Supporting Information

Mechanism and Origin of Remote Stereocontrol in the Organocatalytic C(sp^2)-H Alkylation using Nitroalkanes as Alkylating Agents

Sharath Chandra Mallojjala,[a]‡ Rahul Sarkar,[b]‡ Rachael W. Karugu, [a] Madhu Sudan Manna,[b] Santanu Mukherjee,*[b] and Jennifer S. Hirschi*[a]

[a] S. C. Mallojjala, R. W. Karugu, Prof. J. S. Hirschi
Department of Chemistry
Binghamton University
Vestal, NY 13850
E-mail: jhirschi@binghamton.edu
[b] Dr. R. Sarkar, Dr. M. S. Manna, Prof. S. Mukherjee
Department of Organic Chemistry
Indian Institute of Science
Bangalore, 560012 (India)
E-mail: sm@iisc.ac.in
‡ These authors contributed equally

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Computational Methods

Kohn Sham density functional theory (DFT) was used to study the mechanism of C(sp^2)-H alkylation. B3LYP\(^1\) and B97-D\(^17,18\) functionals as implemented in Gaussian 09\(^2\) were paired with def2-SVP\(^3\) basis set for geometry optimizations, transition state (TS) optimizations, and computing vibrational frequencies. B3LYP functional is routinely employed for computational studies of these systems while B97-D incorporates long range dispersion corrections thereby accounting for the sundry non-covalent interactions operative in these systems. Furthermore, density fitting was employed for B97-D/def2-SVP computations. Integral equation formulation of polarized continuum model (IEFPCM)\(^46,47\) as implemented in Gaussian 09 was used to account for solvent effects. Cavity of toluene was paired with the optical and dielectric constants of trifluoromethyl toluene using the keyword guess=read. Ultrafine grid was employed to reduce the errors associated with low-frequency modes in computing thermal corrections and kinetic isotope effects. Thermal corrections were computed using Grimme’s quasi-rigid rotor harmonic oscillator approximation.\(^4\) ISOEFF code developed by Paneth and coworkers\(^5\) was used to compute the KIEs. Single point energies were computed at M06-2X/6-311+G(d, p)\(^6-8\) using Gaussian 09. To gain insights into the origins of enantioselectivity, distortion-interaction analysis (activation-strain model) was performed on the lowest-lying transition states for each enantiomer. Finally, interactions energies were also computed using SAPTO/jun-cc-pVDZ, developed by Sherrill and coworkers\(^9,12\) as implemented in psi4.\(^13\). Molecular graphics were generated using CYLView.\(^4\)

RMSD of selected transition state structures at the chosen level of theories

Lowest-lying transition state structures (TSS) computed at B3LYP/def2-SVP and B97-D/def2-SVP were overlayed using Pymol to identify the functional dependance on the geometry/TS optimizations. Figure S1 shows the overlay of the B3LYP (yellow) and B97-D (magenta) optimized transition state structures for alkylation step (A) and the elimination step (B). RMSD values for these figures were computed using Pymol’s align keyword.
For the alkylation step and for the elimination step the overall RMSD was found to be 0.4 Å. Majority of the deviation was identified to be due to the orientation of the quinoline substituent of the urea moiety and the benzyl substituent of the dione owing to their fluxionality. Upon removing the quinoline substituent, the RMSD was found to be improved to 0.3 Å as shown in Figure 2. Based on these data, all the TSS search and geometry optimizations reported in the paper were carried out at PCM(trifluoromethyl toluene) - B3LYP/def2-SVP with ultrafine grid.
Figure 2 RMSD for the elimination step for functionals B3LYP and B97-D after truncating the quinoline substituent.

**Mechanistic pathways**

A general pathway for this C-H functionalization reaction involves four key steps, *viz.* deprotonation or activation of the nucleophile, alkylation or C-C bond formation, elimination of the activated or ionic nitro group, and protonation of the resulting alkene as depicted in Figure 7. Of these steps, alkylation, elimination, and protonation are the steps in which both the nucleophilic carbon and the electrophilic carbon are part of the reaction centers.
Figure 3 A general mechanistic scheme for the urea catalyzed C-H alkylation reaction.

**Pathway 1:**

**Deprotonation or activation of nucleophile:** For the deprotonation step, TSS were modelled in the presence of the electrophile. The TS corresponding to the nucleophile coordinated to the cinchona amine and the electrophile coordinated to the urea (Binding Mode DP1) was found to be disfavored to the binding mode where one of the urea hydrogens was bound to the nucleophile (Binding mode DP2) by 1.2 kcal/mol (Figure 4 and Table 1).
Table 1 Energies of the lowest-lying transition states for different binding modes of nitro alkane activation computed at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

| Species                | Single Point Energy (Hartree) | Free Energy Correction (Hartree) | Free Energy (Hartree) | Rel. Free Energy (kcal/mol) |
|------------------------|------------------------------|---------------------------------|-----------------------|-----------------------------|
| Separated Reactants    | -2989.4750697                | 0.722836                        | -2988.752234          | 0.0                         |
| Binding Mode DP1       | -2989.48693770               | 0.761937                        | -2988.725001          | 17.1                        |
| Binding Mode DP2       | -2989.48792395               | 0.761092                        | -2988.726832          | 15.9                        |

Alkylation: For the deprotonation step, three different binding modes were investigated. In binding mode 1, the electrophile was bound to the cinchona ammonium through a hydrogen bond while the nucleophile was bound to the urea via dual hydrogen bonds. In binding mode 2, the electrophile was bound to the urea while the nucleophile to the cinchona ammonium. Finally, binding mode 3 involves a shared hydrogen bond between one of the urea hydrogens and the nucleophile and the electrophile. In line with Grayson’s reports on the Mannich reaction of nitroalkanes with an α,β unsaturated ketone, binding mode 1 (Figure 5) was identified as the preferred mode for the alkylation step by 1.4 kcal/mol over binding mode 2 at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP level of theory. However, at B97-D/def2-SVP level of theory, both the binding modes were found to be equally viable with a free energy difference of 0.1 kcal/mol favoring mode 2. Finally, binding mode 2 was favored by 1.5 kcal/mol at B3LYP/def2-SVP level of theory. Based on the previous benchmarks by Grayson, we conclude binding mode 1 as the preferred mode for alkylation.
Figure 5 Different binding modes investigated for the alkylation step.

However, very little differences in the TS geometry were observed across different functionals and the computed $^{13}$C KIEs for all the binding modes gave 2.8% (1.028) on the electrophilic carbon. The free energy barriers for all three modes are presented in table 2.

![Binding Mode 1](image1.png)
![Binding Mode 2](image2.png)

Figure 6 Lowest-lying binding modes for alkylation.

| Species          | Single Point Energy (Hartree) | Free Energy Correction (Hartree) | Free Energy (Hartree) | Rel. Free Energy (kcal/mol) |
|------------------|-------------------------------|----------------------------------|-----------------------|-----------------------------|
| Separated Reactants | -2989.4750697                | 0.722836                         | -2988.752234           | 0.0                         |
| Binding Mode 1    | -2989.49126142               | 0.768580                         | -2988.72268142         | 18.5                        |
| Binding Mode 2    | -2989.48923614               | 0.768707                         | -2988.72052914         | 19.9                        |

Table 2 Energies of the lowest-lying transition states for different binding modes of alkylation of dione computed at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.
**Elimination of Nitro group:** For the elimination step, binding mode EL2 was found to be favored by over 3.5 kcal/mol over binding mode EL1 across all the above mentioned levels of theory (Figure 7 and Figure 8). $^{13}$C KIEs for the nucleophilic carbon for both the modes was found to be 1.033 while it was found to be 0.983 for the electrophilic carbon center. The free energy barrier was computed to be 22.0 kcal/mol for Binding mode EL2 (table 3).

![Binding Mode EL1](image1)

![Binding Mode EL2](image2)

**Figure 7** Different binding modes investigated for the elimination step.

![Binding Mode DP1](image3)

![Binding Mode DP2](image4)

**Figure 8** Lowest-lying binding modes for the elimination step.

| Species          | Single Point Energy (Hartree) | Free Energy Correction (Hartree) | Free Energy (Hartree) | Rel. Free Energy (kcal/mol) |
|------------------|------------------------------|---------------------------------|-----------------------|-----------------------------|
| Separated Reactants | -2989.4750697               | 0.722836                        | -2988.752234          | 0.0                         |
| Binding Mode EL1  | -2989.47856839              | 0.766676                        | -2988.71189239        | 25.3                        |
| Binding Mode EL2  | -2989.48386292              | 0.766858                        | -2988.71700492        | 22.0                        |
Table 3 Energies of the lowest-lying transition states for different binding modes of nitro elimination computed at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

**Protonation of alkene:** For the final step, two lowest-lying TS (Figure 9) were identified. Similar to the previous TS, both the orientations gave the same $^{13}$C isotope effects. $^{13}$C KIE on the nucleophilic carbon center was found to be 1.014 while that on the electrophilic carbon center was found to be 0.985 as shown in figure 10.

![Binding Mode PA1 (18.8 kcal/mol)](image1)

![Binding Mode PA2 (18.3 kcal/mol)](image2)

**Figure 9** Lowest-lying TSS for the protonation step.

The free energy barrier for the mode PA1 was found to be 18.8 kcal/mol while PA1 it was found to be 18.3 kcal/mol (table 4). The free energy of HNO2 molecule was added to the free energies of PA1 and PA2 TSS to make them isoelectronic with the rest of the pathway.

![Intermolecular Experimental $^{13}$C KIEs](image3)

![Intramolecular Experimental $^{13}$C KIEs](image4)

**Figure 10** Computed $^{13}$C KIEs for the final protonation step computed at PCM-B3LYP/def2-SVP level of theory at 263 K.

| Species          | Single Point Energy (Hartree) | Free Energy Correction (Hartree) | Free Energy (Hartree) | Rel. Free Energy (kcal/mol) |
|------------------|-------------------------------|----------------------------------|-----------------------|-----------------------------|
| Separated Reactants | -2989.4750697                 | 0.722836                          | -2988.752234          | 0.0                         |
| Binding Mode PA1   | -2989.4619138                 | 0.739602                          | -2988.7223118         | 18.8                        |
Table 4 Energies of the lowest-lying transition states for different binding modes for the final protonation step computed at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

Pathway 2:

For pathway 2, activation of the nucleophile and the alkylation remain the same as pathway 1. The nitro group leaves as NO$_2^-$ while the cinchona amine abstracts the proton leading to an E2 like transition state (Figure 11).

![Figure 11 Binding mode and $^{13}$C KIEs for the computed E2 pathway.](image)

A very high (1.048) $^{13}$C KIE on the nucleophilic carbon and an inverse $^{13}$C KIE (0.985) consistent with electronic crowding around the electrophilic carbon were computed for this TS. The free energy barrier for this transition state was found to be 70.2 kcal/mol (Figure 12, Table 5), and is prohibitively higher to be a feasible pathway under the reaction conditions.
For pathway 3, activation of the nucleophile and the alkylation remain the same as pathway 1. The nitro group leaves as HNO$_2$ in an E1 like pathway. However, as the resultant cation is an unstable primary cation, it immediately rearranges via a 1,2-hydride shift to give a more stable tertiary carbocation (Figure 13).
Figure 13 Binding mode and computed $^{13}$C KIEs for E1-like pathway.

A very high (1.047) $^{13}$C KIE on the nucleophilic carbon and a slight inverse $^{13}$C KIE (0.994) around the electrophilic carbon were computed for this TS. The free energy barrier was again found to be very high (72.1 kcal/mol) making it unfeasible under the reaction conditions (Figure 14, Table 6).
Figure 14 Lowest-lying TS for the E1-like elimination step.

| Species       | Single Point Energy (Hartree) | Free Energy Correction (Hartree) | Free Energy (Hartree) | Rel. Free Energy (kcal/mol) |
|---------------|-------------------------------|----------------------------------|-----------------------|-----------------------------|
| Separated Reactants | -2989.4750697                 | 0.722836                         | -2988.752234          | 0.0                         |
| TS-E1         | -2989.3960140                 | 0.758614                         | -2988.6374003         | 72.1                        |

Table 6 Computed energies for the lowest-lying TSS for the E1-like pathway at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

**Pathway 4:**

For pathway 4, we investigated the mechanism proposed by Mukherjee and coworkers in their earlier synthetic work (Figure 15).

Figure 15 Initial mechanistic hypothesis proposed by Mukherjee and coworkers.15
For this pathway, a syn E2 like elimination pathway was identified as the lowest-lying pathway with a free energy barrier of 37.1 kcal/mol. A slight inverse $^{13}$C KIE was observed on the electrophilic carbon and a normal KIE of 1.023 was observed on the nucleophilic carbon.

![Binding Mode](image)

**Figure 16** Binding mode and computed $^{13}$C KIEs for a pathway 4.

This elimination TS subsequently generates the alkene which will then abstract a proton from the cinchona amine to generate the alkylated dione. The rate and stereodetermining step for this pathway was identified as the simultaneous elimination of the nitro group and the proton.
Table 7 Computed energies for the lowest-lying TSS for the pathway 4 at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

Pathway 5:

Pathway 5 is a mechanistic alternative to pathway 4 proposed earlier. In this pathway, the first deprotonation step, and the alkylation steps remain the same as previous pathways. However, before the elimination step, the electrophilic carbon is deprotonated by the amine. The elimination TS was found to have a barrier of 14.7 kcal/mol. Similar to pathway 4, a slight inverse $^{13}$C KIE was observed on the electrophilic carbon, while a very high $^{13}$C KIE was observed on the nucleophilic carbon (Figure 18).
Next, we looked into the step preceding the elimination step to verify if the isotope effects match with the experimental $^{13}$C KIEs (Figure 19). TS Deprot-P5 was identified as the rate determining step for this pathway with a barrier of 26.1 kcal/mol (Figure 20). The isotope effects were found to be not in agreement with the experimental KIEs.
Figure 19 Binding mode proposed for the deprotonation step of pathway 5. The resultant alkene then abstracts a proton from the cinchona amine as discussed in the protonation section to give the desired product.

Figure 20 Computed lowest-lying TSS for the elimination and deprotonation steps for pathway 5.
| Species                | Single Point Energy (Hartree) | Free Energy Correction (Hartree) | Free Energy (Hartree) | Rel. Free Energy (kcal/mol) |
|------------------------|-------------------------------|---------------------------------|-----------------------|-----------------------------|
| Separated Reactants    | -2989.4750697                 | 0.722836                        | -2988.752234          | 0.0                         |
| TS-Elim-P5             | -2989.4960373                 | 0.767176                        | -2988.728861          | 14.7                        |
| TS-Depro-P5            | -2783.78291459                | 0.761268                        | -2783.02164659        | 26.1                        |

Table 8 Computed energies for the lowest-lying TSS for the pathway 5 at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

**Pathway 6:**

Pathway 6 is mechanistically similar to pathway 1 until the alkylation step. However, in this pathway, alkylation is followed by a protonation resulting in an enol. This enol subsequently undergoes nitro elimination to give an alkene (Figure 21).

![Figure 21 Binding mode and $^{13}$C KIEs for the elimination step of pathway 6.](image)

The free energy barrier for this TS was found to be 38.8 kcal/mol making it unfeasible under the reaction conditions despite a good agreement with the experimentally measured $^{13}$C KIEs.
Figure 22 Lowest-lying TSS computed for the elimination step for pathway 6.

| Species        | Single Point Energy (Hartree) | Free Energy Correction (Hartree) | Free Energy (Hartree) | Rel. Free Energy (kcal/mol) |
|----------------|-------------------------------|----------------------------------|-----------------------|-----------------------------|
| Separated Reactants | -2989.4750697                  | 0.722836                         | -2988.752234          | 0.0                         |
| TS-Pathway-6   | -2989.4573486                  | 0.766981                         | -2988.690367          | 38.8                        |

Table 9 Computed energies for the lowest-lying TSS for the elimination step for pathway 6 at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

Pathway 7:

Pathway 7 involves the protonation of the enolate after alkylation step. The TS leading to the elimination of the nitro group was found to have a much weaker hydrogen bond network than the previous elimination TSS investigated. The $^{13}$C KIEs for this TS were found to be 3.2% on the nucleophilic carbon and a small inverse KIE of 0.4% on the electrophilic carbon.
Figure 23 Binding mode and $^{13}$C KIEs computed for the elimination step for pathway 7.

The free energy barrier for this TS was found to be 26.6 kcal/mol and involved the elimination of the unactivated nitro group as NO$_2^-$. 

Figure 24 Lowest-lying elimination TSS for pathway 7.
Table 10 Computed energies for the lowest-lying elimination TSS for pathway 7 at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

**Origin of Enantioselectivity**

After examining different mechanistic alternatives, we moved towards understanding the origin of enantioselectivity for this reaction. For this, we first chose to model reactions of **1** with **2a** (Scheme 1).

![Scheme 1](image)

As previously identified, the rate and stereo determining step is the elimination of the activated nitro group. The free energy difference for the lowest-lying TSS for the formation of **3a** was found to be 2.1 kcal/mol (Figure 25). This translates to an ee of 96% at 263K. Upon accounting for all the TS with a free energy difference under 5 kcal/mol with respect to the lowest lying
TS, via a Boltzmann distribution curve, the computed ee was still 96% but the effective free energy difference was found to be 2.0 kcal/mol.

Figure 25 Lowest-lying TSS for the competing enantiomers and their electronic and free energy differences computed at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

The key differences between the TS leading to the major enantiomer and the minor enantiomer are shorter NH…O interaction and the absence of non-classical CF…H hydrogen bonds. Furthermore, the C-N bond breaking distance is much shorter in the TS major compared to TS minor. As the catalyst backbones for both the enantiomeric TSS look identical, we performed a distortion-interaction/activation-strain analysis on the TS and along the IRCs. From this, we identified that the catalysts suffer identical distortions from their minimum energy conformation. Overlaying the catalyst fragment from both the TS geometries further demonstrated the remarkable conformational similarities between the two low-lying enantiomeric TSS (RMSD 0.01, Figure 26). The net distortion in the reactants at the TS geometry was found to be 1.2 kcal/mol favoring the major enantiomer. The interaction energy was also found to favor the major enantiomer by 1.6 kcal/mol.

Figure 26 An overlay of the catalyst fragments of TS 3a_major (Green) and TS 3a_minor (Magenta).
To further gain insights into the origin of this interaction energy and to quantify the strength of CH…F interactions present in the major enantiomer, we employed Wheeler and coworkers’ fragmentation analysis. The CF$_3$ group responsible for CF…H interactions in the lowest-lying TSS were removed, and the resultant structures were capped with hydrogens. The capping hydrogens were then optimized, and single point energies were computed and compared against the original single point energies (Figure 27).

![Fragmentation analysis of TS 3a$_{\text{major}}$ and TS 3a$_{\text{minor}}$ with cyan indicating the absence of CF$_3$ group and its favorable interaction in TS 3a$_{\text{major}}$.](image)

The single point energy difference between the enantiomeric chopped structures was computed to be 2.0 kcal/mol. This shows that the CF$_3$ groups contribute a net stabilizing interaction energy of 0.8 kcal/mol at PCM-M06-2X/6-311+G(d,p) level of theory. SAPT0$^9$–$^{12}$ a variant of symmetry-adapted perturbation theory, was applied to the lowest-lying major and minor enantiomeric TSS to further breakdown the interaction energy. From this, we identified electrostatic stabilization (+2.6 kcal/mol) of the TSS leading to the major enantiomer as the predominant contributor to the observed selectivity. Very small preference (+0.5 kcal/mol) to the major enantiomer was observed in the dispersion component of the SAPT0 energy. However, the major enantiomer was found to suffer from significant destabilizing steric interactions compared to the minor enantiomer as demonstrated by a much larger exchange-repulsion term (+1.5 kcal/mol). Finally, intrinsic bond orbitals were obtained after partitioning a pre-computed wavefunction at M06-2X/6-311+G(d,p) using IBOView code developed by Knizia and coworkers.$^{16-17}$ These IBOs are known to reflect the arrow pushing mechanisms that are commonly employed to understand the mechanism. Here, we observe that there is a strong hydrogen bonding overlap between the amine proton and the leaving nitro group. Moreover, the orbital overlaps indicate the extensive delocalization occurring throughout the molecule due to the elimination of the nitro group (Figure 28).
Figure 28 Intrinsic bond orbitals demonstrating the electron motion for the lowest-lying TSS for the elimination step.

The lowest-lying TSS for the reaction of 1 with 2b catalyzed by 4 were also located at PCM-M06-2X/6-311+G(d,p)/B3LYP/def2-SVP level of theory (Figure 29). The free energy difference for these TSS was computed to be 1.7 kcal/mol (ee 93%) at 263 K. A Boltzmann weighting of all the TS under 3 kcal/mol gave a difference in free energies between the competing TS as 1.6 kcal/mol (ee 90%) at 263 K.

Figure 29 Lowest-lying TSS for the competing enantiomers and their electronic and free energy differences computed at PCM-M06-2X/6-311+G(d,p)/B3LYP/def2-SVP at 263 K.

An overlay of the catalyst fragment from the competing TSS again demonstrated little difference (RMSD 0.05, Figure 30). Furthermore, SAPT0 analysis of the lowest-lying TSS revealed that the origin of selectivity is primarily driven by the favorable electrostatic
interactions (+2.3 kcal/mol) enjoyed by the TS leading to the major enantiomer. Furthermore, a slight increase in the favorability dispersion component of the interaction energy was observed for TS 3b_{major} over TS 3b_{minor} (+0.7 kcal/mol) compared to TS 3a_{major} (+0.5 kcal/mol). Finally, a slight increase in the destabilizing steric interactions for TS 3b_{major} was observed (+1.7 kcal/mol) when compared to TS 3a_{major} (+1.5 kcal/mol). These changes can be attributed to the presence of the bulky benzyl substituent in 2b.

Finally, the rate and stereo determining elimination of the nitro group was investigated for the reaction of 1 with 2a catalyzed by a thiourea catalyst 5 (Scheme 1). The experimental free energy difference between the competing TS for this reaction at 263 K was found to be 1.6 kcal/mol, while the computed free energy difference between the lowest-lying TSS was found to be 2.1 kcal/mol, a slight overestimation of the selectivity (Figure 31). SAPT0 analysis revealed a similar electrostatic preference for the TS 4b_{major} over TS 4b_{minor} (1.8 kcal/mol). However, the difference in dispersion component of SAPT0 between the competing TSS was found to be much higher than the previous two example (+1.3 kcal/mol favoring TS 4b_{major}). A significantly higher charge transfer term (+1.2 kcal/mol) favoring TS 4b_{major} was also observed. Finally, TS 4b_{major} was found to suffer significant destabilizing steric interactions compared to TS 4b_{minor} (+1.9 kcal/mol).
Figure 31 Lowest-lying TSS for the competing enantiomers and their electronic and free energy differences computed at PCM-M06-2X/6-311+G(d,p)//B3LYP/def2-SVP at 263 K.

References:

1. Becke, A. D., Density-functional thermochemistry. III. The role of exact exchange. *The Journal of Chemical Physics* **1993**, *98* (7), 5648-5652.
2. Frisch, M.; Trucks, G.; Schlegel, H.; Scuseria, G.; Robb, M.; Cheeseman, J.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H.; Izmaylov, A.; Bloino, J.; Zheng, G.; Sonnenberg, J.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J., JA; Peralta, J.; Ogliaro, F.; Bearpark, M.; Heyd, J.; Brothers, E.; Kudin, K.; Staroverov, V.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J.; Iyengar, S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J.; Klene, M.; Knox, J.; Cross, J.; Bakken, V.; Adamo, C.; Cammi, R.; Ochterski, J.; Martin, R.; Morokuma, K.; Zakrzewski, V.; Voth, G.; Salvador, P.; Dannenberg, J.; Dapprich, S.; Daniels, A.; Farkas, O.; Foresman, J.; Ortiz, J.; Cioslowski, J.; Fox, D. *Gaussian 09, Revision D.01*, Gaussian, Inc.: 2009.
3. Weigend, F.; Ahlrichs, R., Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297-3305.
4. Legault, C. Y. *CYLview, 1.0b: Université de Sherbrooke*, 2009 (*http://www.cylview.org*).
5. Anisimov, V.; Paneth, P., *Journal of Mathematical Chemistry* **1999**, *26* (1/3), 75-86.
6. Hehre, W. J.; Stewart, R. F.; Pople, J. A., Self-Consistent Molecular-Orbital Methods. I. Use of Gaussian Expansions of Slater-Type Atomic Orbitals. *The Journal of Chemical Physics* **1969**, *51* (6), 2657-2664.
7. Wheeler, S. E.; Houk, K. N., Integration Grid Errors for Meta-GGA-Predicted Reaction Energies: Origin of Grid Errors for the M06 Suite of Functionals. *J. Chem. Theory Comput.* **2010**, *6* (2), 395-404.
8. Zhao, Y.; Truhlar, D. G., The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and
transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. Theor. Chem. Acc. 2008, 120 (1-3), 215-241.

9. Jeziorski, B.; Moszynski, R.; Szalewicz, K., Perturbation-Theory Approach to Intermolecular Potential-Energy Surfaces of Van-Der-Waals Complexes. Chem. Rev. 1994, 94 (7), 1887-1930.

10. Szalewicz, K., Symmetry-adapted perturbation theory of intermolecular forces. Wiley Interdisciplinary Reviews-Computational Molecular Science 2012, 2 (2), 254-272.

11. Hohenstein, E. G.; Sherrill, C. D., Density fitting of intramonomer correlation effects in symmetry-adapted perturbation theory. J. Chem. Phys. 2010, 133 (1), 014101.

12. Hohenstein, E. G.; Sherrill, C. D., Density fitting and Cholesky decomposition approximations in symmetry-adapted perturbation theory: Implementation and application to probe the nature of pi-pi interactions in linear acenes. J. Chem. Phys. 2010, 132 (18), 184111.

13. Turney, J. M.; Simmonett, A. C.; Parrish, R. M.; Hohenstein, E. G.; Evangelista, F. A.; Fermann, J. T.; Mintz, B. J.; Burns, L. A.; Wilke, J. J.; Abrams, M. L.; Russ, N. J.; Leininger, M. L.; Janssen, C. L.; Seidl, E. T.; Allen, W. D.; Schaefer, H. F.; King, R. A.; Valeev, E. F.; Sherrill, C. D.; Crawford, T. D., PSI4: an open-source ab initio electronic structure program. Wiley Interdisciplinary Reviews-Computational Molecular Science 2012, 2 (4), 556-565.

14. Grayson, M. N., Mechanism and Origins of Stereoselectivity in the Cinchona Thiourea- and Squaramide-Catalyzed Asymmetric Michael Addition of Nitroalkanes to Enones. J Org Chem 2017, 82 (8), 4396-4401.

15. Manna, M. S.; Mukherjee, S., Organocatalytic enantioselective formal C(sp(2))-H alkylation. J Am Chem Soc 2015, 137 (1), 130-3.

16. Knizia, G., Intrinsic Atomic Orbitals: An Unbiased Bridge between Quantum Theory and Chemical Concepts. J Chem Theory Comput 2013, 9 (11), 4834-43.

17. Knizia, G.; Klein, J. E. M. N., Electron Flow in Reaction Mechanisms—Revealed from First Principles. Angewandte Chemie International Edition 2015, 54 (18), 5518-5522.