L. You, *Org. Lett.* 2008, **10**, 2031.

16. G. Li and J. C. Antilla, *Org. Lett.* 2009, **11**, 1075.

17. S. Hoffmann, A. M. Seayad and B. List, *Angew. Chem.* 2005, **117**, 7590.

18. R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc*. 2006, **128**, 84.
19. M. Rueping, E. Sugiono, C. Azap, T. Theissmann and M. Bolte, *Org. Lett.,* 2005, **7**, 3781.
20. A. Henseler, M. Kato, K. Mori and T. Akiyama, *Angew. Chem. Int. Ed.* 2011, **50**, 8180.
21. C. Zhu and T. Akiyama, *Org. Lett.* 2009, **11**, 4180.
22. K. Saito and T. Akiyama, *Chem. Commun.* 2012, **48**, 4573.
23. T. Sakamoto, K. Mori and T. Akiyama, *Org. Lett.* 2012, **14**, 3312.
24. K. Saito, K. Horiguchi, Y. Shibata, M. Yamanaka and T. Akiyama, *Chem. Eur. J.* 2014, **20**, 7616.
25. K. Saito, Y. Shibata, M. Yamanaka and T. Akiyama, *J. Am. Chem. Soc.* 2013, **135**, 11740.
26. K. Saito, H. Miyashita and T. Akiyama, *Org. Lett.* 2014, **16**, 5312.
27. K. Horiguchi, E. Yamamoto, K. Saito, M. Yamanaka and T. Akiyama, *Chem. Eur. J.* 2016, **22**, 8078.
28. M.-W. Chen, Q. Yang, Z. Deng, Y. Zhou, Q. Ding and Y. Peng, *J. Org. Chem.* 2018, **83**, 8688.
29. X.-Y. Liu and C.-M. Che, *Org. Lett.* 2009, **11**, 4204.
30. A. A. Rexit, S. Luo and M. Mailikezati *J. Org. Chem.* 2016, **81**, 11384.
31. A. D. Lackner, A. V. Samant and F. D. Toste, *J. Am. Chem. Soc.* 2013, **135**, 14090.
32. K.-H. Kim, C.-Y. Lee and C.-H. Cheon, *J. Org. Chem.* 2015, **80**, 6367.
33. K.-H. Kim, T. Akiyama and C.-H. Cheon, *Chem. Asian J.* 2016, **11**, 274.

Friedel-Crafts Reactions

34. Q. Kang, Z.-A. Zhao and S.-L. You, *J. Am. Chem. Soc*. 2007, **129**, 1484.
35. F. Xu, D. Huang, C. Han, W. Shen, X. Lin and Y. Wang, *J. Org. Chem*. 2010, **75**, 8677.
36. C.-H. Xing, Y.-X. Liao, J. Ng and Q.-S. Hu, *J. Org. Chem*. 2011, **76**, 4125.
37. Q. Kang, X.-J. Zheng and S.-L. You, *Chem. Eur. J*. 2008, **14**, 3539.
38. S. Nakamura, Y. Sakurai, H. Nakashima, N. Shibata and T. Toru, *Synlett* 2009, 1639.
39. Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang and Q.-L. Zhou, *Angew. Chem. Int. Ed*. 2007, **46**, 5565.
40. Q. Yin and S.-L. You, *Chem. Sci*. 2011, **2**, 1344.
41. M. Rueping, S. Raja and A. Núñez, *Adv. Synth. Catal*. 2011, **353**, 563.
42. X. Yu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, *Eur. J. Org. Chem*. 2011, 3060.

Mannich Reactions (and related types)

43. D. Uraguchi and M. Terada, *J. Am. Chem. Soc*. 2004, **126**, 5356.

44. M. Terada, H. Tanaka and K. Sorimachi, *Synlett* 2008, **11**, 1661.

45. J. Kikuchi, N. Momiyama and M. Terada, *Org. Lett*. 2016, **18**, 2521.

46. E. P. Ávila, R. M. S. Justo, V. P. Gonçalves, A. A. Pereira, R. Diniz and G. W. Amarante, *J. Org. Chem*. 2015, **80**, 590.

47. Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu and L.-Z. Gong, *J. Am. Chem. Soc*. 2007, **129**, 3790.

48. M. Rueping, E. Sugiono and F. R. Schoepke, *Synlett* 2007, 1441.

Strecker Reaction

49. M. Rueping, E. Sugiono and C. Azap, *Angew. Chem., Int. Ed*. 2006, **45**, 2617.

50. M. Rueping, E. Sugiono and S. A. Moreth, *Adv. Synth. Catal*. 2007, **349**, 759.

Addition of alcohols

51. G. Li, F. R. Fronczek and J. C. Antilla, *J. Am. Chem. Soc.* 2008, **130**, 12216.

Addition of thiols

52. G. K. Ingle, M. G. Mormino, L. Wojtas and J. C. Antilla, *Org. Lett*. 2011, **13**, 4822.

Addition of amines

53. G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang and J. C. Antilla, *J. Am. Chem. Soc.* 2005, **127**, 15696.

Addition of imides

54. Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman and J. C. Antilla, *Chem. Commun*. 2007, 4477.

Peroxidation of imines

55. W. Zheng, L. Wojtas and J. C. Antilla, *Angew. Chem., Int. Ed*. 2010, **49**, 6589.

Hydrophosphonylation of imines

56. T. Akiyama, H. Morita, J. Ito and K. Fuchibe, *Org. Lett.* 2005, **7**, 2583.

Addition of dialkyl α-diazomethylphosphonates

57. H. Zhang, H. Wen, L. Gan and Y. Peng, *Org. Lett.* 2012, **14**, 2126.

Addition of α-diazoesters

58. D. Uraguchi, K. Sorimachi and M. Terada, *J. Am. Chem. Soc.* 2005, **127**, 9360.

59. T. Akiyama, T. Suzuki and K. Mori, *Org. Lett.* 2009, **11**, 2445.

Addition of diazoacetamides

60. X. Zeng, X. Zeng, Z. Xu, M. Lu and G. Zhong, *Org.Lett.* 2009,**11**, 3036.

Addition of enamides/enamines

61. M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem. Int. Ed.* 2006, **45**, 2254.

62. G. Dagousset, F. Drouet, G. Masson and J. Zhu, *Org. Lett.* 2009, **11**, 5546.

63. J.-H. Lin, G. Zong, R.-B. Du, J.-C. Xiao, S. Liu, *Chem. Commun.* 2012, **48**, 7738.

64. J. Brioche, T. Courant, L. Alcaraz, M. Stocks, M. Furber, J. Zhu and G. Masson, *Adv. Synth. Catal.* 2014, **356**, 1719.

65. G. Dagousset, W. Erb, J. Zhu and G. Masson, *Org. Lett.* 2014, **16**, 2554.

66. G. Dagousset, J. Zhu and G. Masson, *J. Am. Chem. Soc.* 2011, **133**, 14804.

67. H. Liu, G. Dagousset, G. Masson, P. Retailleau and J. Zhu, *J. Am. Chem. Soc.* 2009, **131**, 4598.

68. M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem. Int. Ed.* 2009, **48**, 2553.

69. B. Baudequin, A. Zamfir and S. B. Tsogoeva, *Chem. Commun.* 2008, 4637.

70. E. Richmond, I. U. Khan and J. Moran, *Chem. Eur. J.* 2016, **22**, 12274.

Other reactions

Isolated accounts of different combinations of imines and nucleophiles make it difficult to generalize beyond the initial report. Although these reactions fit the decision tree they have been omitted from the BINOPtimal database to avoid overly adapted rules for special cases.

Addition of thiols

J. Sućˊ, I .Dokli and M. Gredičak, *Chem. Commun*. 2016, **52**, 2071.

R. A. Unhale, N. Molleti, N. K. Rana, S. Dhanasekaran, S. Bhandary and V. K. Singh, *Tetrahedron Lett*. 2017, **58**, 145.

Friedel-Crafts Reactions

T. Kano, R. Takechi, R. Kobayashi and K. Maruoka, *Org. Biomol. Chem*. 2014, **12**, 724.

K.-F. Zhang, J. Nie, R. Guo, Y. Zheng and J.-A. Ma, *Adv. Synth. Catal*. 2013, **355**, 3497.

M. Terada and K. Sorimachi, *J. Am. Chem. Soc*. 2007, **129**, 292.

Addition of enamides/enamines

L. He, G. Laurent, P. Retailleau, B. Folléas, J.-L. Brayer and G. Masson, *Angew. Chem. Int. Ed.* 2013, **52**, 11088.

C. Gelis, G. Levitre, J. Merad, P. Retailleau, L. Neuville and G. Masson, *Angew. Chem. Int. Ed*. 2018, **57**, 12121.

Amination

G. A. Shevchenko, G. Pupo and B. List, *Synlett* 2015, **26**, 1413.

X. Yang and F. D. Toste, *J. Am. Chem. Soc*. 2015, *137*, 3205.

Petasis-Ferrier Rearrangement

M. Terada, T. Komuro, Y. Toda and T. Korenaga, *J. Am. Chem. Soc*. 2014, **136**, 7044.

M. Terada and Y. Toda, *J. Am. Chem. Soc*. 2009, **131**, 6354.

Transfer hydrogenations of ketimines

W. Wen, Y. Zheng, P. Li-Yu, F. Li-Na and G. Qi-Xang, *Org. Lett.* 2015, **17**, 3922.

Q. Kang, Z.-A. Zhao, S.-L. You, *Adv. Synth. Catal.* 2007, **349**, 1657.

G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* 2007, **129**, 5830.

Friedel-Crafts

Y. Zhao, Y. Wang and J. Zhao, *Tetrahedron Lett*. 2017, **58**, 213.

J.-H. Xue, M. Shi, F. Yu, X.-Y. Li, W. Ren, L.-N. Fu, Q.-X. Guo, *Org*. *Lett*. 2016, **18**, 3874.

R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping, C. Bolm, *Org*. *Lett*. 2011, **13**, 1044.

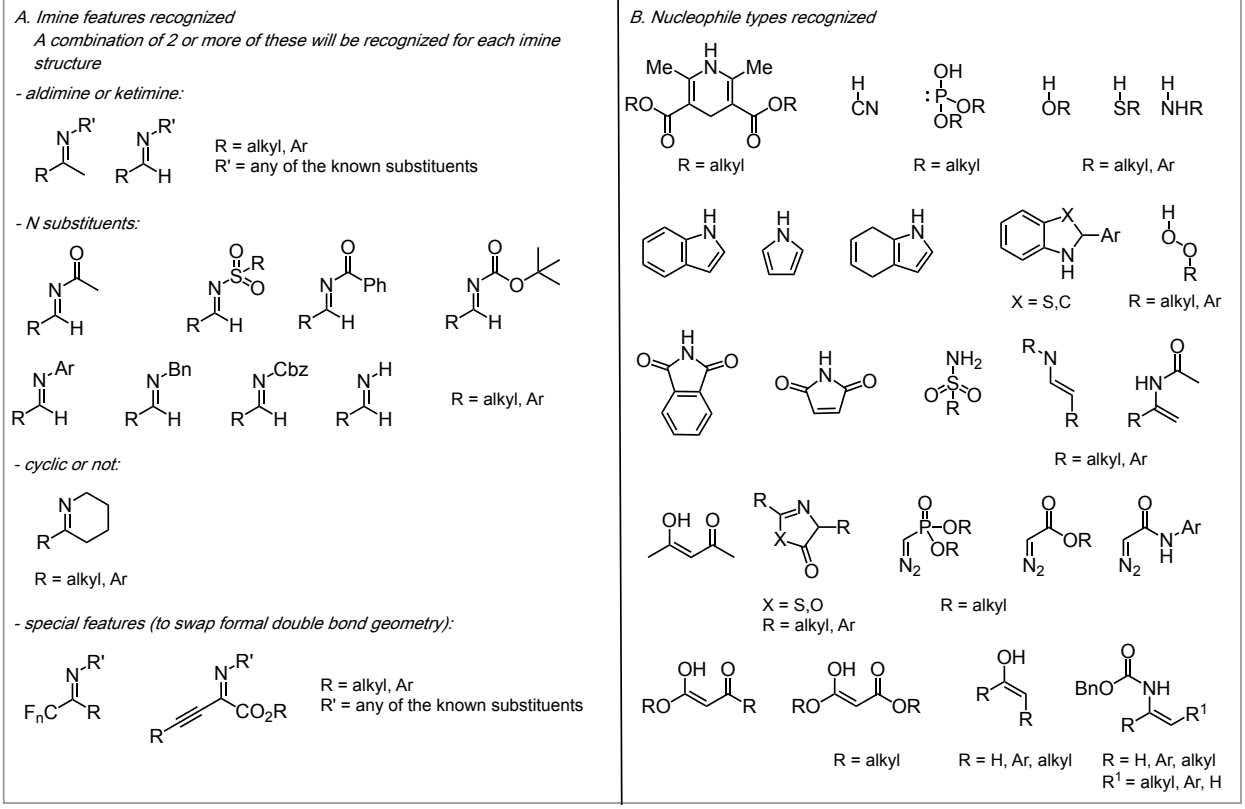
Biginelli

N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan and L.-Z. Gong, *J*. *Am*. *Chem*. *Soc*. 2009, **131**, 15301.

X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J*. *Am*. *Chem*. *Soc*. 2006, **128**, 14802.

Summary of imines and nucleophile types recognized

Figure 4. Reactants recognized by BINOPtimal



Imine-nucleophile steric relationship table

A key decision in the tree is whether the *N*-substituent is small or large, but this generally depends on the nucleophile, so both reaction variables must be considered. For this purpose, we have analyzed a series of literature reactions for different combinations and developed general rules for when the *N*-substituent is small and when it can be considered large. Our level of confidence in assignment for a particular combination is tabulated. This can be either confident assignment (direct literature precedent), L or S, or probable assignment, PL or PS. The probable assignment is weighted on trends from similar combinations. For example, benzoyl is confidently determined to be large for reactions involving hydrogen peroxides, thiols and alcohols. It is therefore highly probable that it reacts comparably with similar nucleophiles (HCN, amines, imides etc.). In isolated cases the *N*-substituent size can be dictated by the size of the substituents at the carbon of the imine leading to a situation in which the combination can be both large, L and small, S. Although these reactions fit the decision tree they have been omitted from the BINOPtimal

database to avoid overly adapted rules for special cases. For these few isolated cases, BINOPtimal, indicates that it cannot make a prediction.

	***N*-substituent**							
Nucleophile	Acetyl	Boc	Cbz	Aromatic	Benzyl	Benzoyl	Sulfonyl	Cyclic
HCN	PL	PL	PL	PL	L	PL	PL	PS
hydrogen peroxides	PL	PL	PL	PL	PL	L	PL	PL
amines	PL	L	PL	PL	PL	PL	PL	PS
thiols	PL	PL	PL	PL	PL	L	PL	S
imides	PL	L	PL	PL	PL	PL	PL	PL
diazoesters	PL	L	PL	L	PL	PL	PL	PL
diazoamides	PL	L	PL	PL	PL	PL	PL	PL
diazophosphonates	PL	L	L	L	PL	PL	PL	PL
alcohols	PL	PL	PL	PL	PL	L	PL	PS
phosphonate	PL	PL	PL	L	PL	PL	PL	PL
Hantzsch esters	L	PL	PL	L	PL	PL	PL	L
benzothiazolines	PL	PL	PL	L	PL	PL	PL	PL
N-heterocycles	S	S/L	PL	PL	PL	PL	L	S/L
enols	S	S/L	PL	S	PL	PL	L	PS
acetylacetone	PL	L	PL	PL	PL	PL	PL	PL
enamines/enamides	S	S	PL	S	PL	PL	PL	PS
thiazolones	PS	PL	PL	PL	PL	L	L	PL

Table 2. Imine-nucleophile steric relationship table. Nucleophile and imine (aldimine and ketimine) combination determine if the *N*-substituent can be considered L, large or S, small. Literature evidence does not exist for each combination. General rules have been developed based on theoretical studies and extensive literature surveys to determine if the combination would lead to a probably large, PL or small, PS, *N*-substituent.

References

(1) B. Bienfait and P. Ertl. JSME: a Free Molecule Editor in JavaScript. *J. Cheminf.* 2013, **5**, 24.

(2) https://www.python.org/downloads/release/python-2715/

(3) RDKit: Cheminformatics and Machine Learning Software. 2013, [http://www.rdkit.org].

(4) https://httpd.apache.org/

(5) MacroModel, version 9.9, Schrodinger, LLC, New York, NY, 2009.

(6) G. A. Kaminski, R. A. Friesner, J. Tirado-Rives, and W. L. Jorgensen, *J. Phys. Chem. B* 2001, **105**, 6474.

(7) W. L. Jorgensen, D. S. Maxwell and J. Tirado-Rives, *J. Am. Chem. Soc.* 1996, **118,** 11225.

(8) W. L. Jorgensen and J. Tirado-Rives, *J. Am. Chem. Soc.* 1988, **110**, 1657.

(9) M. J. Frisch, et al. Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford, CT, 2013.

(10) A. D. Becke, *Phys. Rev. A* 1988, **38**, 3098.

(11) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B* 1988, **37**, 785.

(12) R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.* 1980, **72**, 650.

(13) P. M. W. Gill, B. G. Johnson, J. A. Pople and M. J. Frisch, M. J. *Chem. Phys. Lett.* 1992, **197**, 499.

(14) A. K. Rappe, C. J. Casewit, K. S. Colwell, W. A. Goddard and W. M. Skiff, *J. Am. Chem. Soc.* 1992, **114**, 10024.

(15) L. Simón and J. M. Goodman, *J. Am. Chem. Soc.* 2009, **131**, 4070.

(16) L. Simón and J. M Goodman, *J. Org. Chem.* 2010, **75***,* 589.

(17) M. N. Grayson, S. C. Pellegrinet and J. M. Goodman, *J. Am. Chem. Soc.* 2012, **134***,* 2716.

(18) L. M. Overvoorde, M. N. Grayson, Y. Luo and J. M. Goodman, *J. Org. Chem.* 2015, **80**, 2634.

(19) J. P. Reid and J. M. Goodman, *J. Am. Chem. Soc.* 2016, **138**, 7910.

(20) J. P. Reid and J. M. Goodman, *Chem. Eur. J.* 2017, **23**, 14248.

(21) J. P. Reid and J. M. Goodman, *Org. Biomol. Chem*, 2017, **15**, 6943.

(22) Zhao, Y.; Truhlar, D. *Theor. Chem. Acc.* 2008, **120**, 215.

(23) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* 1997, **106**, 5151.

(24) CYL view, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009.

(25) J. P. Reid, L. Simón and J. M. Goodman, *Acc. Chem. Res.* 2016, **49**, 1029.

(26) Schrödinger Release 2017-3: Maestro, Schrödinger, LLC, New York, NY, 2017.

(27) M, Zgarbova, M. Otyepka, J. Sponer, P. Hobza and P. Jurecka, *Phys. Chem. Chem. Phys*. 2010, **12**, 10476.