Supporting information

Computational insights on the origin of enantioselectivity in reactions with diarylprolinol silyl ether catalysts via a radical pathway

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1. Computational methodologies

In this study, conformational searches with force field (FF) and density functional theory (DFT) calculations were performed.

Conformational searching calculations were conducted in MacroModel (v11.7)¹ with Maestro (release 2019-01) to provide initial estimations on the geometries of rotationally flexible molecules. The Merck molecular force field (MMFF)² was used with the mixed torsional / low-mode sampling method and a setting of 2000-4000 steps as the maximum number of steps. Conformers within an energy window of 41 kJ mol⁻¹ were saved for further analyses.

DFT optimised structures were verified through frequency analyses. All the geometries were confirmed to correspond to a minimum or a first-order saddle point (i.e. in cases of transition state (TS) structures) on the potential energy surface (PES). Intrinsic reaction coordinate (IRC) or quick reaction coordinate (QRC)³ calculations were performed to ensure that the TSs correspond to the processes of interest.

The used packages and existing Python scripts were as follows: NumPy (1.19.2), Pandas (1.1.3), Matplotlib (3.3.2), Collection (0.1.6), Biopython (1.78)⁴, Scikit-learn⁵ and GoodVibes⁶. 3D images of the optimised structures were generated with CYLview20⁷, PyMOL⁸ and Visual Molecular Dynamics (VMD)⁹.

2. Number of optimised structures and the associated computational cost

2.1. MMFF calculations

| searching calculations | | | |
|------------------------|----------------------|---------------------------------------|--|
| Adduct SR | Adduct SS | Iminium | |
| $R^1 = Me; R^2 = Me$ | $R^1 = Me; R^2 = Me$ | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}$ | |
| | Catalyst A | | |
| 224 | 204 | 83 | |
| | Catalyst A_OTDS | | |
| 683 | 684 | 987 | |
| | Catalyst B | | |
| 621 | 581 | 198 | |
| | Catalyst C | | |
| 1508 | 1686 | 2228 | |

SI Table 1. Number of conformers from force field conformational searching calculations

2.2. ONIOM calculations

SI Table 2. Number of conformers optimised at the ONIOM level (i.e. ONIOM(B3LYP/6-31g(d):UFF))

| Adduct SR | Adduct SS | Iminium |
|--|--|---------------------------------------|
| $\mathbf{R}^1 = \mathbf{M}\mathbf{e}; \ \mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}; \ \mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}$ |
| | Catalyst B | |
| 26 | 29 | - |
| | Catalyst C | |
| 30 | 30 | 64 |

2.3. DFT calculations

SI Table 3. Number of adduct and iminium conformers optimised at the DFT level (i.e. B3LYP/6-31g(d))

| - | <u> </u> | | | | | | | | |
|----------------------|--|---------------------------------------|---------------------------------------|--|--|--|--|--|--|
| Adduct SR | Adduct SS | Iminium | Iminium | | | | | | |
| $R^1 = Me; R^2 = Me$ | $\mathbf{R}^1 = \mathbf{Me}; \mathbf{R}^2 = \mathbf{Me}$ | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^1 = \mathbf{P}\mathbf{h}$ | | | | | | |
| | Catalyst A | | | | | | | | |
| 37 | 33 | 44 | - | | | | | | |
| Catalyst A_OTDS | | | | | | | | | |
| 33 | 34 | 52 | 17 | | | | | | |
| | Catalyst B | | | | | | | | |
| 21 | 21 | 50 | 8 | | | | | | |
| | Catalyst C | | | | | | | | |
| 18 | 16 | 23 | 11 | | | | | | |
| | | | | | | | | | |

SI Table 4. Number of TS conformers optimised at the DFT level (i.e.

| B3LYP/6-31g(d)) | | | | | | | | | | |
|-----------------|--|--|---------------------------------------|--|--|--|--|--|--|--|
| | $\mathbf{R}^{1} = \mathbf{M}\mathbf{e};$ | $\mathbf{R}^{1} = \mathbf{M}\mathbf{e};$ | $\mathbf{R}^{1} = \mathbf{Ph};$ | $\mathbf{R}^{1} = \mathbf{P}\mathbf{h};$ | | | | | | |
| | $\mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^2 = \mathbf{P}\mathbf{h}$ | $\mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^2 = \mathbf{P}\mathbf{h}$ | | | | | | |
| | | Catalyst B (sir | nplified) | | | | | | | |
| SR | 16 | 15 | - | - | | | | | | |
| SS | 14 | 14 | - 14 | | | | | | | |
| | Catalyst B (simplified) OTDS | | | | | | | | | |
| SR | 12 | 10 | 10 | - | | | | | | |
| SS | 14 | 7 | 7 | - | | | | | | |
| | | Catalyst | B | | | | | | | |
| SR | 12 | 6 | 8 | 8 | | | | | | |
| SS | 15 | 8 | 8 | 8 | | | | | | |
| | | Catalyst | C | | | | | | | |
| SR | 12 | 7 | - | 8 | | | | | | |
| SS | 12 | 7 | - | 8 | | | | | | |

SI Table 5. MMFF to DFT conversion percentage, i.e. number of conformers optimised at the DFT level as a percentage of the number of conformers from the MMFF calculations.

| Adduct SR | Adduct SS | Iminium | | | | | | |
|------------------------------|---|---------------------------------------|--|--|--|--|--|--|
| $R^1 = Me; R^2 = Me$ | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}; \mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}$ | | | | | | |
| | Catalyst B (simplified) | | | | | | | |
| 16.52% | 16.18% | 53.01% | | | | | | |
| Catalyst B (simplified) OTDS | | | | | | | | |
| 4.83% | 4.97% | 5.27% | | | | | | |
| | Catalyst B | | | | | | | |
| 3.38% | 3.61% | 25.25% | | | | | | |
| | Catalyst C | | | | | | | |
| 1.19% | 0.95% | 1.03% | | | | | | |

3. Mechanistic studies

In the mechanistic study, a system with reduced complexity (i.e. only the basic framework was retained) was employed. Two possible mechanistic proposals of the photocatalytic synthesis of 1,4-dicarbonyl compounds using amine catalysts were investigated computationally. Mechanism 1 was proposed by Melchiorre *et al.* (SI Figure 1A).¹⁰ Mechanism 2 was derived based on the notion that the iminium ion can also be excited upon absorption of a photon (SI Figure 1B).^{11,12} As reported in the main text, the radical addition step from mechanism 1 is more kinetically favourable compared to the radical coupling process from mechanism 2. Furthermore, the experiments were conducted with radiation at $\lambda_{max} = 460$ nm, which is not optimal for exciting iminium ion. The optimal wavelength used for exciting conjugated iminium is at 420 nm as reported in the literature.¹¹



SI Figure 1. Possible mechanisms for the enantioselective synthesis of 1,4-dicarbonyls with amine catalysts: A: In mechanism 1,¹⁰ the C-C bond formation step is a radical addition process. B: In mechanism 2,^{11,12} the C-C bond formation step is a radical coupling process.

The sequential step of the radical addition process (i.e. the hydrogen atom transfer (HAT)) in mechanism 1 was investigated regarding its feasibility and the mechanism of action. Conformational searching calculations with DFT reoptimisations were carried out on the cationic radical adduct and DHP dimeric system. Geometries of ground state dimeric conformers provide insights into the possible TS structures and assist in the discovery of potential reaction pathways. (SI Figure 2) In pathway C1 and C2, H atoms from DHP are directly transferred to the site of carbon in the adduct. Pathway O is derived based on the strong H bond between the H-N in the DHP ring and the O in the carbonyl group of the adduct, which appears in many adduct-DHP conformer systems. In pathway O, the H atom is transferred to the O in the carbonyl group and sequential rearrangements are required to arrive at the desired product.

Pathway O is thermodynamically unfavourable. Optimisations of the product dimers from various distinct conformations always led to the inverse of the pathway O process. Converged geometries of the reactants were obtained instead. No TS structure has been found upon further studies with bond scan calculations. Therefore, pathway O can be eliminated from the list of possible pathways. Pathway C1 and C2 are competing processes and likely to coexist in the reaction flask. Both processes are exothermic and have similar a kinetic barrier. The ΔG^{\ddagger} of pathway C1 ($\Delta G^{\ddagger} = 6.3$ kcal mol⁻¹) and C2 ($\Delta G^{\ddagger} = 7.1$ kcal mol⁻¹) differ by less than 1 kcal mol⁻¹. Pathway C2 leads to the generation of a DHP radical species, which cannot release the carbonyl radical spontaneously. We have repeated the calculations for the HAT process with the full catalyst structure (i.e. inclusion of the bulky substituent). Similar results were obtained and pathway C1 and C2 are in competition with each other. As DHP is the limiting reagent of the reaction, the HAT process might be a percentage yield-limiting step due to the existence of pathway C2.



SI Figure 2. Three possible pathways of the H atom transfer (HAT) process and the associated adduct-DHP conformers: The possible pathways are deduced based on the conformation of the adduct-DHP dimers. (Unit: kcal mol⁻¹)

4. Structural feature labels

4.1. Descriptions on the structural feature labels

Figure 3 in the main text summarises the derivations of structural feature labels. Here, the details of the derivations are elaborated.

The iminium (E/Z) structural feature classification has been described in the main text. The classification of the ene-iminium (Figure 3A) was based on the value of the 'C-C=N-C' and 'C-C=C-C' dihedral angles, which gives 4 possible labels (EE, EZ, ZE and ZZ). The label classification for the ene-iminium rotation (Figure 3A) and COR rotation of the adduct (Figure 3F) also follows a similar logic based on specific dihedral angle values. The ene-iminium rotation classification was based on the rotation about the C-C bond within the N=C-C=C dihedral, i.e. N=C and C=C can be 'cis' or 'trans' to each other (Figure 3A). The 'in' and 'out' label of COR rotation refers to the relative orientation between the COR group and the large bulky substituent on the 5-membered ring, i.e., 'inward' towards or 'outward' away from the bulky substituent (Figure 3F). 13

Rotational geometries of the large bulky substituent on the 5-membered ring were described and categorised by the rotamer classification (i.e. syn_exo/syn_endo/app; Figure 3B). The classification was based on the value of the N-C-C-O dihedral angle. 'Syn' and 'app' refers to the relative orientation of the N and O atom. 'App' stands for antiperiplanar, while 'syn' implies that N and O are pointing towards the same direction. The 'syn_exo' and 'syn_endo' conformers are differed by the relative orientation between the O atom and the ring.¹⁴

The heterocyclic 5-membered ring can either adopt an envelope or a twist conformation (Figure 3C). When only the combinations of adjacent atoms are considered, there are five distinct dihedral angles within a 5-membered ring. The values of the five dihedral angles were measured. For an envelope conformation, the dihedral angle of the four non-endo atoms should be in between -10° to 10°. Based on the above criteria, the endo atoms can be identified. A label between '1' and '5' was given for conformers with an envelope ring, where the number refers to the endo atom position. If none of the five dihedral angles has a value between -10° and 10°, the conformer shall be classified as having a twist ring and given a label of '0'. The ring conformation label was not included in the conformation label of the conformer in filtering for selecting MMFF conformers to optimise at the ONIOM or DFT level. The ring has a very flat potential surface and the geometry commonly changed upon DFT optimisations.¹⁵ The changes in conformation were unpredictable as the shifts did not follow any pattern.

The relative orientation between one of the Ph groups and the other two groups on the large bulky substituent on the 5-membered ring was considered with the Ph rotation classification (Figure 3D). The Ph ring can either be in a parallel or perpendicular (i.e. 'para' or 'per') orientation relative to two other groups. As both Ph rings need to be considered, values of four O-C-C-C bonds dihedral angles were measured. The conformer was identified as having a 'perpendicular' Ph rotation orientation if any of the four dihedral angles were within the range of $60^{\circ} - 110^{\circ}$ or $-60^{\circ} - -110^{\circ}$. Otherwise, the conformer would be grouped into the 'parallel' category.

A summary of the OTDS chain labelling system has been given in the main text. Here, we want to include a note on the data processing. A k-nearest neighbours model⁵ based on FF data has been employed to label the OTDS orientation in terms of stability. The data set consists of 221 conformers. In labelling the conformers from the training data set, we first separated the conformers according to their 'rotamer' (syn_exo/syn_endo/app) label. Within each data group, the ΔG value of the conformers was normalised to a value between 0 and 1. The three sets of data were then combined. A label of '1' (i.e. a stable structure) was given if the normalised ΔG of the conformer was less than 0.2. Otherwise, a label of '0' (i.e. a less stable structure) was given. In addition, we have reoptimised all the conformers at the $\omega B97X$ -D/6-311G(d,p)//B3LYP/6-31G(d) level of theory and repeated the k-nearest neighbour model training based on these data. We found that the model based on data from DFT calculations produce similar results compared to results from FF calculations.

4.2. Dihedral angle distribution studies

Most label assigning was based on defined ranges of key dihedral angle measurements. In the case of the rotamer, iminium and ring conformation structural feature, borders can be easily identified based on the distribution of key dihedral angle values (SI Figure 3). In the Ph rotation, cut-off values that minimise the number of borderline examples were chosen when deciding the ranges of dihedral angle measurements for the classification. (SI Figure 4)



SI Figure 3. Dihedral angle distribution studies for the 'rotamer' and 'iminium' structural feature. These cases are straightforward when assigning the category based on dihedral angle values. The data used in creating the histograms above are from the MMFF conformational search calculation for catalyst C iminium.

O SiMe₃







'Per' if any of the (O-C-C-C) angles is between $60^{\circ} - 110^{\circ}$ or $-60^{\circ} - -110^{\circ}$; otherwise, classify as 'para'

| no | filename | value1 | value2 | value3 | value4 | مرجر | s2 and s3 |
|----|-----------|-------------|-------------|-------------|------------|-------------------|--------------|
| 1 | C_Me_EE_1 | -102.171153 | 73.378300 | -16.469699 | 167.167591 | | 0 0 |
| 2 | C_Me_EE_2 | 73.234881 | -102.301427 | -16.338549 | 167.247212 | _s1 and s4 | |
| 3 | C_Me_EE_3 | 76.191045 | -99.568731 | 166.574783 | -16.567563 | 7-8-3 | |
| | | | Sor | ting | | S-S- | for some |
| | | select | 1 select2 | select3 | select4 | s1 and s4; | |
| | | -16.46969 | 9 73.378300 | -102.171153 | 167.167591 | s2 and s3 | |
| | | -16.33854 | 9 73.234881 | -102.301427 | 167.247212 | belongs to the s | ame Ph group |
| | | -16.56756 | 3 76.191045 | -99.568731 | 166.574783 | i.e. s1 = select1 | |
| | | | | | | | |
| | 0.04 | | | | | | s 4 |
| | £ 0.03 | | | | | | s3 |
| | abili | | | 1 | | | sz |
| | qo 0.02 | | | | | | |
| | 0.01 | | 4 | _ | | | |
| | | | | | | | 4 |
| | 0 | Para | Per | Para | F | Per Para | |
| | - | - | | | | 1 | - |
| | | | | | | | |
| | | | | | | | |
| | | -150 - | 100 -5 | 0 0 | 50 | 100 150 | |

SI Figure 4. Dihedral angle distribution studies for the 'Ph rotation' structural feature. A probability vs. dihedral angle value plot is presented above. The data used are from MMFF conformational search calculations for catalyst C iminium. The dihedral value data was sorted before the graph plotting. Cut-off values that minimise the number of borderline examples were chosen.

Dihedral angle value

5. Filters

The details of the filters in the proposed procedure are elaborated below.



SI Figure 5. The filter for selecting conformers samples that are diverse in energy and conformation. The pyrrolidine ring conformation label was not included in the conformation label of the conformer. The ring has a very flat potential surface and the geometry commonly changes upon DFT optimisations. The changes in conformation are unpredictable as the shifts do not follow any pattern. A: The flow chart of the process; B: The conformation label generation and grouping of the label; C: Criterion for selecting the conformer based on the conformation label.

Filter: Remove high energy / repetitive structure DFT/ONIOM structures in xyz format Conformation labels generation \leftarrow Specify dihedral angle of interest for structural feature identifications Data frame generation \leftarrow Import ΔG data Selection of conformers ------ Select conformers with $\Delta G < 5$ kcal mol⁻¹ Select the conformer with the lowest ΔG in each group of conformation labels

SI Figure 6. The filter for removing high energy and repetitive conformers.

6. ONIOM calculations

All the ONIOM calculations were conducted at the ω B97X-D/6-311++G(d,p)//ONIOM(B3LYP/6-31G(d):UFF) level of theory. Ideally, the border between the DFT and UFF layers should be set at an inert C(sp³)-C(sp³) bond. We have examined border division o4 and o5 with iminium conformers with catalyst A_OTDS (R¹ = Me). Despite more bonds at the border, Δ G of structures at the ONIOM level with division o4 shows a closer match to Δ G at the DFT level (SI Figure 7). The conformation label of the ONIOM structures also remains almost the same upon DFT reoptimisations. The differences are mainly at the pyrrolidine ring, which is known to have a flat potential energy surface.



First layer Second layer

SI Figure 7. Border division studies for ONIOM calculations: border division o4 and o5 were tested in this study. In the structural diagrams, the core DFT layer is black and the UFF layer is blue. The ONIOM level ΔG values of the conformers are plotted against their DFT level ΔG values. The Pearson's r value for the plot of o4 is significantly higher compared to the value for o5. (Unit: kcal mol⁻¹)

7. Grid screening style sampling

Diagrammatic illustrations are given below using catalyst B TSs (R^1 =Me and R^2 = Me) as an example. The three steps in the grid screening style sampling process are as the following:

- 1. Construct the energy-conformation profile: i.e. the box plots of $\Delta\Delta G^{\ddagger}$ vs structural feature labels (SI Figure 8)
- 2. Identify 'competing' structural features: More than one structural feature label may contribute to a stable conformation. In this case, '3' vs. '4' (ring conformation), 'EE' vs. 'EZ' (eneiminium) and 'in' vs. 'out' (COR rotation) are 'competing' structural features. The corresponding features have been highlighted in blue. (SI Figure 8)
- 3. Grid screening and further sampling at the DFT level: Conformers with the 'syn_exo' and 'per' labels are noticeably more stable than other conformers. With these two structural labels stayed the same, TS conformers with different combinations of competing structural features were sampled and optimised. (SI Figure 9)



 ω B97X-D/6-311++G(d,p)//B3LYP/6-31G(d) $\Delta\Delta$ G[‡] vs. structural feature labels

SI Figure 8. Box plots of $\Delta\Delta G^{\ddagger}$ values vs. key structural feature labels for the TSs with catalyst B i.e. the energy-conformation profile: The actual data points are included next to the box plots in each graph. The energetically 'competing' structural features have been highlighted in blue. (Unit: kcal mol⁻¹)

| Conformation label | RS | No | ΔΔG‡ | Conformation label | RS | No | ΔΔG‡ | | | |
|--|----|------------------|-------------|----------------------|----|-----|------|--|--|--|
| Syn_exo EE 3 out per | R | <mark>801</mark> | 0.00 | Syn_exo EZ 3 in per | R | 809 | 1.67 | | | |
| Syn_exo EE 4 out per | R | 71 | 1.25 | Syn_exo EZ 4 in per | R | 807 | 1.71 | | | |
| <mark>Syn_exo EE 3</mark> in per | S | <mark>901</mark> | 1.05 | Syn_exo EZ 3 out per | S | 805 | 1.25 | | | |
| | S | 807 | 1.44 | Syn_exo EZ 4 out per | S | 149 | 3.67 | | | |
| Most stable SR and SS TS Most stable SR and SS TS | | | | | | | | | | |

SI Figure 9. Further samplings at the DFT level: Based on the box plots in SI Figure 8, further samplings were conducted. Structures in blue already existed in the data set before the grid screening style sampling. The structures in black were the newly sampled data points and the input to the calculations were derived from existing optimised structures. The most stable structures are highlighted in yellow. (Unit: kcal mol⁻¹)

8. <u>The scripts</u>

The relevant scripts for facilitating the pipeline have been compiled into several Jupyter notebooks (.ipynb files) under the Script_im directory in GitHub (https://github.com/Goodman-lab/Script_im). The summary of the files, instructions and examples are given in the notebooks and the README.md file.

Script_im/

- B_Me_RMe_R.xyz
- C_Me_RMe_dft_r2.csv
- C_Me_RMe_R.xyz
- conformation_label_generation.ipynb
- Filter_diversity_incl_label_generation_and_selection.ipynb
- gjf_generation.ipynb
- Goodvibes_output_B_Me_RMe_R_TS.xyz
- Goodvibes_output_C_Me_RMe_R_TS.xyz
- Goodvibes_output_test.xyz
- README.md
- ring-out.csv
- --- Selection_remove_repetitive_structures.ipynb

9. Benchmarking

Energetic and structural data sets at the ω B97X-D/6-311++G(d,p)/SMD/CH₃CN//B3LYP/6-31G(d) level of theory are as below:

SI Table 7. The conformation label of the most stable iminium (ω B97X-D/6-311++G(d,p)/SMD/CH₃CN//B3LYP/6-31G(d)). All the structures presented below have a 'trans-ene-iminium' label.

| $\mathbf{R}^{1} = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^{1} = \mathbf{P}\mathbf{h}$ |
|---|---|
| | Catalyst A |
| syn_exo EE 3 per | - |
| | Catalyst A_OTDS |
| syn_exo EE 3 per 1 | syn_exo EE 0 per 1 |
| | Catalyst B |
| syn_exo EE 3 per | syn_exo EE 4 per |
| | Catalyst C |
| syn_exo E 0 per 1 | syn_exo E 0 per 0 |
| | |

SI Table 8. The computational kinetic data at the ω B97X-D/6-311++G(d,p)/SMD/CH₃CN //B3LYP/6-31G(d) level of theory (Unit: kcal mol⁻¹)

| | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}; \ \mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | | $\mathbf{R}^1 = \mathbf{Me}; \mathbf{R}^2 = \mathbf{Ph}$ | | $\mathbf{R}^1 = \mathbf{P}\mathbf{h}$ | ; $\mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^1 = \mathbf{Ph}; \mathbf{R}^2 = \mathbf{Ph}$ | | |
|----|--|-----------------------------|--|-----------------------------|---------------------------------------|---|--|-----------------------------|--|
| | ΔG^{\ddagger} | $\Delta\Delta G^{\ddagger}$ | ΔG^{\ddagger} | $\Delta\Delta G^{\ddagger}$ | $\Delta \mathbf{G}^{\ddagger}$ | $\Delta\Delta G^{\ddagger}$ | $\Delta \mathbf{G}^{\ddagger}$ | $\Delta\Delta G^{\ddagger}$ | |
| | | | | Cataly | st A | | | | |
| SR | 10.3 | 0.0 | 12.2 | 0.4 | - | - | - | - | |
| SS | 11.2 | 0.9 | 11.7 | 0.0 | - | - | | | |
| | | | | Catalyst A | OTDS | | | | |
| SR | 9.8 | 0.0 | 11.6 | 0.0 | - | - | - | - | |
| SS | 11.2 | 1.4 | 12.0 | 0.4 | - | - | - | - | |
| | | | | Cataly | rst B | | | | |
| SR | 10.2 | 0.0 | 11.8 | 0.3 | 9.4 | 0.0 | 12.4 | 0.0 | |
| SS | 10.9 | 0.7 | 11.5 | 0.0 | 12.6 | 3.2 | 14.7 | 2.3 | |
| | | | | Cataly | st C | | | | |
| SR | 10.5 | 0.0 | 11.6 | 0.0 | - | - | 11.2 | 0.0 | |
| SS | 12.7 | 2.2 | 13.6 | 2.0 | - | - | 13.7 | 2.5 | |

| SI | Table | 9. | The | conformation | label | of | the | most | stable | TSs | at | the | ωB97X-D/6- |
|-----|-----------|-------|--------|----------------------------|--------|-------|--------|--------|-----------|--------|-------|--------|---------------|
| 311 | ++G(d,p |)/SN | /ID/CH | I ₃ CN//B3LYP/6 | -31G(d |) lev | vel of | theory | v. All th | e stru | cture | es pre | esented below |
| hav | e a 'tran | s- en | e-imin | ium' label. | | | | | | | | | |

| nave | | a001. | | |
|------|---|--|----------------------|--|
| | $\mathbf{R}^1 = \mathbf{Me}; \mathbf{R}^2 = \mathbf{Me}$ | $\mathbf{R}^1 = \mathbf{Me}; \mathbf{R}^2 = \mathbf{Ph}$ | $R^1 = Ph; R^2 = Me$ | $\mathbf{R}^1 = \mathbf{P}\mathbf{h}; \mathbf{R}^2 = \mathbf{P}\mathbf{h}$ |
| | | Catalyst | Α | |
| SR | syn_exo EE 3 out per | syn_exo E 3 out per | - | - |
| SS | syn_exo EE 3 in per | syn_exo E 3 in per | - | - |
| | | Catalyst A C | DTDS | |
| SR | syn_exo EE 3 out per | syn_exo EE 3 out per | - | - |
| | 1 | 1 | | |
| SS | syn_exo EE 3 in per 0 | syn_exo EE 3 in per 0 | - | - |
| | | Catalyst | B | |
| SR | syn_exo EE 3 out per | syn_exo EE 3 out per | syn_exo EE 4 out per | syn_exo EE 3 out |
| | | | | per |
| SS | syn_exo EZ 3 out per | syn_exo EZ 3 out per | syn_exo EE 3 in per | syn_exo EZ 3 out |
| | | | | per |
| | | Catalyst | С | |
| SR | syn_exo EE 4 out per | syn_exo EE 4 out per | - | syn_exo EE 0 out |
| | 1 | 1 | | per 1 |
| SS | syn_exo EE 4 in per 1 | syn_exo EZ 4 in per 1 | - | syn_exo EZ 5 out |
| | | | | per 1 |





SI Fig. 10. The structure of the most stable TSs and iminium ($R^1 = Ph$; $R^2 = Ph$): A: Catalyst C systems; B: Catalyst B systems; C: Catalyst A_OTDS systems; D: Catalyst A_OTDS systems. The bond length values of the forming C-C bonds are labelled in the diagrams.

Initially, the investigations were conducted at the ω B97X-D/6-311++G(d,p) // ω B97X-D/6-31G(d) level of theory, i.e. without the solvent model. The results are presented below:

SI Table 10. The conformation label of the most stable iminium (ω B97X-D/6-311++G(d,p)//B3LYP/6-31G(d)). All the structures presented below have a 'trans-ene-iminium' label.

| $\mathbf{R}^1 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^1 = \mathbf{P}\mathbf{h}$ |
|---------------------------------------|---------------------------------------|
| | Catalyst A |
| syn_exo EE 3 per | - |
| | Catalyst A_OTDS |
| syn_exo EE 3 per 1 | syn_exo EE 0 per 1 |
| | Catalyst B |
| syn_exo EE 3 per | syn_exo EE 4 per |
| | Catalyst C |
| syn_exo E 0 per 1 | syn_exo E 0 per 0 |
| | |

SI Table 11. The conformation label of the most stable SR and SS adducts ($R^1 = Me$; $R^2 = Me$) and the associated ΔG between the two structures ($\omega B97X-D/6-311++G(d,p)//B3LYP/6-31G(d)$)

| | Conformation label | $\Delta \mathbf{G}$ | | | |
|------------------------------|------------------------------|---------------------|--|--|--|
| Catalyst B (simplified) | | | | | |
| SR | syn_exo E 3 in per | 1.0 | | | |
| SS | syn_exo E 3 in per | 0.0 | | | |
| Catalyst B (simplified) OTDS | | | | | |
| SR | syn_exo E 3 out per 1 | 1.0 | | | |
| SS | syn_exo E 3 in per 1 | 0.0 | | | |
| Catalyst B | | | | | |
| SR | Syn_exo E 4 in per | 1.1 | | | |
| SS | SS App E 3 in per 0.0 | | | | |
| Catalyst C | | | | | |
| SR | app E 4 in per 1 | 0.0 | | | |
| SS | app E 4 in per 1 | 0.7 | | | |

| | $\mathbf{R}^{1} = \mathbf{M}\mathbf{e}; \ \mathbf{R}^{2} = \mathbf{M}\mathbf{e}$ | | $R^1 = Me; R^2 = Ph$ | | $\mathbf{R}^1 = \mathbf{Ph}; \ \mathbf{R}^2 = \mathbf{Me}$ | | $\mathbf{R}^1 = \mathbf{P}\mathbf{h}; \mathbf{R}^2 = \mathbf{P}\mathbf{h}$ | |
|-----------------|--|-----------------------------|-----------------------|-----------------------------|--|-----------------------------|--|-----------------------------|
| | ΔG^{\ddagger} | $\Delta\Delta G^{\ddagger}$ | ΔG^{\ddagger} | $\Delta\Delta G^{\ddagger}$ | ΔG^{\ddagger} | $\Delta\Delta G^{\ddagger}$ | ΔG^{\ddagger} | $\Delta\Delta G^{\ddagger}$ |
| Catalyst A | | | | | | | | |
| SR | 7.3 | 0.0 | 6.7 | 0.5 | - | - | - | - |
| SS | 8.2 | 0.9 | 6.2 | 0.0 | - | - | | |
| Catalyst A_OTDS | | | | | | | | |
| SR | 6.3 | 0.0 | 5.6 | 0.0 | 4.6 | 0.0 | - | - |
| SS | 7.9 | 1.7 | 6.3 | 0.7 | 6.5 | 1.9 | - | - |
| Catalyst B | | | | | | | | |
| SR | 5.6 | 0.0 | 4.5 | 0.0 | 5.2 | 0.0 | 4.6 | 0.0 |
| SS | 6.6 | 1.1 | 4.6 | 0.1 | 6.5 | 1.3 | 5.6 | 1.0 |
| Catalyst C | | | | | | | | |
| SR | 4.8 | 0.0 | 3.3 | 0.0 | - | - | 2.6 | 0.0 |
| SS | 7.9 | 3.1 | 4.3 | 1.0 | - | - | 3.7 | 1.1 |

SI Table 12. The conformation label of the most stable TSs at the ω B97X-D/6-311++G(d,p)//B3LYP/6-31G(d) level of theory (Unit: kcal mol⁻¹).

SI Table 13. The computational kinetic data of the most stable TSs at the ω B97X-D/6-311++G(d,p)//B3LYP/6-31G(d) level of theory. All the structures presented below have a 'transene-iminium' label.

| | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}; \ \mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | $\mathbf{R}^1 = \mathbf{Me}; \ \mathbf{R}^2 = \mathbf{Ph}$ | $R^1 = Ph; R^2 = Me$ | $\mathbf{R}^1 = \mathbf{P}\mathbf{h}; \mathbf{R}^2 = \mathbf{P}\mathbf{h}$ | | | |
|------------|--|--|----------------------|---|--|--|--|
| | Catalyst A | | | | | | |
| SR | syn_exo EE 3 out per | syn_exo EE 3 out per | - | - | | | |
| SS | syn_exo EE 3 in per | syn_exo EE 3 in per | - | - | | | |
| | Catalyst A_OTDS | | | | | | |
| SR | syn_exo EE 3 out per | syn_exo EE 3 out per | syn_exo EE 3 out | - | | | |
| | 1 | 1 | per 1 | | | | |
| SS | syn_exo EE 3 in per 0 | syn_exo EE 3 in per | syn_exo EE 3 in per | - | | | |
| | | 0 | 0 | | | | |
| Catalyst B | | | | | | | |
| SR | syn_exo EE 3 out per | syn_exo EE 3 out per | syn_exo EE 4 out | syn_exo EE 3 out | | | |
| | | | per | per | | | |
| SS | syn_exo EE 3 in per | syn_exo EZ 3 out per | syn_exo EE 3 in per | app EE 3 in para | | | |
| Catalyst C | | | | | | | |
| SR | syn_exo EE 4 out per | syn_exo EE 4 out per | - | syn_exo EE 0 out | | | |
| | 1 | 1 | | per 1 | | | |
| SS | app EE 4 in per 1 | app EE 4 in per 1 | - | app EE 4 in per 1 | | | |



SI Figure 11. Comparison of ΔG values at the MMFF, ONIOM and DFT level of theory for catalyst C iminium conformers. The DFT calculations are conducted at the ω B97X-D/6-311G(d,p)/SMD/CH3CN//B3LYP/6-31G(d) level of theory. The ONIOM calculations are conducted at the ω B97X-D/6-311G(d,p)//ONIOM(B3LYP/6-31G(d):UFF) level of theory. A: The plot of ΔG (DFT) vs. ΔG (MMFF); B: The plot of ΔG (MMFF) vs. ΔG (ONIOM): the conformers of blue data points were reoptimised at the DFT level of theory; C: The plot of ΔG (DFT) vs. ΔG (ONIOM) (unit: kcal mol⁻¹)

10. Non-covalent interactions plots (NCI plots)

NCI plot analyses provide visualisations of the position and strength of NCIs within a structure.¹⁶ The rendering of the structural diagram was conducted with Visual Molecular Dynamics (VMD).⁹ s vs. $sign(\lambda_2)\rho$ plots were also drawn. s is the reduced density gradient and $sign(\lambda_2)\rho$ is the product of density (ρ) and the sign of second density Hessian eigenvalue ($sign(\lambda_2)\rho$). The nature of the interactions is determined by the sign of the $sign(\lambda_2)\rho$ value. A positive $sign(\lambda_2)\rho$ indicates attractive NCIs and a negative $sign(\lambda_2)\rho$ implies repulsive NCIs. In the s vs. $sign(\lambda_2)\rho$ plots and structural diagrams below, blue regions indicate strong attractive interactions (e.g. H-bonds) and red regions represent repulsive interactions. (SI Figure 12)

Various TS conformers, including the less stable conformers, have been studied and consistent results have been obtained. The NCIs between the COR² radical and the iminium ion are mainly weak van der Waals interactions.



A: TSs with Catalyst A OTDS (R^1 = Me; R^2 = Me)



B: TSs with Catalyst B ($R^1 = Ph$; $R^2 = Ph$)

SS807 ΔG[‡] = 14.7; ΔΔG[‡] = 2.3 syn_exo EE 4 in per



SI Figure 12. s vs. $sign(\lambda_2)\rho$ plots and visualisation of the NCIs on within the TS structures: The colour scale for $sign(\lambda_2)\rho$ values is from -0.03 to 0.03. Data points with $sign(\lambda_2)\rho < -0.03$ are in blue and data points with $sign(\lambda_2)\rho > -0.03$ are in red. The kinetic and structural data are given at the ω B97X-D/6-311++G(d,p)/SMD/CH₃CN//B3LYP/6-31G(d) level of theory (unit: kcal mol⁻¹). A: TSs with Catalyst A_OTDS (R¹ = Me; R² = Me). SR803 and SS806 are the most stable SR and SS TS conformer.; B: TSs with Catalyst B (R¹ = Ph; R² = Ph): SR801 and SS805 are the most stable SR and SS TS conformer; C: TSs with Catalyst C (R¹ = Ph; R² = Ph): SR1807 and SS1819 are the most stable SR and SS TS conformer.

11. Distortion/interaction analyses

The complete distortion/interaction analysis data set is given below.¹⁷ The relative energy is the difference in single-point energy of the iminium structure from the TS relative to the ground state iminium from QRC (SI Figure 13). Single point energy values were computed at the ω B97X-D/6-311++G(d,p) level of theory.



Level of theory for the single point energy: ω B97X-D/6-311++G(d,p)

Key: TS structure; ground state iminium from QRC

SI Figure 13. The derivation of relative energy – a diagrammatic illustration.

| SI Table 14. Distortion/interaction analyses. The conformation label and $\Delta\Delta G^{\ddagger}$ of the TSs are given |
|--|
| along with the relative energy. The kinetic ($\Delta\Delta G^{\ddagger}$) and structural data are given at the $\omega B97X$ -D/6- |
| 311++G(d,p)/SMD/CH ₃ CN//B3LYP/6-31G(d) level of theory. All the TSs presented below have a |
| 'trans-ene-iminium' label. (Unit: kcal mol ⁻¹) |

| Entry | Catalyst | SR/SS? | $\Delta\Delta G^{\ddagger}(TS)$ | Relative energy | Conformation label (TS) | |
|-------|--|--------|---------------------------------|-----------------|--------------------------------|--|
| | $\mathbf{R}^1 = \mathbf{M}\mathbf{e}; \ \mathbf{R}^2 = \mathbf{M}\mathbf{e}$ | | | | | |
| 1 | Α | SR | 0.0 | 2.4 | syn_exo E 3 out per | |
| 2 | Α | SS | 0.9 | 3.4 | syn_exo E 3 in per | |
| 3 | A_OTDS | SR | 0.0 | 2.5 | syn_exo EE 3 out per 1 | |
| 4 | A_OTDS | SS | 1.4 | 3.6 | syn_exo EE 3 in per 0 | |
| 5 | A_OTDS | SS* | 2.0 | 4.6 | syn_exo EE 3 in per 1 | |
| 6 | В | SR | 0.0 | 2.1 | syn_exo EE 3 out per | |
| 7 | В | SS | 0.7 | 2.5 | syn_exo EE 3 in per | |
| 8 | С | SR | 0.0 | 1.1 | syn_exo EE 4 out per 1 | |
| 9 | С | SS | 2.2 | 3.6 | syn_exo EE 4 in per 1 | |
| | | | $R^1 = 1$ | $Me; R^2 = Ph$ | | |
| 10 | Α | SR | 0.4 | 4.0 | syn_exo E 3 out per | |
| 11 | Α | SS | 0.0 | 4.1 | syn_exo E 3 in per | |
| 12 | A_OTDS | SR | 0.0 | 4.0 | syn_exo EE 3 out per 1 | |
| 13 | A_OTDS | SS | 0.4 | 4.2 | syn_exo EE 3 in per 0 | |
| 14 | A_OTDS | SS* | 2.5 | 7.5 | syn_exo EE 3 in per 1 | |
| 15 | В | SR | 0.5 | 4.0 | syn_exo EE 3 out per | |
| 16 | В | SS | 0.0 | 1.7 | syn_exo EZ 3 out per | |
| 17 | В | SS* | 5.1 | 5.9 | syn_exo EE 3 in per | |
| 18 | С | SR | 0.0 | 4.4 | syn_exo EE 4 out per 1 | |
| 19 | С | SS | 2.0 | 6.2 | syn_exo EE 4 in per 1 | |
| | $\mathbf{R}^1 = \mathbf{P}\mathbf{h}; \mathbf{R}^2 = \mathbf{P}\mathbf{h}$ | | | | | |
| 20 | В | SR | 0.0 | 4.6 | syn_exo EE 3 out per | |
| 21 | В | SS | 2.3 | 2.0 | syn_exo EZ 3 out per | |
| 22 | В | SS* | 5.4 | 10.1 | syn_exo EE 4 in per | |
| 23 | С | SR | 0.0 | 3.4 | syn_exo EE 0 out per 1 | |
| 24 | С | SS | 2.5 | 2.8 | syn_exo EZ 5 out per 1 | |
| 25 | С | SS* | 5.7 | 12.8 | syn_exo EE 4 in per 1 | |

* The structure is not the most stable (i.e preferred) conformer of its group.



SI Figure 14. Relative energy vs. change in activation energy $(\Delta\Delta G^{\ddagger})$ plots. Relative energy measures the extent of distortion between the iminium structure from the TS relative to the ground state iminium from QRC in terms of energy (see SI Figure 13). The data points are coloured by A. stereochemistry (i.e. SS or SR); B the catalyst involved (i.e. A, A_OTDS, B and C); C. the R¹/R² substituent. 'SS*' refers to SS TSs that are not the most stable (i.e preferred) conformer of their group, but the iminium ions in the TSs adopts the same conformation as the most stable ground state iminium. (Unit: kcal mol⁻¹)

Catalyst A; $R^1 = R^2 = Me$ systems



A

Key: TS structure; ground state iminium from QRC

Catalyst A OTDS; R1 = R2 = Me systems From SR/SS TS? SS SS: preferred SR: most stable syn_exo EE 3 out per syn_exo EE 4 in per syn_exo EZ 3 out per Relative energy 4.6 3.6 2.5 TS ΔΔG‡ 2.0 0.0 1.4 Iminium ∆G 0.0 0.7 0.0

В

Key: TS structure; ground state iminium from QRC

Catalyst B; R¹ = R² = Ph systems



С

SI Figure 15. Distortion-interaction analyses for the iminium structure from TSs of the radical addition process: A: Catalyst A systems; B: Catalyst A_OTDS; C: Catalyst B systems. The kinetic and structural data are given at the ω B97X-D/6-311++G(d,p)/SMD/CH₃CN//B3LYP/6-31G(d) level of theory (unit: kcal mol⁻¹). The conformation label of the TSs is included in the table. All the TSs presented have a 'trans-ene-iminium' label.

Key: TS structure; ground state iminium from QRC

12. Charge Analyses



SI Figure 16. Hirshfeld Charge analyses on the iminium ion. The analyses are performed at the ω B97X-D/6-311++G(d,p)/SMD/CH₃CN//B3LYP/6-31G(d) level of theory.

13. Key structures

The key structures are included in the 'SI_key_structure' folder as Gaussian calculation output files. All the structures are the most stable conformer in their corresponding group. Both the opt+freq calculation and its associated single point energy output (i.e. _solv_wb.out files) are included for each structure. The corresponding level of theory is ω B97X-D/6-311++G(d,p)/SMD/CH₃CN//B3LYP/6-31G(d). The filename should be self-explanatory. For example, 'B_Me_RPh_R_801_TS.out' implies a catalyst B SR TS (R¹ = Me; R² = Ph) and 'C_Me_EE_2.out' implies a catalyst C iminium (R¹ = Me) structure.

The directory tree of 'SI key structure' is presented below.

SI_key_structure/

· A/ - A Me EE 2.out - A Me EE 2 solv wb.out - A_Me_RMe_R_1_TS.out - A Me RMe R 1 TS solv wb.out - A Me RMe S E 6 TS.out - A Me RMe S E 6 TS_solv_wb.out - A_Me_RPh_R_1_TS.out - A Me RPh R 1 TS solv wb.out - A Me RPh S E 6 TS.out A Me RPh S E 6 TS solv wb.out A OTDS/ -OTDS Me EE 2.out -OTDS Me EE 2 solv wb.out - OTDS Me RMe R 2 TS.out -OTDS Me RMe R 2 TS solv wb.out -OTDS Me RMe S 806 TS.out -OTDS Me RMe S 806 TS solv wb.out - OTDS_Me_RPh_R_801_TS.out -OTDS Me RPh R 801 TS solv wb.out -OTDS Me RPh S 806 TS.out -OTDS Me RPh S 806 TS solv wb.out $\mathbf{B}/$ - B Me EE 3.out - B Me EE 3 solv wb.out - B Me EE 5 Ph.out - B Me EE 5 Ph solv wb.out - B Me RMe R 801 TS.out - B Me RMe R 801 TS solv wb.out - B Me RMe S 805 TS.out - B Me RMe S 805 TS solv wb.out - B Me RPh R 801 TS.out - B Me RPh R 801 TS spe solv.out - B Me RPh S 805 TS.out - B Me RPh S 805 TS spe solv.out - B_Ph_RMe_R_71_TS.out - B Ph RMe R 71 TS solv wb.out - B Ph RMe S 901 TS.out - B Ph RMe S 901 TS solv wb.out - B Ph RPh R 801 TS.out - B Ph RPh R 801 TS solv wb.out - B Ph RPh S 805 TS.out

- B_Ph_RPh_S_805_TS_solv_wb.out
 C/
 C_Me_EE_10_Ph.out
 C_Me_EE_10_Ph_solv_wb.out
 C_Me_EE_2.out
 C_Me_EE_2_solv_wb.out
 C_Me_RMe_R_1807_TS_solv_wb.out
 C_Me_RMe_S_1813_TS_solv_wb.out
 C_Me_RPh_R_1807_TS_solv_wb.out
 C_Me_RPh_R_1807_TS_solv_wb.out
 C_Me_RPh_S_1821_TS_solv_wb.out
 C_Me_RPh_R_1807_TS_solv_wb.out
 C_Me_RPh_S_1821_TS_solv_wb.out
 C_Ph_RPh_R_1807_TS_solv_wb.out
 C_Ph_RPh_R_1807_TS_solv_wb.out
 C_Ph_RPh_R_1807_TS_solv_wb.out
 C_Ph_RPh_R_1807_TS_solv_wb.out
 C_Ph_RPh_R_1807_TS_solv_wb.out
 C_Ph_RPh_R_1807_TS_solv_wb.out
 C_Ph_RPh_R_1807_TS_solv_wb.out
 - C_Ph_RPh_S_1819_TS_solv_wb.out

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