

# Computational Insights into the Synthesis and Medicinal Potential of 5-Trifluoromethylpyrazoles via [3 + 2] Cycloaddition: An ELF and NCI Analysis

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## Appendix A. Supplementary data

### 1. Thermodynamic study

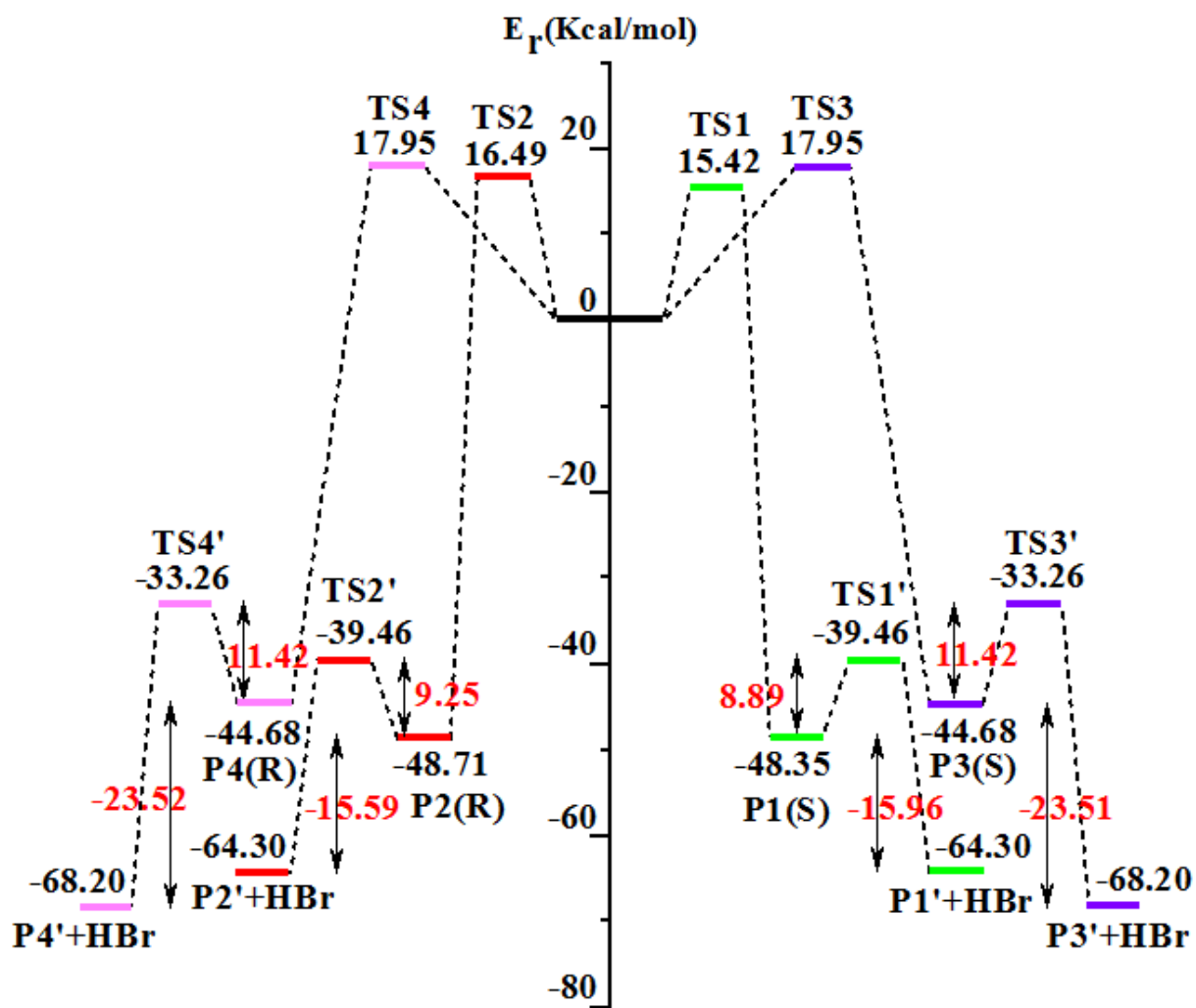
#### 1. 1. Calculated at B3LYP/6-31+g(d,p)/ LANL2DZ

##### 1. 1. 1. In the absence of the NEt<sub>3</sub> base

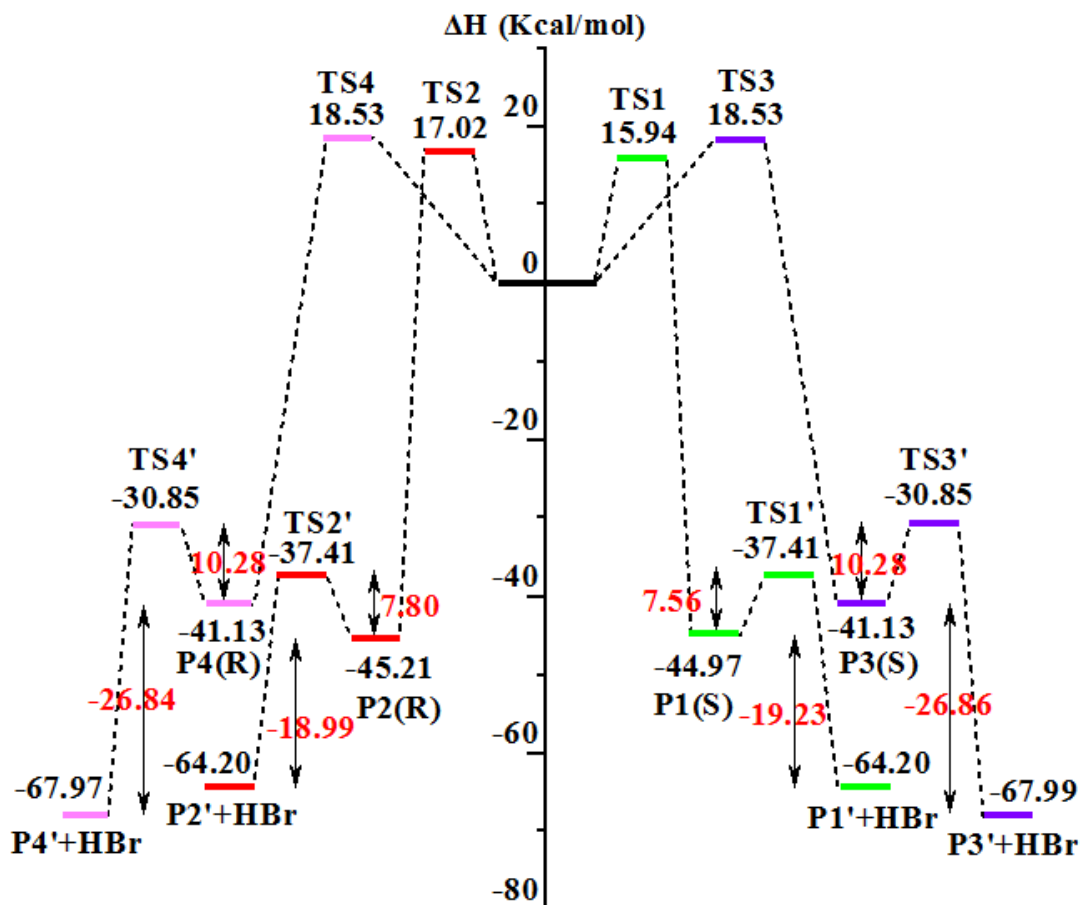
The energies of the corresponding stationary points in toluene without the NEt<sub>3</sub> base calculated at B3LYP/6-31+g(d,p)/ LANL2DZ are listed in **Table S1**, and the energy profiles are shown in **Figures S1** and **S2**.

**Table S1.** B3LYP/6-31+g(d,p)/LANL2DZ calculated Gibbs free energies  $\Delta G$  (Kcal/mol), relative enthalpies  $\Delta H$  (Kcal/mol) and relative energies  $\Delta E$  (Kcal/mol) in Toluene solvent.

System	$\Delta E$	$\Delta H$	$\Delta G$
TS1	15.42	15.94	29.78
TS2	16.49	17.02	30.91
TS3	17.95	18.53	32.75
TS4	17.95	18.53	32.75
P1(S)	-48.35	-44.97	-28.94
P2(R)	-48.71	-45.21	-29.09
P3(S)	-44.68	-41.13	-24.69
P4(R)	-44.68	-41.13	-24.69
TS1'	8.89	-37.41	-22.53
TS2'	9.25	-37.41	-22.54
TS3'	11.42	-30.85	-16.37
TS4'	11.42	-30.85	-16.37
P1'+HBr	-64.30	-64.20	-59.12
P2'+HBr	-64.30	-64.20	-59.12
P3'+HBr	-68.20	-67.99	-62.62
P4'+HBr	-68.20	-67.97	-62.58



**Figure S1.** Relative energies profiles for the [3+2] reaction of R1 with BTP in Toluene at B3LYP/6-31+g(d,p)/LANL2DZ



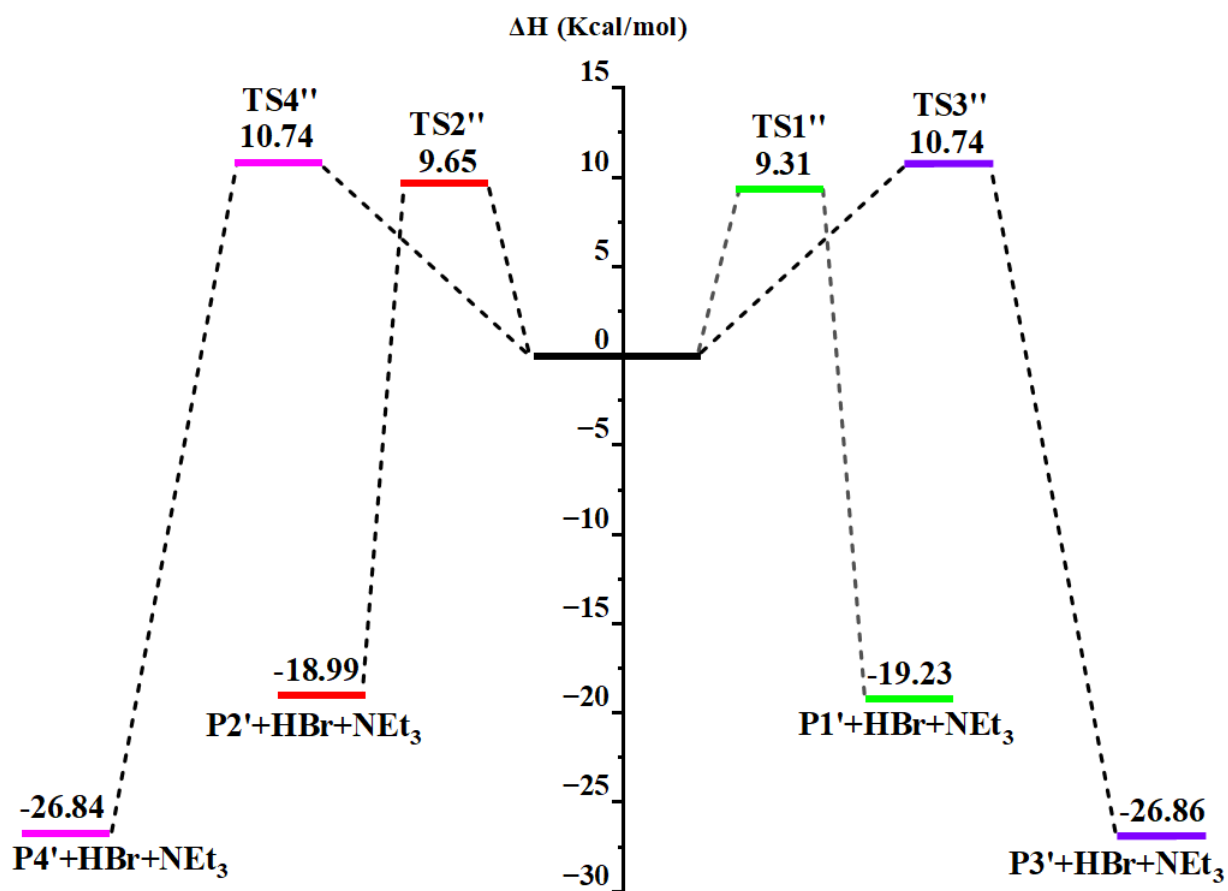
**Figure S2.** Relative enthalpies profiles for the [3+2] reaction of **R1** with **BTP** in Toluene at B3LYP/6-31+g(d,p)/LANL2DZ

### 1. 1. 2. In the presence of the NEt<sub>3</sub> base

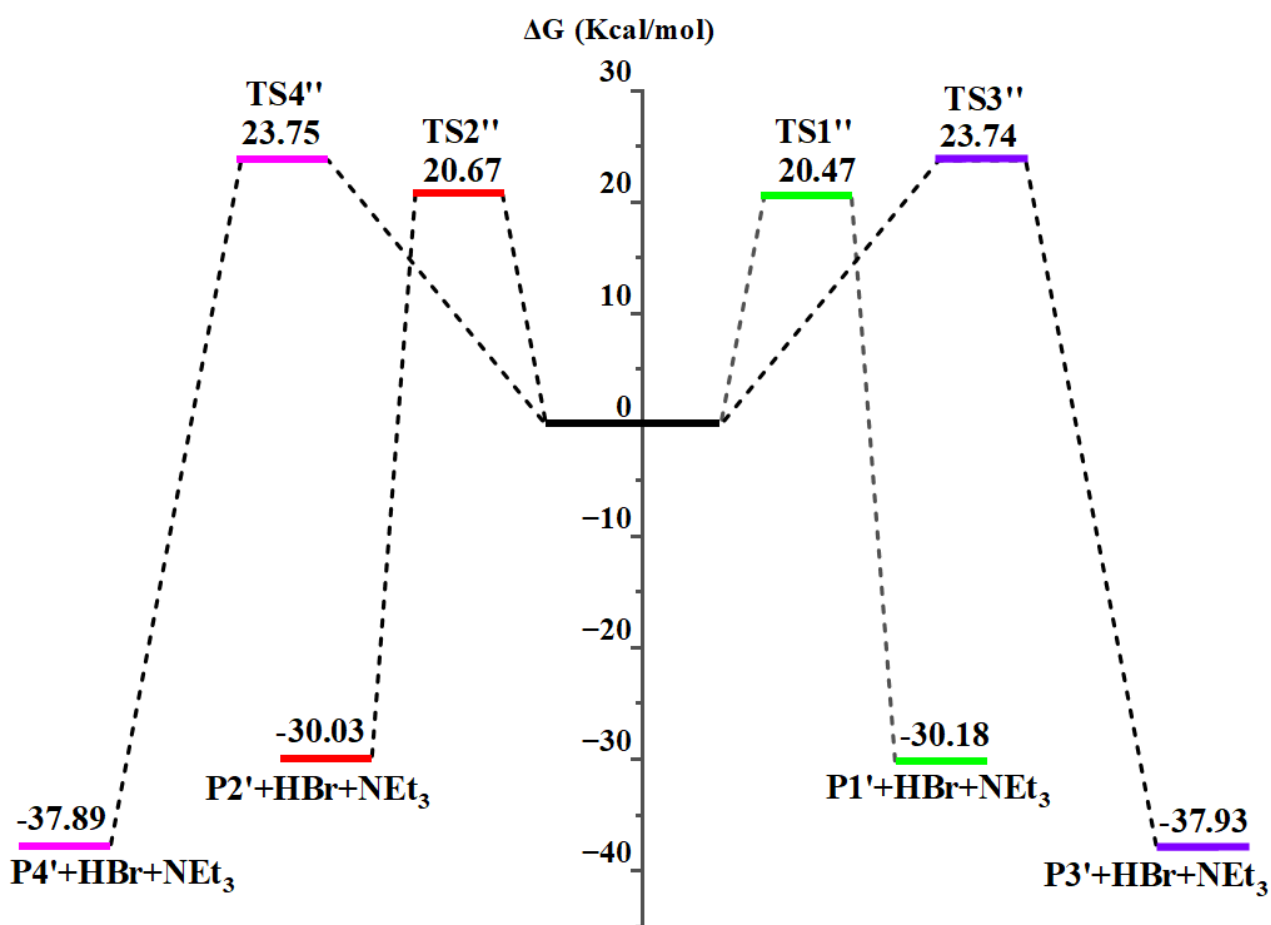
The energies of the corresponding stationary points in toluene in the presence of the NEt<sub>3</sub> base calculated at B3LYP/6-31+g(d,p)/ LANL2DZ are listed in **Table S2**, and the energy profiles are shown in **Figures S3** and **S4**.

**Table S2.** B3LYP/6-31+g(d,p)/LANL2DZ calculated Gibbs free energies  $\Delta G$  (Kcal/mol), relative enthalpies  $\Delta H$  (Kcal/mol) and relative energies  $\Delta E$  (Kcal/mol) in Toluene solvent in the presence of NEt<sub>3</sub> base.

System	$\Delta E$	$\Delta H$	$\Delta G$
TS1''	8.64	9.31	20.47
TS2''	8.97	9.65	20.67
TS3''	10.67	10.74	23.74
TS4''	10.67	10.74	23.75
P1'+HBr+NEt <sub>3</sub>	-15.96	-19.23	-30.18
P2'+HBr+NEt <sub>3</sub>	-15.59	-18.99	-30.03
P3'+HBr+NEt <sub>3</sub>	-23.51	-26.86	-37.93
P4'+HBr+NEt <sub>3</sub>	-23.52	-26.84	-37.89



**Figure S3.** Relative enthalpies profiles for the the dehydrobromination reactions in toluene in the presence of NEt<sub>3</sub> base at B3LYP/6-31+g(d,p)/LANL2DZ level of theory.



**Figure S4.** Relative Gibbs free energies profiles for the the dehydrobromination reactions in toluene in the presence of  $NEt_3$  base at B3LYP/6-31+g(d,p)/LANL2DZ level of theory.

## 1. 2. Calculated at B3LYP/6-31+g(d,p)/MWB28

The energies of the corresponding stationary points in toluene calculated at B3LYP/6-31+g(d,p)/MWB28 are listed in **Table S3**, and the energy profiles are shown in **Figures S5** and **S6**.

**Table S3.** B3LYP/6-31+g(d,p)/MWB28 calculated Gibbs free energies  $\Delta G$  (Kcal/mol), relative enthalpies  $\Delta H$  (Kcal/mol) and relative energies  $\Delta E$  (Kcal/mol) in Toluene solvent.

System	$\Delta E$	$\Delta H$	$\Delta G$
TS1	16.12	16.64	30.44
TS2	17.07	17.58	31.42
TS3	18.57	19.14	33.28
TS4	18.57	19.14	33.27
P1(S)	-48.07	-44.70	-28.77
P2(R)	-48.40	-44.91	-28.87
P3(S)	-44.24	-40.70	-24.34
P4(R)	-44.24	-40.70	-24.34
TS1'	-40.32	-38.11	-23.22
TS2'	-40.32	-38.11	-23.22
TS3'	-33.97	-31.43	-16.89
TS4'	-33.97	-31.43	-16.88
P1'+HBr	-66.15	-65.98	-60.90
P2'+HBr	-66.15	-65.98	-60.90
P3'+HBr	-70.04	-69.77	-64.40
P4'+HBr	-70.04	-69.75	-64.36

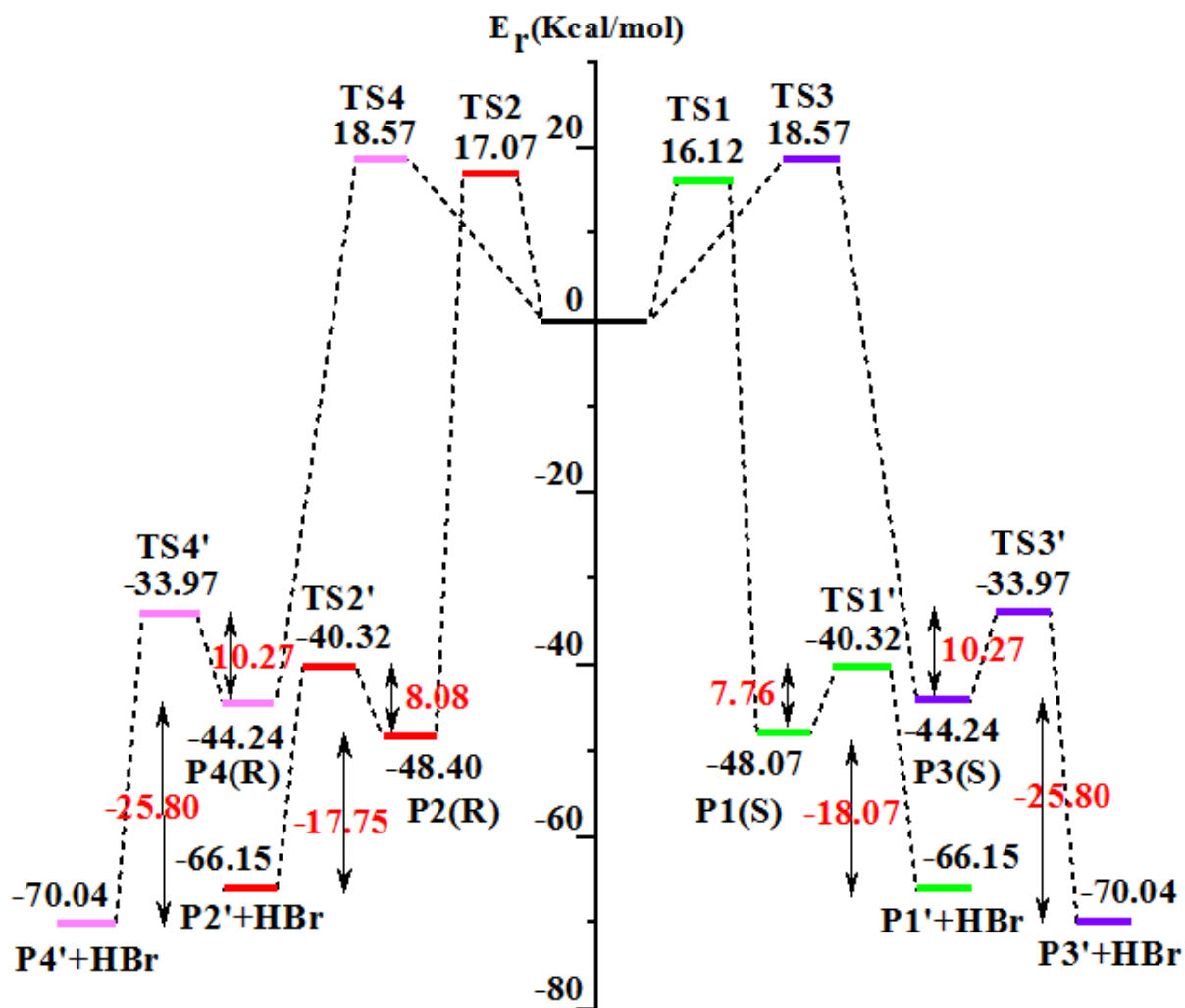


Figure S5. Relative energies profiles for the [3+2] reaction of R1 with BTP in Toluene at B3LYP/6-31+g(d,p)/MWB28

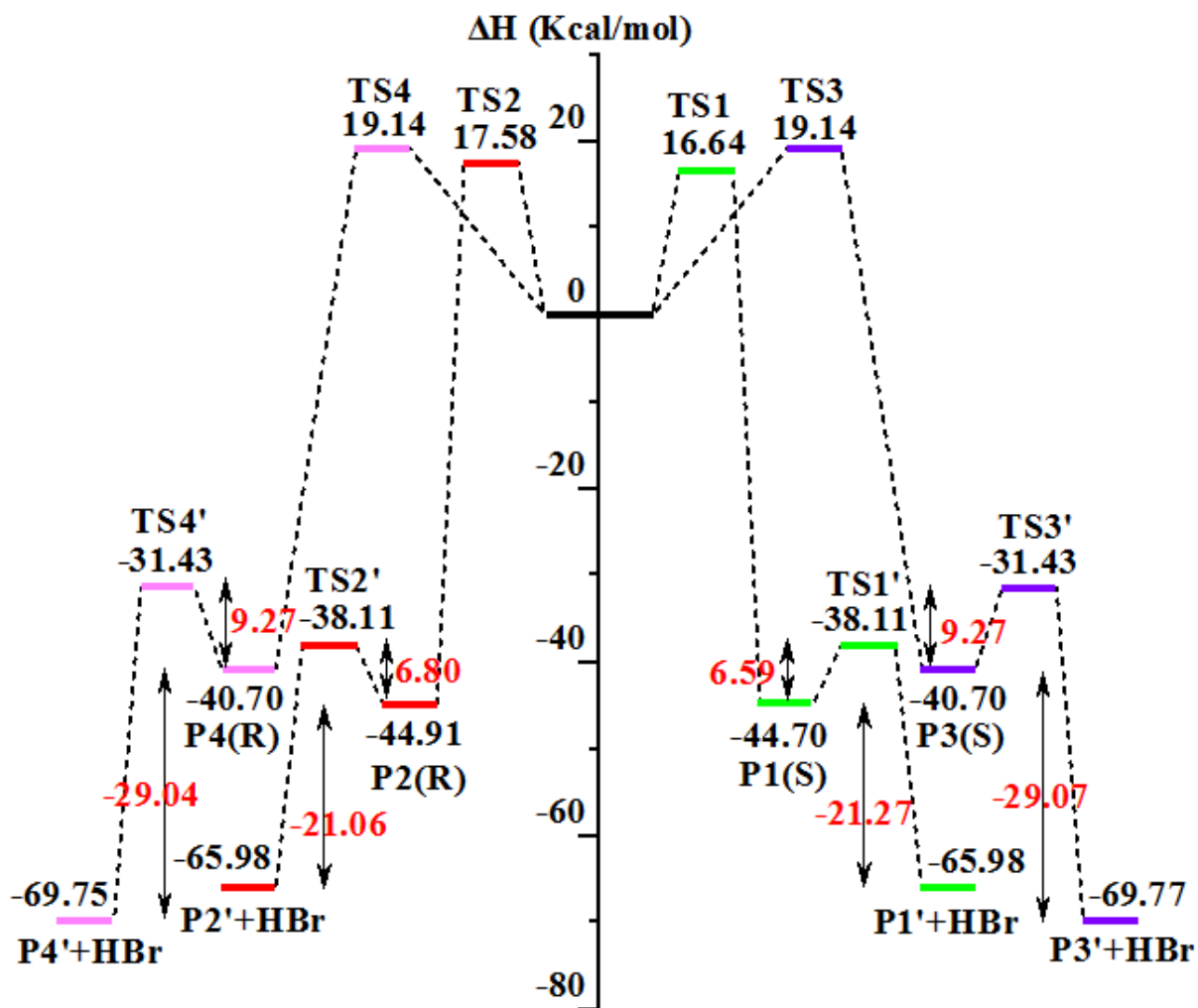


Figure S6. Relative enthalpies profiles for the [3+2] reaction of R1 with BTP in Toluene at B3LYP/6-31+g(d,p)/MWB28