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Electronic Supplementary Information

for

Two Chiral Catalysts in Action: Insights on Cooperativity and Stereoselectivity in Proline and Cinchona-Thiourea Dual Organocatalysis

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PART-A

PART-B

Optimized Cartesian Coordinates of All Stationary Points (See a separate file)

(I) Scheme 1(a) Details: Michael Addition using Butanone

(1) Enamine formation between proline and butanone



Scheme S1 Formation of enamine between butanone and proline



Scheme S2 Mechanism of formation of enamine between butanone and proline (Scheme S1).



Fig. S1 The Gibbs free energy profile obtained at the SMD_(benzene)/M06-2X/6-31G** level of theory for the formation of enamine as shown in Scheme S2.

(2) Enamine formation between proline and butanone with cinchona-thiourea



Scheme S3 Important elementary steps in the formation of enamine in the presence of cinchona-thiourea (Scheme 1(a), 2-3).



 \bigcirc = S \bigcirc = O \bigcirc = N \bigcirc = C \bigcirc = H \bigcirc = -C₆H₃(CF₃)₂ \bigcirc =Quinoline *anti-(E)-enamine syn-(E)-enamine* Fig. S2 Free energy profile for the formation of enamine intermediate and the optimized geometries of the key transition states obtained at the SMD_(benzene)/M06-2X/6-31G** level of theory of Scheme S3. All distances are in angstroms and energies in kcal/mol.

	[2-3] [‡]	[3-4] [‡]	[4-5] _{syn} [‡]	[4-5] _{anti} ‡	[6-7] _{syn} ‡	[6-7] _{anti} ‡
proline	9.3	8.5	15.7	16.3	13.7	14.0
proline with	8.1	1.1	11.0	13.6	7.2	14.7
cinchona-thiourea						

Table S1. Elementary Step Barriers^{*a*} (kcal/mol) of Enamine Formation in the Presence of only Proline and Proline-Cinchona Thiourea Catalyst Combination

^a The reference points of proline enamine formation in the case of proline-only pathway (Fig. S1) and in the presence of cinchona-thiourea catalyst (Fig. S2) are respectively proline and proline-thiourea complex along with the corresponding dicarbonyl compound. The catalytic dyad of proline and cinchona thiourea is 11.3 kcal/mol lower than the separated non-interacting proline and cinchona thiourea.

(3) Comparison of two possibilities (denoted here as path-A and path-B) for the Michael Addition [8-9][‡]

Table S2. Relative Gibbs Free Energies (in kcal/mol) for the C-C Bond Formation Transition States between the Prochiral Faces of the Nucleophile and the Electrophile (Fig. 2) Obtained at the $SMD_{(benzene)}/M06-2X/6-31G^{**}$ Level of Theory for Catalyst Combination (Proline (**P**) and Cinchnoa-Thiourea(**C**)).

Nucleophile-	path-A	path-B	Absolute
Electrophile			Configuration
si-si	0.0	0.0	RS
si-re	3.8	3.0	RR
re-si	2.2	1.8	SS
re-re	2.8	0.6	SR

Table S3. Relative Gibbs Free Energies (in kcal/mol) for the Michael addition C–C Bond Formation Transition States between the Prochiral Faces of the Nucleophile and the Electrophile. Experimental values of *%ee* and *%de* are respectively 90.0 and 92.0 (Scheme 1(a) and Fig. 3)

nucleophile-electrophile	Method 1	Method 2	Method 3	Method 4
si-si	0.0	0.0	0.0	0.0
si-re	3.8	4.4	4.9	5.9
re-si	2.2	3.0	3.2	2.6
re-re	2.8	4.5	4.9	9.5

%de	95.2	98.7	99.0	97.5
%ee	98.2	>99.0	>99.0	>99.0

Method $1 = \text{SMD}_{(\text{benzene})}/\text{M06-2X}/6-31G^{**}$

Method 2 = $SMD_{(benzene)}/M06-2X/6-311+G**//SMD_{(benzene)}/M06-2X/6-31G**$

Method 3 = $SMD_{(benzene)}/M06-2X-D3/6-311+G**//SMD_{(benzene)}/M06-2X/6-31G**$

Method 4 = SMD_(benzene)/B3LYP-D3/6-311+G**//SMD_(benzene)/M06-2X/6-31G**



Fig. S3 Gibbs free energy profile for formation Michael adduct (9) between the butanone and nitrostyrene in the presence of proline (P) and cinchona-thiourea (C) dual chiral catalyst combination (Scheme 3) obtained at the $SMD_{(benzene)}/M06-2X/6-31G^{**}$ Level of Theory.

(II) Scheme 1(b) Details: Cascade Michael-Michael addition using Dicarbonyl compound

(4) Details of Mechanism of Proline Enamine Formation in the Absence of Cinchona-Thiourea



Scheme S4 Formation of enamine from the dicarbonyl compound by engaging the aldehyde moiety by proline catalyst.



Scheme S5 Mechanism of formation of enamine with proline (Scheme S4).



Fig. S4 Gibbs free energy profile (in kcal/mol) for the formation of proline enamine as shown in Scheme S5.

(5) Different Possibilities for the formation of a Catalyst Dyad between Proline and Cinchona-Thiourea)





Fig. S5 Different modes of interaction between proline and cinchona-thiourea. The relative Gibbs free energies are calculated at the $SMD_{(toluene)}/M06-2X/6-31G^{**}$ level of theory. The relative total energies (ΔE) are shown in parenthesis. All distances are in angstroms.

(6) Elementary Step Barriers for the Formation of Proline Enamine Intermediate, with and without Cinchona-Thiourea

Table S4. Elementary Step Barriers^a (kcal/mol) of Enamine Formation in the Presence of only Proline and Proline-Cinchona Thiourea Catalyst Combination

	[2-3] [‡]	[3-4] [‡]	[4-5] _{syn} [‡]	[4-5] _{anti} ‡	[6-7] _{syn} ‡	[6-7] _{anti} ‡
proline	4.8	0.4	17.8	15.0	8.2	11.6
proline with	7.0	3.5	10.0	9.9	8.4	10.8
cinchona-thiourea						

^{*a*} The reference points of proline enamine formation in the case of proline-only pathway (Fig. S4) and in the presence of cinchona-thiourea catalyst (Fig. 1, in main text) are respectively proline and proline-thiourea complex along with the corresponding dicarbonyl compound. The catalytic dyad of proline and cinchona thiourea is 12.7 kcal/mol lower than the separated non-interacting proline and cinchona thiourea.

(7) Conformational Analysis of the Transition States Involved in Enamine Formation in Proline-only Pathway and Proline Cinchona-Thiourea Dual Catalytic Pathway

(i) Proline-enamine Formation (in the Absence of Cinchona-Thiourea)







[4-5][‡]



Important dihedral angles considered are,

D1 = C1'-N2'-C1-C2; D2 = N2'-C1-C2-C7; D3 = C1-C2-C7-C6; D4 = C2-C7-C6-C5 Fig. S6 Depiction of different dihedral angles considered in conformational analysis

Table S5. Relative Gibbs Free Energies (in kcal/mol) of Various Conformer of the Transition States Involved in Proline-enamine Formation in the Absence of Cinchona-Thiourea.

Conformation		ΔG^{\ddagger}						
Comorniation	D1	D2	D3	D4	(kcal/mol)			
		N-C bond form	ation [2-3] [‡]					
1	117.7	69.0	-136.6	72.6	0.0			
2	-150.4	-57.0	-46.2	82.4	2.6			
3	-108.1	78.2	-166.4	73.1	2.9			
4	125.7	70.7	-134.4	64.4	3.1			
5	-152.5	-66.0	178.5	63.6	3.3			
6	-148.6	-139.4	60.1	43.8	4.4			
	N-H proton transfer [3-4] [‡]							
1	-71.8	179.2	55.4	53.2	0.0			
2	-71.0	-179.4	57.0	54.0	0.9			
3	169.3	-44.3	-72.6	166.9	1.0			
4	162.6	172.2	-91.6	54.1	1.2			
5	-72.0	179.7	173.1	60.1	1.9			
6	163.4	-61.2	94.0	-178.9	3.3			
7	-69.5	-153.4	-50.9	85.9	3.5			
8	-72.0	-112.8	-79.3	60.1	3.8			
9	-75.5	168.7	-119.0	56.6	4.7			
10	-72.8	165.4	-110.3	55.1	5.0			
11	169.4	171.4	-91.4	53.4	7.3			

Dehydration [4-5] [‡]							
<i>syn</i> -[4-5] [‡]							
1	-20.1	-74.6	-178.2	67.1	0.0		
2	-19.9	171.6	48.6	52.9	0.7		
3	-20.0	-162.2	-58.9	83.6	1.1		
4	-19.9	-165.3	-69.5	-61.1	2.5		
5	-23.4	62.0	169.5	60.2	2.7		
6	-23.4	62.0	169.5	60.2	2.7		
7	-20.7	-162.4	-74.7	-74.7	3.0		
8	-20.3	-160.7	56.7	44.2	3.1		
		anti-[4-	5] [‡]				
1	-169.0	-177.8	-176.6	-62.4	0.0		
2	-168.6	-179.9	-179.9	-65.0	0.1		
3	-168.3	158.9	55.9	-90.2	0.4		
4	-169.3	73.6	49.4	-79.9	0.5		
5	-165.2	-176.3	133.2	-61.1	0.7		
6	-169.8	-178.1	-175.2	-60.8	2.1		
		Proton abstract	tion [6-7] [‡]				
		syn-[6-	7] [‡]				
1	1.1	-162.4	177.3	53.5	0.0		
2	1.2	-165.0	170.8	50.7	1.1		
3	0.1	-164.5	-85.6	64.3	2.0		
4	-2.5	-162.2	82.0	-65.4	2.5		
5	2.3	-162.2	-113.8	-66.9	2.9		
6	-2.4	-163.0	-154.9	-175.8	3.0		
7	-1.6	-162.1	78.9	63.2	3.4		
8	-2.1	-162.1	-143.8	-57.9	3.8		
9	-3.1	-163.6	-152.1	-61.6	4.1		
10	-2.5	-153.9	57.0	42.7	5.6		
11	-2.0	-162.7	-39.3	-56.0	5.9		
		anti-[6-	7] [‡]				
1	159.1	171.7	49.0	53.0	0.0		

2	161.0	165.4	-79 7	61.1	13
	101.0	100.1		01.1	1.5
3	159.3	176.2	58.9	-81.6	1.9
4	160.1	174.9	75.1	-58.8	2.0
5	161.0	168.3	-72.7	-57.2	2.4
6	160.4	172.8	44.8	169.4	2.9
7	160.5	172.5	37.8	168.7	3.0
8	159.6	176.0	47.2	-85.0	3.2

(ii) Proline-enamine Formation in the Presence of Cinchona-Thiourea











Important dihedral angles considered are,

D1 = C1'-N2'-C1-C2; D2 = N2'-C1-C2-C7; D3 = C1-C2-C7-C6; D4 = C2-C7-C6-C5Fig. S7 Depiction of different dihedral angles considered in conformational analysis

Table S6. Relative Gibbs Free Energies (in kcal/mol) of Various Conformer of the TransitionStates Involved in Proline-enamine Formation in the Presence of Cinchona-Thiourea.

Conformation		ΔG^{\ddagger}			
Comornation	D1	D2	D3	D4	(kcal/mol)

N-C bond formation [2-3] [‡]								
1	-160.7	-164.4	179.4	-65.6	0.0			
2	125.2	66.2	163.8	167.2	0.8			
3	178.7	83.2	87.2	-58.6	2.1			
4	-85.4	-103.8	-58.9	-52.6	2.3			
5	179.9	91.4	96.0	-53.5	2.4			
6	-85.8	-104.1	-59.0	-53.3	2.9			
7	176.2	87.2	72.7	-177.9	6.0			
8	176.9	86.6	73.7	72.6	7.0			
		N-H proton tran	sfer [3-4] [‡]					
1	168.1	-179.0	136.9	57.5	0.0			
2	170.9	-175.5	-87.7	49.6	0.5			
3	-71.0	-122.6	-61.4	-66.7	0.9			
4	173.9	-173.4	-68.0	176.6	1.4			
5	-69.5	-129.1	-54.5	-61.8	2.2			
6	-69.1	-121.3	-62.6	-66.8	2.5			
7	-65.0	-169.1	-167.2	-59.4	3.1			
8	-64.9	-155.1	-83.8	-67.3	3.5			
9	-61.7	-159.5	110.6	-49.8	4.3			
		Dehydration	[4-5] [‡]					
		syn-[4-5	5] [‡]					
1	-17.1	-81.0	178.6	56.8	0.0			
2	-18.5	-79.2	-179.7	56.4	0.3			
3	-16.4	-82.0	171.2	52.7	0.4			
4	-25.3	-71.5	177.4	61.7	3.5			
5	-21.0	-69.0	-55.2	78.3	4.4			
6	-16.1	-73.7	118.9	53.5	4.5			
7	-18.7	-74.6	-173.7	-52.8	4.8			
	anti- [4-5] [‡]							
1	-166.6	68.6	75.7	-56.8	0.0			
2	-165.5	72.6	60.9	-72.8	2.2			
3	-162.8	95.7	-69.1	-67.7	4.3			

4	-163.7	147.0	-43.2	-38.1	8.3			
	Proton abstraction [6-7] [‡]							
		syn- [6- '	7] [‡]					
1	0.9	-161.7	78.6	176.5	0.0			
2	0.7	-163.3	-64.0	-177.0	0.5			
3	4.1	-157.3	-55.7	-65.0	0.7			
4	0.3	-162.1	77.6	177.4	1.2			
5	-1.1	-166.2	-61.6	-131.1	1.7			
6	-3.7	-162.2	-158.3	178.4	2.0			
7	0.7	-165.7	-80.7	54.2	2.4			
8	-2.5	-167.8	-81.5	50.4	2.7			
9	-0.2	-162.3	-31.3	86.3	3.9			
		anti- [6-	7] [‡]					
1	158.9	167.4	-87.3	-67.7	0.0			
2	159.9	161.1	-176.8	-64.0	0.2			
3	159.1	164.7	-71.6	-56.3	0.9			
4	158.5	174.9	54.7	119.9	2.0			
5	160.7	166.0	161.4	61.6	2.4			
6	160.7	166.0	161.7	61.5	2.5			
7	160.5	164.5	122.8	51.9	4.4			

(8) Comparison of two possibilities (denoted here as path-A and path-B) for the first Michael Addition $[8-9]^{\ddagger}$



path-A (0.0)



path-B (2.4)



Fig. S8 Different modes of the stereocontrolling C-C bond formation transition states $[8-9]^{\ddagger}$ between proline *syn*-(*E*)-enamine (6) and *trans*- β -nitrostyrene in the intermolecular Michael addition.

Table S7. Relative Gibbs Free energies (kcal/mol) of path-A and path-B of First Michael Addition (as shown in Fig. S8) Obtained at the SMD_(toluene)/M06-2X/6-31G** Level of Theory

Nucleophile-Electrophile	path-A	path-B
si-si	10.6	13.0
si-re	13.6	15.8
re-si	13.6	15.1
re-re	12.7	13.2

(9) Conformational Analysis of the Transition States for the C-C Bond Formation between Nucleophile and Electrophile (First Michael Addition)



Fig. S9 Different dihedral angles considered are **D3**= C1-C2-C7-C6, **D4**= C2-C7-C6-C5, **D5**= C1-C2-C3-C4]

Table S8. Conformational Sampling of the Stereocontroling Transition states (*si-si, si-re, re-si, re-re*) of first Michael addition [**8-9**]^{\ddagger} between path-A and path-B in C-C Bond Formation (Fig. S9). The relative Gibbs free energies are calculated at the SMD_(toluene)/M06-2X/6-31G** level of theory. The lowest energy conformers in each stereochemically distinct modes are highlighted

path-A							
conformer	D3	D4	D5	ΔG			
				(kcal/mol)			
	si-si						
si-si_1	-170.4	-58.1	-165.3	0.0			
si-si_2	-167.6	-50.2	-161.9	0.7			
si-si_3	96.2	63.5	-176.0	1.2			
si-si_4	104.9	51.6	-168.8	2.2			
si-si_5	75.9	-80.2	-40.0	3.0			
si-si_6	83.9	-69.7	-48.7	4.8			
si-si_7	89.6	-68.0	-36.1	7.0			
si-si_8	-157.0	-50.4	-170.2	10.6			
	I	si-re	I				
si-re_1	90.7	61.3	-83.5	0.0			
si-re_2	88.0	62.2	-64.8	0.8			
si-re_3	154.8	64.3	-63.2	2.3			
si-re_4	102.6	66.3	-77.5	2.4			
si-re_5	-9.5	71.8	-63.6	2.7			
si-re_6	-175.0	-177.0	-67.6	3.5			
si-re_7	-176.6	170.9	-62.4	3.9			
si-re_8	-15.8	73.1	75.0	8.3			
re-si							
re-si_1	-70.0	61.7	-91.3	0.0			
re-si_2	16.7	155.6	-91.0	0.3			
re-si_3	163.8	53.0	-82.9	2.7			
re-si_4	32.1	67.8	-37.0	8.3			
re-si_5	11.4	75.4	-31.6	13.2			
	re-re						

re-re_1	-89.6	58.4	31.8	0.0
re-re_2	-9.9	76.6	25.0	1.4
re-re_3	0.2	68.4	29.2	1.7
re-re_4	11.0	70.9	33.7	1.9
re-re_5	11.0	70.9	33.7	2.4
re-re_6	10.9	70.9	33.5	2.5
re-re_7	28.4	167.4	25.6	2.6
re-re_8	27.6	68.3	37.2	2.7
re-re_9	-116.2	67.9	29.8	3.4
<i>re-re</i> _10	-116.2	67.8	29.8	3.5
<i>re-re</i> _11	-73.5	62.6	14.3	3.6
<i>re-re</i> _12	-138.7	63.2	39.8	3.8
<i>re-re</i> _13	-79.9	72.6	24.4	3.9
<i>re-re</i> _14	4.0	66.9	29.3	4.4
<i>re-re</i> _15	-136.0	57.3	38.5	4.5
<i>re-re</i> _16	153.9	63.1	26.4	4.8
<i>re-re</i> _17	58.9	-45.0	32.0	4.9
<i>re-re</i> _18	154.0	63.2	26.3	5.2
<i>re-re</i> _19	-173.4	44.6	27.6	5.8
<i>re-re</i> _20	95.4	83.1	14.8	11.4
		path-B		
		si-si		
si-si_1	115.9	54.8	174.0	0.0
si-si_2	87.5	-65.6	-36.0	0.1
si-si_3	116.1	55.1	173.4	0.2
si-si_4	87.5	-65.6	-36.0	0.4
si-si_5	87.5	-65.7	-35.9	0.8
si-si_6	111.1	63.3	161.1	1.3
si-si_7	86.0	-70.2	-38.6	1.8
si-si_8	-13.6	67.5	-39.8	2.4
si-si_9	85.4	-79.8	-37.1	2.5
si-si_10	94.2	-173.7	-35.4	2.8

si-si_11	94.1	-173.6	-35.3	2.9			
si-si_12	-28.3	-170.8	-35.6	3.4			
si-si_13	57.8	-96.4	-41.7	3.5			
si-si_14	-16.5	-169.9	-37.9	4.2			
si-si_15	153.7	-64.6	-46.1	4.9			
si-si_16	-26.3	-175.0	-36.1	5.1			
si-si_17	147.4	-65.4	-41.8	5.2			
		si-re					
si-re_1	-165.3	-60.8	-75.9	0.0			
si-re_2	-164.4	-61.2	-70.6	0.2			
si-re_3	-14.6	-170.7	-61.6	1.3			
si-re_4	165.5	62.3	-73.6	2.5			
si-re_5	-22.5	67.5	76.1	3.8			
		re-si					
re-si_1	-87.1	-66.8	-85.9	0.0			
re-si_2	15.6	-75.6	-93.6	0.1			
re-si_3	-87.2	-66.8	-85.9	0.3			
re-si_4	15.3	-74.7	-90.6	1.0			
re-si_5	14.5	-72.5	-87.9	1.4			
re-si_6	165.1	50.9	-81.4	3.0			
re-si_7	174.7	-163.2	-103.9	4.8			
re-re							
re-re_1	27.9	66.7	39.6	0.0			
re-re_2	-90.0	61.9	32.6	1.6			
re-re_3	-174.2	54.5	22.8	1.8			
re-re_4	153.8	61.6	25.5	5.6			
re-re_5	37.4	139.1	24.5	6.5			

Table S9. The Relative Gibbs Free Energies Computed using Boltzmann Distribution AcrossDifferent Conformers (as listed in Table S8) of the Corresponding StereocontrollingTransition States

nucleophile-electrophile	path-A
si-si	0.0
si-re	2.3
re-si	4.2
re-re	2.2

Table S10. Relative Gibbs Free Energies (in kcal/mol) for the First Michael addition C–C Bond Formation Transition States between the Prochiral Faces of the Nucleophile and the Electrophile.

nucleophile-electrophile	Method 1	Method 2	Method 3	Method 4
si-si	0.0	0.0	0.0	0.0
si-re	3.0	3.8	3.1	2.6
re-si	3.0	2.7	1.6	1.5
re-re	2.1	7.6	5.5	3.1
%de	98.7	97.9	87.3	85.2
%ee	94.3	>99.0	>99.0	98.9

Method $1 = \text{SMD}_{\text{(toluene)}}/\text{M06-2X}/\text{6-31G}^{**}$

 $\begin{array}{l} \mbox{Method $2 = SMD_{(toluene)}/M06-2X/6-311+G^{**}//SMD_{(toluene)}/M06-2X/6-31G^{**}$} \\ \mbox{Method $3 = SMD_{(toluene)}/M06-2X-D3/6-311+G^{**}//SMD_{(toluene)}/M06-2X/6-31G^{**}$} \\ \mbox{Method $4 = SMD_{(toluene)}/B3LYP-D3/6-311+G^{**}//SMD_{(toluene)}/M06-2X/6-31G^{**}$} \\ \end{array}$

(10) Activation Strain Analysis of [8-9][‡] for the First Michael Addition

 $E_{act} = E_{(i)interaction} + E_{(d)distortion}$

 $E_{d} = \{ (E_{f1(TS)} + E_{f2(TS)}) + E_{f3(TS)}) - (E_{f1} + E_{f2} + E_{f3}) \}$

 $Ei = \{ (E_{(TS)} - (E_{f1(TS)} + E_{f2(TS)} + E_{f3(TS)}) \}$

Here $E_{f1(TS)}$ is the single point energy of fragment f1 at the geometry of the TS, E_{f1} is the energy of undistorted f1 in the ground state geometry; $E_{(TS)}$ is the energy of the TS. f1= proline-enamine, f2= nitrostyrene, and f3= cinchona-thiourea catalyst



Fig. S10 Activation Strain Model for the lowest energy C-C bond formation transition state between the proline-enamine and *trans*- β -nitrostyrene in the presence of cinchona-thiourea.

Table S11. Computed Relative Distortion Energies in each Fragment, Total Relative Distortion Energies $(\Delta \Delta E^{\ddagger}_{d})$ and Relative Interaction Energies $(\Delta \Delta E^{\ddagger}_{i})$ in the Stereocontrolling TS of path-A at the SMD_(toluene)/M06-2X/6-31G** Level of Theory. All Energies are in kcal/mol

Nucleophile-		Distortion en	Interaction	Activation		
Electrophile	enamine	nitrostyrene	catalyst	Total	energy	strain energy
si-si	0.0	0.0	0.0	0.0	0.0	0.0
si-re	5.3	2.2	3.6	11.1	-6.7	4.3
re-si	-1.6	3.1	2.0	3.5	-0.4	3.1
re-re	1.9	2.2	2.1	6.1	-1.2	4.9

(11) Hydrogen Bond Energies in the TS Involved in path-A for the First Michael addition

Bader's quantum theory of atoms in molecules (AIM) is employed for the analysis of topological distribution of electron density.¹⁶ In this approach, each point in space is characterized by a charge density $\rho(r)$. If there is any chemical bond between two atoms they are connected by a line called as bond path. The point with the minimal ρ value along the bond path is called bond critical point (BCP). This analysis provides important topological parameters like electron density $\rho(r)$ at the BCP and the Laplacian of the electron density

 $\nabla^2 \rho$, and kinetic energy density G at this BCP. These are helpful to understanding the nature of H-bond. Espinosa and coworkers formulated an equation wherein the energy of a hydrogen bond (E_{int}) is related with the local potential energy density V at BCP.¹⁸

$$E = \frac{1}{2} V$$

By using this equation one can quantitatively estimate the strength of the H-bonds. The local potential energy density V can be obtained from the viral equation as

$$V = [(1/4)\nabla^2 \rho - 2G]$$

Different energetic quantities of interest (V and E at BCP) can be calculated using the AIM data such as ρ , $\nabla^2 \rho$ and G values are shown in the Table S12

Table S12. Estimation of Hydrogen Bond Energies in the Transition States at the $SMD_{(toluene)}/M06-2X/6-31G^{**}$ level of theory. The Topological Quantities are Derived from Atoms In Molecule (AIM) Computations^{*a*}

N-H…O	ρ	$\nabla^2 \rho$	G	$V=1/4\nabla^2\rho-2G$	H=G+V	E=1/2(V)	E (kcal/mol)	
si-si								
al	0.043	-0.032	0.033	-0.074	-0.041	-0.037	-23.2	
a2	0.041	-0.029	0.031	-0.068	-0.038	-0.034	-21.4	
a3	0.040	-0.030	0.031	-0.069	-0.038	-0.034	-21.6	
				si-re				
a1	0.041	-0.030	0.031	-0.070	-0.039	-0.035	-22.0	
a2	0.037	-0.027	0.028	-0.063	-0.035	-0.031	-19.7	
a3	0.041	-0.030	0.031	-0.070	-0.039	-0.035	-22.1	
				re-si				
al	0.039	-0.029	0.030	-0.067	-0.037	-0.033	-20.9	
a2	0.041	-0.029	0.031	-0.069	-0.038	-0.034	-21.5	
a3	0.043	-0.031	0.033	-0.073	-0.040	-0.037	-22.9	
re-re								
a1	0.040	-0.030	0.031	-0.069	-0.038	-0.034	-21.6	
a2	0.035	-0.025	0.027	-0.060	-0.033	-0.030	-18.8	
a3	0.018	-0.014	0.014	-0.031	-0.017	-0.016	-9.9	
a4	0.011	-0.011	0.010	-0.022	-0.012	-0.011	-6.9	

 $^{{}^{}a}\rho$ = electron density, $\nabla^{2}\rho$ = Laplacian of the electron density; G, V, and H are respectively the kinetic, potential, and total electron energy densities at the bond critical points). Notations of N-H…O bond distances are shown as a1, a2, a3, and a4 in optimized transition state geometries (Fig. 4 in the main text)

(12) Different Possible Pathways of the Second Michael Addition Transition State [10-11] ‡



path-D (without proline) (4.0)path-E (9.9)path-F (2.9)Fig. S11 Comparison of different pathways for the second Michael addition. Relative Gibbsfree energies (kcal/mol) in parentheses are calculated at the SMD_(toluene)/M06-2X/6-31G**level of theory.

(13) Different Possibilities of the Protonation Transition State [12-13][‡]



Fig. S12 Comparison of different modes of protonation of the enolate carbon and the corresponding relative Gibbs free energies (kcal/mol) are calculated at the SMD_(toluene)/M06-2X/6-31G**.

(14) Energetic Span Calculations

The overall Gibbs free energy profile is analyzed using the Shaik–Kozuch energetic span model.³⁴ In this approach, the energetic span (δE) for a catalytic cycle is calculated first by identifying the turnover frequency determining transition state (TDTS) and the TOF determining intermediate (TDI). The lowest energy intermediate in the energy profile is considered as the TDI, and the TDTS is the transition state which maximizes the energetic

span (δE), calculated using the following equations. For the present reaction, equation (2) is applicable for calculating both TDI (**13**) and TDTS (**6-7**) (Fig. S13). The Gibbs free energy of reaction (ΔG_r) is -22.1 kcal/mol (**13**).



Fig. S13 Gibbs free energy profile for formation of 2,3-*syn* product between the dicarbonyl compound and nitrostyrene in the presence of proline (**P**) and cinchona-thiourea (**C**) dual chiral catalyst combination obtained at the $SMD_{(toluene)}/M06-2X/6-31G^{**}$ Level of Theory.

(15) Detailed Mapping of Non-covalent Interactions in 2S,3R_si-si TS



2S,3R_si-si (4.1) [2S,3R,4S,5S]

Fig. S14 Optimized geometry of the C-C bond formation transition states $[10-11]^{\ddagger}$ involving *SR_si-si* face for the second Michael addition step. Important interaction distances (Å) are showing as a1, a2, a3= N-H···O; b1, b2, b3 = C-H··· π and d1, d2, d3 = π ··· π . The absolute configuration of the final product that would arise from each of the transition states is given in square brackets.

Table S13. Relative Gibbs Free Energies (in kcal/mol) for the Second Michael addition C–C Bond Formation Transition States between the Prochiral Faces of the Nucleophile and the Electrophile Computed at Different Level of Theories. Experimental values of %*ee* and %*de* are respectively 99.0 and 92.0 (Scheme 1)

nucleophile-electrophile	Method 1	Method 2	Method 3	Method 4
2R,3S_re-re	0.0	0.0	0.0	0.0
2R,3S_re-si	3.5	4.3	4.8	2.6
2S,3R_si-si	4.1	4.7	4.4	1.1
%de	99.4	>99.0	>99.0	97.5
%ee	>99.0	>99.0	>99.0	72.9

Method $1 = \text{SMD}_{(\text{toluene})}/\text{M06-2X}/6-31\text{G}^{**}$

Method 2 = $SMD_{(toluene)}/M06-2X/6-311+G^{**}//SMD_{(toluene)}/M06-2X/6-31G^{**}$

Method 3 = SMD_(toluene)/M06-2X-D3/6-311+G**//SMD_(toluene)/M06-2X/6-31G** Mothod 4 = SMD_//D21 VD_D2/6-211+C**//SMD_//M06-2X/6-21C**

 $Method \ 4 = SMD_{(toluene)}/B3LYP-D3/6-311+G**//SMD_{(toluene)}/M06-2X/6-31G**$

(16) Activation Strain Analysis of [10-11][‡] for the Second Michael Addition

Table S14. Computed Relative Distortion Energies in each Fragment, Total Relative Distortion Energies $(\Delta \Delta E^{\ddagger}_{d})$ and Relative Interaction Energies $(\Delta \Delta E^{\ddagger}_{i})$ in the Stereocontrolling TS at the SMD/M06-2X/6-31G** Level of Theory. All Energies are in kcal/mol

Nucleophile-	Distor	tion energy	Interaction	Activation	
Electrophile	Michael adduct	catalyst	Total	energy	strain energy
2R,3S_re-re	0.0	0.0	0.0	0.0	0.0
2R,3S_re-si	7.6	3.3	10.9	-6.6	4.3
2S,3R_si-si	9.2	3.8	13.1	-7.2	5.9

(17) Probing the Effect of π -Stacking using Modified Catalyst and Substrates

Conformational and configurational sampling of the transition states for the C-C bond formation with the modified catalyst/substrate have been performed similar to that of the

unmodified system described earlier. These modifications are (i) substituents of the aryl group of thiourea by nitro group and (ii) phenyl group of the nitrostyrene by a methyl group. A large number of conformers (~40) were identified by varying the dihedral angles in the branched chain of the carbonyl compound as shown in Fig. S9 and the corresponding energies are shown in Table S17.

Table S15. Effect of Replacing Various Substituents in the Catalyst and Substrates that are Involved in π -Stacking Interaction in the Stereocontrolling Transition States for the First Michael Addition

prochiral	region and	substituents of the	aryl group of	nitrostyrene
faces	nature of	aryl group of	thiourea	
	modification	thiourea		
nucleophile-	unmodified	$Ar(3,5-CF_3) \rightarrow$	$Ar(3,5-CF_3) \rightarrow$	$Ph \rightarrow CH_3$
electrophile		$Ar(4-NO_2)$	CH ₃	
si-si	0.0	0.0	0.0	0.0
si-re	3.0	0.6	3.6	0.7
re-re	2.1	1.3	3.5	-0.9
re-si	3.0	2.5	8.6	4.2

Table S16. Effect of Replacing Various Substituents in the Catalyst and Substrates that are Involved in π -Stacking Interaction in the Stereocontrolling Transition States for the Second Michael Addition

Prochiral faces ^a	region and nature of modification	substituents of the aryl group of thiourea	aryl group of thiourea	enone
Nucleophile-	Unmodified	$Ar(3,5-CF_3) \rightarrow$	$Ar(3,5-CF_3) \rightarrow$	$Ph \rightarrow CH_3$
Electrophile		$Ar(4-NO_2)$	CH ₃	
2R,3S_re-re	0.0	0.0	0.0	0.0
2R,3S_re-si	3.5	0.4	2.2	0.9
2S,3R_si-si	4.1	2.2	4.3	3.8

^{*a*} The (2S,3R) configuration of the first Michael adduct is a minor product. Further, the *cis* configuration of nitrostyrene will not be able to develop H-bonding with the cinchona catalyst. Hence, $2S,3R_si$ -re transition state for the second Michael addition was not considered.

(b) Conformational Sampling Relating to Substituent Effect Studies

Table S17. Conformational Sampling of (Table S16) the Stereocontroling Transition states (*si-si, si-re, re-si, re-re*) for the first Michael addition $[8-9]^{\ddagger}$ via path-A (Fig. S9).^{*a*} The relative Gibbs free energies are calculated at the SMD_(toluene)/M06-2X/6-31G** level of theory. The lowest energy conformers in each stereochemically distinct modes are highlighted

Substituents of the aryl group of thiourea		nitrostyrene	
$[Ar(3,5-CF_3) \rightarrow Ar(4-NO_2)]$		$[\mathrm{Ph} \rightarrow \mathrm{CH}_3]$	
conformer	ΔG (kcal/mol)	conformer	ΔG (kcal/mol)
si-si_1	0.0	si-si_1	0.0
si-si_2	0.8	si-si_2	0.5
si-si_3	1.0	si-si_3	0.9
si-re_1	0.6	si-si_4	1.1
si-re_2	1.9	si-si_5	2.2
si-re_3	2.3	si-re_1	0.7
si-re_4	4.4	si-re_2	2.8
si-re_5	4.8	si-re_3	4.0
si-re_6	5.8	si-re_4	6.1
re-si_1	2.5	si-re_5	6.3
re-si_2	5.5	si-re_6	7.3
re-si_3	7.5	re-si_1	4.2
re-re_1	1.3	re-si_2	12.3
re-re_2	1.5	re-re_1	-0.9
re-re_3	1.7	re-re_2	0.9
re-re_4	2.4	re-re_3	1.5
re-re_5	2.6	re-re_4	1.7
re-re_6	3.7	re-re_5	1.8
re-re_7	3.9	re-re_6	2.0
re-re_8	4.0	re-re_7	2.2
re-re_9	5.6	re-re_8	2.7
<i>re-re</i> _10	6.9	re-re_9	3.3
		<i>re-re</i> _10	3.5

^{*a*} In each given configuration, a combination different conformational possibilities were tried as the initial guess geometries. Many such initial geometries converged the ones whose energies are tabulated here, thus leading to unequal number of unique conformers for each combination of prochiral faces of the nucleophile and the electrophile.

(18) Epimerization of 2,3-syn to 2,3-anti product

An interesting observation about this one-pot dual catalytic cascade Michael addition reaction relates to the temperature dependent *syn:anti* diastereomer ratio of the final product. The initially formed 2,3-*syn* diastereomer at room temperature (1 hr) was noted to undergo a complete conversion to the 2,3-*anti* product upon warming the reaction mixture to 40°C for 9 hrs.(ref 7b, in main text) While one can consider an epimerization of this sort as implicitly easy due to the acidity of hydrogen α to the aldehyde, we became curious to examine whether or not a cooperative action of both catalysts is operating in the efficient formation of the *anti* diastereomer as the final product. The 2,3-*syn* to 2,3-*anti* conversion could occur in two steps; an initial deprotonation enabled by the qunuclidine leads to a planar enolate stabilized through effective hydrogen bonding interactions offered by the thiourea moiety. Subsequent re-protonation of the enolate from the axial direction via [16-17][‡] will lead to the 2,3-*anti* diastereomer.

Among different modes of epimerization considered, the one in which thioureacinchona promotes enolization while proline passively interacts with the nitro group denoted as path-A in Scheme S6 is found to be of lower energy. Another epimerization possibility involving only cinchona-thiourea is found to be of higher energy (path-B Scheme S6). A third possibility wherein and proline exhibits an active participation in the form of a prolineiminium ion when cinchona-thiourea is involved in epimerization (path-C, Scheme S6) is found to be of higher energy than both path-A and path-B. Gibbs free energy profiles for all the three pathways are shown in Fig. S15.



Scheme S6 Epimerization of 2,3-syn to 2,3-anti conversion



Fig. S15 Gibbs Free energy profile diagram for epimerization of 1,2-*syn* to 1,2-*anti* cyclohexane products (Scheme S6) obtained at the SMD_(toluene)/M06-2X/6-31G** level of theory.