

Computational Investigations of Enantioselection in Carbon–Carbon Bond Forming Reactions of Ruthenium Guanidinobenzimidazole Second Coordination Sphere Hydrogen Bond Donor Catalysts

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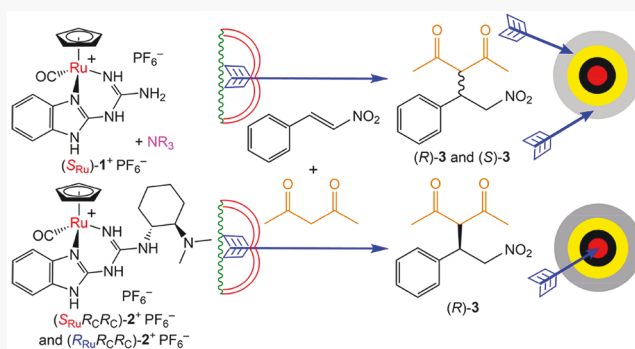


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ABSTRACT: The NH_2 group of 2-guanidinobenzimidazole (GBI) can be replaced by $(R_{\text{C}}R_{\text{C}})\text{-NHCH}(\text{CH}_2)_4\text{CHNMe}_2$ and elaborated to the enantiopure chelate salts $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})\text{-}[(\eta^5\text{-C}_5\text{H}_5)\text{Ru}(\text{CO})(\text{GBICH}(\text{CH}_2)_4\text{CHNMe}_2)]^+\text{PF}_6^-$ ($(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})\text{-}2^+\text{PF}_6^-$) and $(R_{\text{Ru}}R_{\text{C}}R_{\text{C}})\text{-}2^+\text{PF}_6^-$. These catalyze highly enantioselective additions of 1,3-dicarbonyl compounds to nitroalkenes. The mechanism and basis for enantioselection are probed by DFT calculations. First, the parent GBI complex $[(\eta^5\text{-C}_5\text{H}_5)\text{Ru}(\text{CO})(\text{GBI})]^+\text{PF}_6^-$ (1^+PF_6^-) is examined. This species has only ruthenium-centered chirality and must be used with a trialkylamine, as it lacks the internal base of 2^+PF_6^- . The dicarbonyl compound initially hydrogen bonds to the NH triad of the GBI ligand, but the transition states leading to each product enantiomer are essentially equal in energy. In contrast, after similar bonding of the dicarbonyl compound to $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})\text{-}$ or $(R_{\text{Ru}}R_{\text{C}}R_{\text{C}})\text{-}2^+\text{PF}_6^-$, a proton is transferred to the :NMe_2 moiety, giving an enolate and a HNMe_2^+ group. The latter mediates the introduction of *trans*- β -nitrostyrene such that one enolate π face attacks the $\text{C}_{\text{Si}}=\text{C}_{\text{re}}\text{Ph}$ face to give an addition product with an *R* configuration, in agreement with experiment. Thus, the configurations of the catalyst carbon stereocenters control the product stereochemistry. Interactions in competing transition states are analyzed.



INTRODUCTION

There is an extensive literature of chiral “organocatalysts”¹ that serve as hydrogen bond donors and effect a variety of organic reactions with high enantioselectivities.² Over the past few years, we have sought to develop complementary metal-containing chiral hydrogen bond donors,^{3–6} as metal complexes exhibit diverse types of chirality motifs, many of which have proved to be highly successful for other types of enantioselective catalysis. Our efforts have focused on NH donor groups, either directly coordinated or remote from the metal, as exemplified in Figure 1. Related themes have been explored by other research groups.⁷

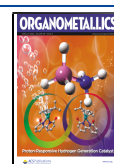
In many of these reactions, enantioselectivities have routinely exceeded 90% ee.^{4b–e,g,5b} However, there is the potential for enhanced mechanistic complexity, as most nitrogenous organic hydrogen bond donor catalysts feature 2 NH groups (e.g., *N,N'*-diaryl thioureas),² whereas the systems in Figure 1 possess 4–12. Although it seems unlikely that the organic substrates would interact with more than 4–5 NH groups in any transition state assembly, a plethora of possibilities nevertheless remain. Hence, it has not been

possible to formulate transition state models that would help to rationally optimize this chemistry.

Accordingly, in this paper we focus on one of the most successful types of catalysts, the bifunctional ruthenium systems $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})\text{-}$ and $(R_{\text{Ru}}R_{\text{C}}R_{\text{C}})\text{-}2^+\text{PF}_6^-$ (Figure 1, bottom), which contain both ruthenium and carbon stereocenters as well as a pendant tertiary amine. As shown in Scheme 1, these effect highly enantioselective Michael additions of malonate esters to *trans*- β -nitroalkenes.^{5b} The monofunctional ruthenium complex 1^+PF_6^- and the related salts $1'^+\text{X}^-$ (Figure 2, middle) can also, in conjunction with the external tertiary amine NEt_3 , serve as catalysts, but it has not yet proved possible to isolate these species in enantiomerically pure form.

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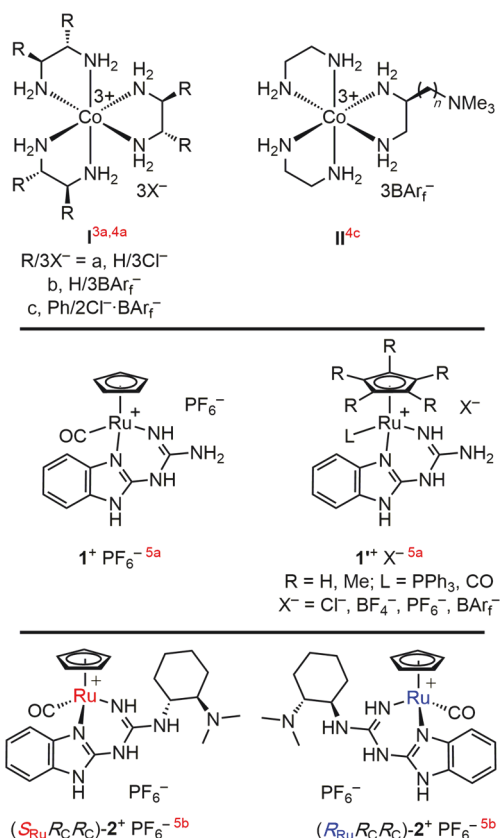
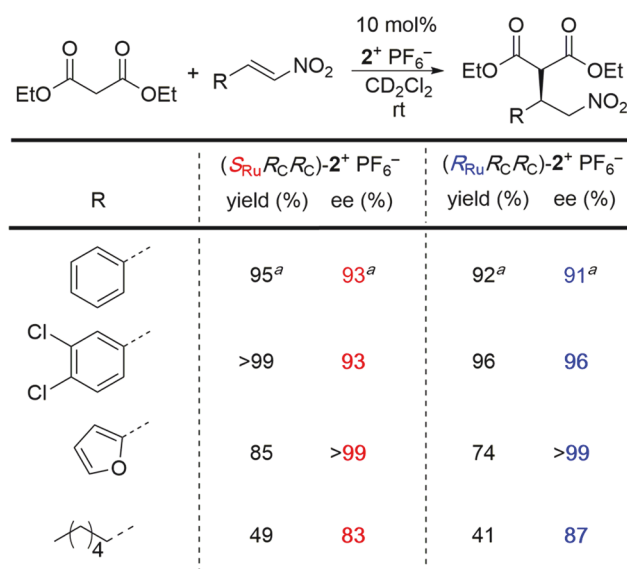


Figure 1. Some previously studied metal-containing chiral hydrogen bond donor catalysts.

Scheme 1. Additions of Diethyl Malonate to Nitroalkenes Catalyzed by $(S_{\text{Ru}}R_C R_C)-$ and $(R_{\text{Ru}}R_C R_C)-2^+ \text{PF}_6^-$



^aData for the analogous reaction of dimethylmalonate: 97%, 91%, 95%, 88%

In this paper, we present an extended series of DFT calculations that establish the most probable modes of substrate binding to 1^+PF_6^- , $(S_{\text{Ru}}R_C R_C)-2^+ \text{PF}_6^-$, and $(R_{\text{Ru}}R_C R_C)-2^+ \text{PF}_6^-$, as well as transition state assemblies that are in accord with the dominant product configurations obtained with 2^+PF_6^- . Transition state assemblies derived from 1^+PF_6^- are also examined, but using NMe_3 in place of NEt_3 to

simplify the computations. These help to define the effect of the added carbon stereocenters and functionality in 2^+PF_6^- upon enantioselectivities, an objective that is not yet addressable experimentally.

EXPERIMENTAL SECTION

Reaction in Scheme 2. A J. Young NMR tube was charged with 2,4-pentanedione (0.0184 g, 0.200 mmol), *trans*- β -nitrostyrene (0.0298 g, 0.200 mmol), and CD_2Cl_2 (1.0 mL). Then $(S_{\text{Ru}}R_C R_C)-$ or $(R_{\text{Ru}}R_C R_C)-2^+ \text{PF}_6^-$ (0.0013 g, 0.0020 mmol, 1.0 mol %) was added. The sample was capped and monitored by NMR and TLC. After 24 h, the solvent was removed. The residue was taken up in hexane/ethyl acetate (30/70 v/v). The sample was passed through a short silica gel column, which was washed with additional hexane/ethyl acetate (50/50 v/v, 5 mL). The solvent was removed from the combined eluate, and a second silica gel chromatography step was carried out. The solvent was removed from the product-containing fractions to give the previously reported 3-(2-nitro-1-phenylethyl)-pentane-2,4-dione (**3**)⁸ as colorless needles (from $(S_{\text{Ru}}R_C R_C)-2^+ \text{PF}_6^-$, 0.0349 g, 0.140 mmol, 70%; from $(R_{\text{Ru}}R_C R_C)-2^+ \text{PF}_6^-$, 0.0374 g, 0.150 mmol, 75%). NMR (δ , CDCl_3): ¹H (500 MHz) 7.34–7.25 (m, 3H), 7.19–7.16 (m, 2H), 4.64–4.61 (m, 2H), 4.36 (d, 1H, $J = 10.7$ Hz), 4.27–4.20 (m, 1H), 2.28 (s, 3H), 1.93 (s, 3H); ¹³C{¹H} (125 MHz) 201.6, 200.9, 135.9, 129.3, 128.5, 127.9, 78.2, 70.7, 42.9, 30.5, 29.7 (11 $\times$ s). The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column, hexane/2-PrOH (85/15 v/v), 1.0 mL/min, $\lambda = 215$ nm; $t_R = 14.9$ min (minor, S), 22.6 min (major, R).¹⁰

General procedures and instrumentation were identical with those given in a previous paper.^{5b} 2,4-Pentanedione was used as received from Aldrich (99%).

Computational Details. All calculations were performed with the Gaussian 09 program, revision D.01.¹¹ A wide variety of alternative structures for intermediates and transition states was explored with numerous arrangements of the substrates and catalysts as well as hydrogen bond interactions. The structures were initially optimized in the gas phase with the ω B97X-D functional (range-separated hybrid generalized gradient approximation RSH-GGA).¹² This functional has been successfully used to study other reactions involving ruthenium catalysts¹³ and was similarly employed for geometry optimizations and frequency calculations in this work with basis set 1 (BS1). BS1 consists of the Stuttgart relativistic small core (RSC) 1997 ECP basis set¹⁴ for ruthenium atoms and the 6-31G(d,p) basis set¹⁵ for other atoms. Solution-phase optimization was important here, as the dipole moments are large and sensitive to the gas-phase and solution-phase structures (see sections S6 and S7 in the Supporting Information). Therefore, all structures were fully optimized in CH_2Cl_2 solvent (per Schemes 1 and 2) using a solvation model based on electron density (SMD; $\epsilon = 8.93$).¹⁶ Frequency calculations were performed to determine free energy corrections (298.15 K) and verify the nature of (1) stationary points of intermediates with no imaginary frequency and (2) transition states with one imaginary frequency.

The ω B97X-D functional with basis set 2 (BS2) was used for single-point energy calculations on the solution-phase optimized structures. BS2 treats ruthenium analogously to BS1 and uses the 6-311++G(d,p) basis set¹⁵ for other atoms. All energies throughout this work refer to the relative Gibbs free energies in CH_2Cl_2 calculated by ω B97X-D/BS2(SMD)// ω B97X-D/BS1(SMD). The conductor-like polarizable continuum model (CPCM)¹⁷ with UFF atomic radii was carried out as single-point calculations on the SMD solution-phase optimized structures. All Gibbs free energies in CH_2Cl_2 obtained by the SMD solvation model parallel those of the CPCM solvation model (see details in the Supporting Information). Standard conditions were corrected to 1.0 mol/L.¹⁸ Additional calculations were also performed with the large TZVP basis set¹⁹ and free energy corrections with Truhlar's quasiharmonic approximation²⁰ (see details in the Supporting Information). The JIMP2 molecular visualizing and manipulating program was used for all 3D molecular structures.²¹

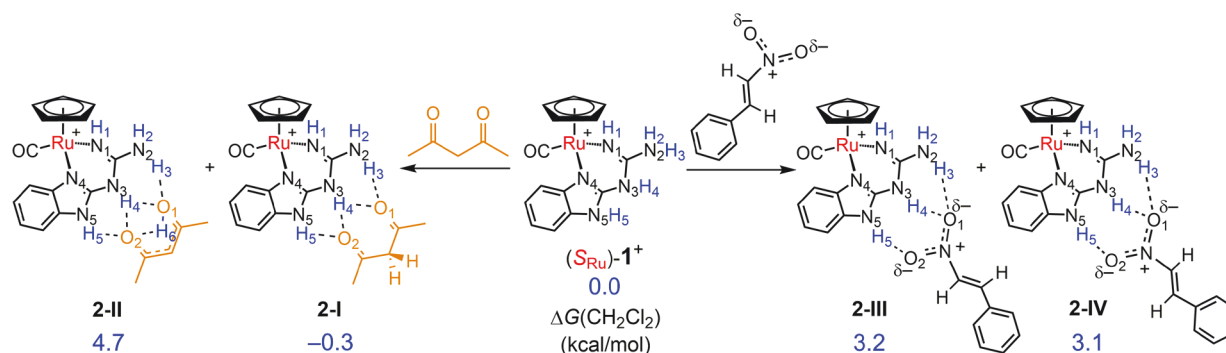


Figure 2. Relative free energy profiles ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) for adducts of $(S_{Ru})-1^+$. Selected distances (Å): **2-I**, $\text{H}_3\cdots\text{O}_1$ 1.93, $\text{H}_4\cdots\text{O}_1$ 2.01, $\text{H}_4\cdots\text{O}_2$ 2.82, $\text{H}_5\cdots\text{O}_2$ 1.80; **2-II**, $\text{H}_3\cdots\text{O}_1$ 2.25, $\text{H}_4\cdots\text{O}_1$ 2.68, $\text{H}_4\cdots\text{O}_2$ 2.08, $\text{H}_5\cdots\text{O}_2$ 2.02, $\text{H}_6\cdots\text{O}_1$ 1.00, $\text{H}_6\cdots\text{O}_2$ 1.64; **2-III**, $\text{H}_3\cdots\text{O}_1$ 2.93, $\text{H}_4\cdots\text{O}_1$ 1.91, $\text{H}_5\cdots\text{O}_2$ 1.93; **2-IV**, $\text{H}_3\cdots\text{O}_1$ 2.70, $\text{H}_4\cdots\text{O}_1$ 1.89, $\text{H}_5\cdots\text{O}_2$ 1.96.

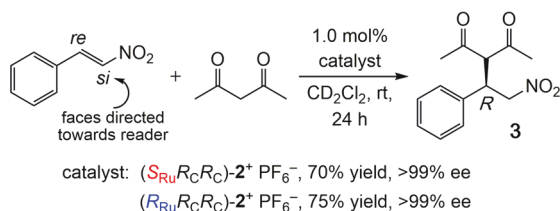
RESULTS

Enantioselective Catalysis: Additional Experimental Data.

In exploratory DFT calculations, various ruthenium-catalyzed additions of dialkyl malonates to *trans*- β -nitrostyrene were investigated (see *inter alia* Scheme 1). However, the degrees of freedom associated with the alkoxy groups, which can adopt *s-cis* (Z) or *s-trans* (E) RO-C(=O) conformations, complicated the computations and analyses. Thus, the possibility of removing this variable by studying additions of a related 1,3-diketone, 2,4-pentanedione, was considered.

As shown in Scheme 2, analogous reactions of 2,4-pentanedione and *trans*- β -nitrostyrene were conducted, but

Scheme 2. Additions of 2,4-Pentanedione to *trans*- β -Nitrostyrene Catalyzed by $(S_{Ru}R_C R_C)-2^+PF_6^-$ and $(R_{Ru}R_C R_C)-2^+PF_6^-$



with reduced loadings of the diastereomeric catalysts $2^+PF_6^-$ (1.0 mol % vs 10 mol %, made possible by the faster additions). Workups gave 3-(2-nitro-1-phenylethyl)pentane-2,4-dione (**3**), which had previously been prepared in nonracemic form,⁸ in 70–75% yields. In both cases, chiral HPLC indicated the formation of (*R*)-**3** in >99% ee. Thus, as seen earlier in Scheme 1, the product configuration is controlled by the carbon configurations of the catalyst; the ruthenium configuration has virtually no influence.

The relative (and absolute) configurations of the *trans*- β -nitrostyrene addition products in Schemes 1 and 2 were identical. Accordingly, it was presumed that the mechanism computed for Scheme 2 would share many features with those operative in Scheme 1.

$(S_{Ru})-1^+$: Binding of Educts. Efforts were first directed at the simpler monofunctional catalyst $1^+PF_6^-$. In a previous paper, it was established that the PF_6^- anion does not appreciably associate with the cation 1^+ in CH_2Cl_2 .²² Hence, the anion was omitted in all computations. As noted in the Experimental Section, all energies correspond to those expected in CH_2Cl_2 solution.

As depicted in Figure 2, two low-energy 1:1 adducts derived from $(S_{Ru})-1^+$ and 2,4-pentanedione were found. In the more stable adduct, **2-I**, the middle NH group of the triad ($\text{N}_3\cdots\text{H}_4$) binds to both dione oxygen atoms (O_1 , O_2 ; $\text{H}_4\cdots\text{O}_1$ and $\text{H}_4\cdots\text{O}_2$, 2.01 and 2.82 Å), and the terminal NH groups of the triad ($\text{N}_2\cdots\text{H}_3$, $\text{N}_5\cdots\text{H}_5$) each bind to a single oxygen atom ($\text{H}_3\cdots\text{O}_1$ and $\text{H}_5\cdots\text{O}_2$, 1.93 and 1.80 Å). In the less stable adduct, **2-II**, tautomerization has occurred to give a cyclic enol ligand. Experimentally, the free cyclic enol is slightly more stable than 2,4-pentanedione in CH_2Cl_2 ($K([\text{enol}]/[\text{dione}]) = 4.2$ at 20 °C;^{23,24} see section S5 in the Supporting Information for similar computational results). The middle NH group of the triad exhibits hydrogen bonding similar to that of **2-I** ($\text{H}_4\cdots\text{O}_2$ and $\text{H}_4\cdots\text{O}_1$, 2.08 and 2.68 Å), but the hydrogen bonds involving the terminal NH groups are longer and presumably weaker ($\text{H}_3\cdots\text{O}_1$ and $\text{H}_5\cdots\text{O}_2$, 2.25 and 2.02 Å).

Similarly, two lower energy 1:1 adducts of $(S_{Ru})-1^+$ and *trans*- β -nitrostyrene were also found, **2-III** and **2-IV** (Figure 2). In both, one of the NO_2 oxygen atoms is hydrogen-bonded to two NH groups ($\text{N}_2\cdots\text{H}_3$, $\text{N}_3\cdots\text{H}_4$), and the other to one group ($\text{N}_5\cdots\text{H}_5$). They differ mainly in the conformation about the $\text{O}_2\text{N}-\text{CH}=\text{CHPh}$ linkage (torsion angles differing by ca. 180°). The π faces of the $\text{CH}=\text{CHPh}$ moiety are diastereotopic (or enantiotopic in the free ligand). That projecting toward the reader in **2-III** can be designated $C_{re}=\text{C}_{si}\text{Ph}$ and that in **2-IV** $C_{si}=\text{C}_{re}\text{Ph}$ (see also Scheme 2). The average $\text{NH}\cdots\text{O}$ distances in the adducts are quite close (2.26 and 2.18 Å), consistent with the negligible energy difference (3.2 and 3.1 kcal/mol). When *trans*- β -nitrostyrene is titrated into a CD_2Cl_2 solution of racemic 1^+BAR_f^- , the corresponding NH ^1H NMR signals shift downfield,^{5a} consistent with the generation of equilibrium quantities of such species. Nonetheless, binding 2,4-pentanedione to $(S_{Ru})-1^+$ remains ca. 3.4 kcal/mol more favorable.

$(S_{Ru})-1^+$: Enolate Generation. The generation of a free or coordinated enolate was presumed to be a prerequisite for carbon–carbon bond formation. The free energies of proton transfer from 2,4-pentanedione to either a NH or NH_2 group of $(S_{Ru})-1^+$ were found to be 55.7–80.7 kcal/mol (Figure S1 in the Supporting Information), which would be prohibitive under the conditions of Scheme 1 or 2. Alternatively, the free energy of proton transfer to NMe_3 was computed to be 21.4 kcal/mol. However, the initial formation of the adducts **2-III** and **2-IV** in Figure 2 would add another 3 kcal/mol to this pathway.

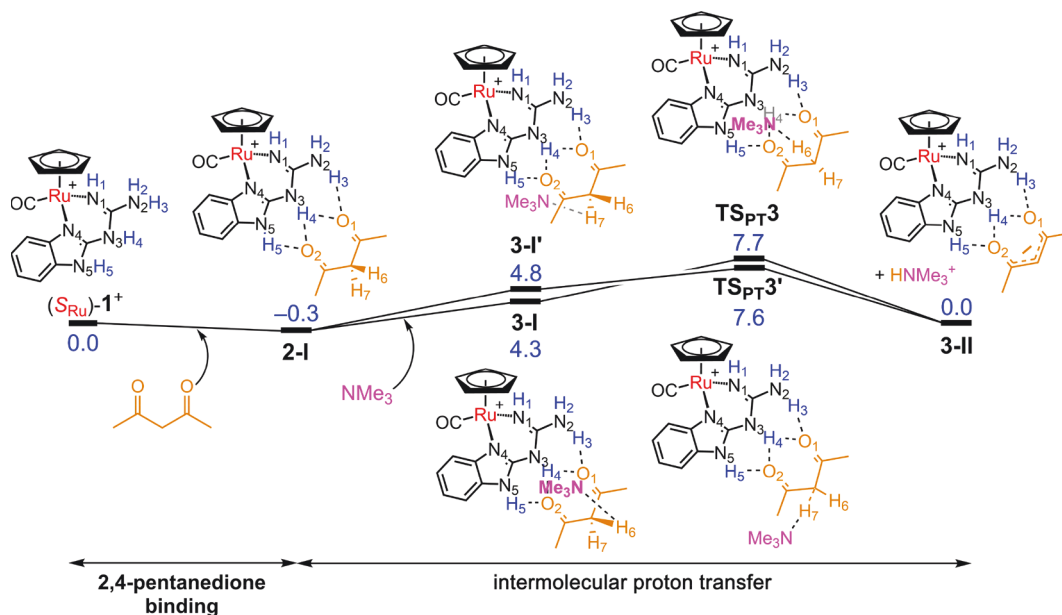


Figure 3. Relative free energy profiles ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) for 2,4-pentanedione binding to $(S_{\text{Ru}})\text{-1}^+$ and subsequent intermolecular proton transfer. Selected distances (Å): **3-I**, $\text{H}_3\text{-O}_1$ 1.87, $\text{H}_4\text{-O}_1$ 2.12, $\text{H}_4\text{-O}_2$ 2.30, $\text{H}_5\text{-O}_2$ 1.82, C-H_6 1.11, $\text{H}_6\text{-N}$ 2.20; **3-I'**, $\text{H}_3\text{-O}_1$ 1.88, $\text{H}_4\text{-O}_1$ 2.10, $\text{H}_4\text{-O}_2$ 2.19, $\text{H}_5\text{-O}_2$ 1.81, C-H_7 1.12, $\text{H}_7\text{-N}$ 2.11; **TS_{PT3}**, $\text{H}_3\text{-O}_1$ 1.81, $\text{H}_4\text{-O}_1$ 2.01, $\text{H}_4\text{-O}_2$ 2.26, $\text{H}_5\text{-O}_2$ 1.73, C-H_6 1.32, $\text{H}_6\text{-N}$ 1.41; **TS_{PT3'}**, $\text{H}_3\text{-O}_1$ 1.82, $\text{H}_4\text{-O}_1$ 2.00, $\text{H}_4\text{-O}_2$ 2.33, $\text{H}_5\text{-O}_2$ 1.72, C-H_7 1.31, $\text{H}_7\text{-N}$ 1.41; **3-II**, $\text{H}_3\text{-O}_1$ 1.70, $\text{H}_4\text{-O}_1$ 1.92, $\text{H}_4\text{-O}_2$ 2.26, $\text{H}_5\text{-O}_2$ 1.60.

Thus, the free energy of proton transfer from the adduct **2-I** (Figure 2) to NMe_3 was examined. As shown in Figure 3, the nitrogen lone pair initially hydrogen bonds to the CH_2 moiety of the dione, via either the hydrogen bond that can be viewed as *syn* to the cyclopentadienyl ligand (**3-I**) or that which is *anti* (**3-I'**). These structures are close in energy and are only 4.3–4.8 kcal/mol above the energies of the educts. Proton transfer transition states (**TS_{PT3}**, **TS_{PT3'}**) with modest 8.0–7.9 kcal/mol barriers (−0.3 vs 7.7–7.6 kcal/mol) then lead to the neutral ylide **3-II** and the protonated amine HNMe_3^+ . The overall free energy change (0.0 kcal/mol) is much lower than those for the other proton transfer processes considered above. Although it is known that calculated proton transfer energies can have significant errors,²⁵ these energies do not contribute to the reaction rate.

The $\text{N-H}\cdots\text{O}$ hydrogen bonds of **3-II** are much shorter than those in the precursor **2-I** (average: 1.87 vs 2.14 Å), reflecting the greater hydrogen bond acceptor strength that would be expected for any conjugate base. Numerous computational experiments were carried out with the enol adduct **2-II** (Figure 2), but no low-lying transition states for deprotonation could be located.

$(S_{\text{Ru}})\text{-1}^+$: Carbon–Carbon Bond Forming Step. Interactions of **3-II** and *trans*- β -nitrostyrene were probed next. For orientation purposes, four limiting outcomes are diagrammed in Figure 4. The GBI/enolate assembly is roughly planar, and one face can be viewed as *syn* to the cyclopentadienyl ligand and the other *anti*. The nitrostyrene ligand can in principle add from both directions, using either enantioface ($\text{C}_{\text{si}}=\text{C}_{\text{re}}\text{Ph}$ or $\text{C}_{\text{re}}=\text{C}_{\text{si}}\text{Ph}$). Two approaches lead to the addition product (*R*)-**3** and the other two to (*S*)-**3**. These may be mediated by attractive noncovalent π/π interactions, $\text{NH}\cdots\text{O}$ hydrogen bonds, or other means.

In Figure 5, the *syn* approach of *trans*- β -nitrostyrene to **3-II** is examined. Two lower lying adducts, **5-I** and **5-I'**, are found (3.0 and 3.6 kcal/mol). In the first, the $\text{C}_{\text{re}}=\text{C}_{\text{si}}\text{Ph}$ face is interacting with the enolate moiety, and in the second the

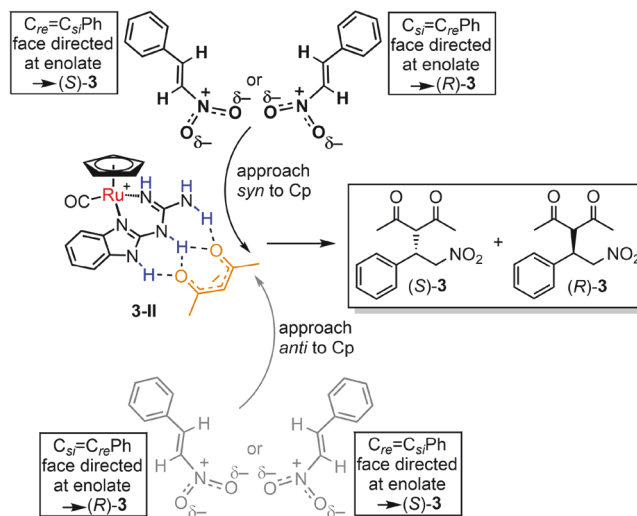


Figure 4. Limiting approaches of *trans*- β -nitrostyrene to the deprotonated adduct of $(S_{\text{Ru}})\text{-1}^+$ and 2,4-pentanedione.

$\text{C}_{\text{si}}=\text{C}_{\text{re}}\text{Ph}$ face is interacting. Accordingly, subsequent carbon–carbon bond formation leads to opposite configurations at the new nitroalkene-derived stereocenter. These steps are mediated by π/π interactions as opposed to hydrogen bonding.

In Figure 6, the *anti* approach of *trans*- β -nitrostyrene to **3-II** is similarly examined. Two lower lying adducts, **6-I** and **6-I'** (1.3 and 3.2 kcal/mol), are again found. In the first, the $\text{C}_{\text{si}}=\text{C}_{\text{re}}\text{Ph}$ face is interacting with the enolate moiety, and in the second the $\text{C}_{\text{re}}=\text{C}_{\text{si}}\text{Ph}$ face is interacting, leading to opposite product enantiomers.

Transition states could be located for each for the four initial adducts in Figures 5 and 6 and are designated **TS_{CC5}**, **TS_{CC5'}**, **TS_{CC6}**, and **TS_{CC6'}**. These constitute the rate-determining steps on the carbon–carbon bond forming coordinate and afford the ylides **5-II**, **5-II'**, **6-II**, and **6-II'**. The ylides feature

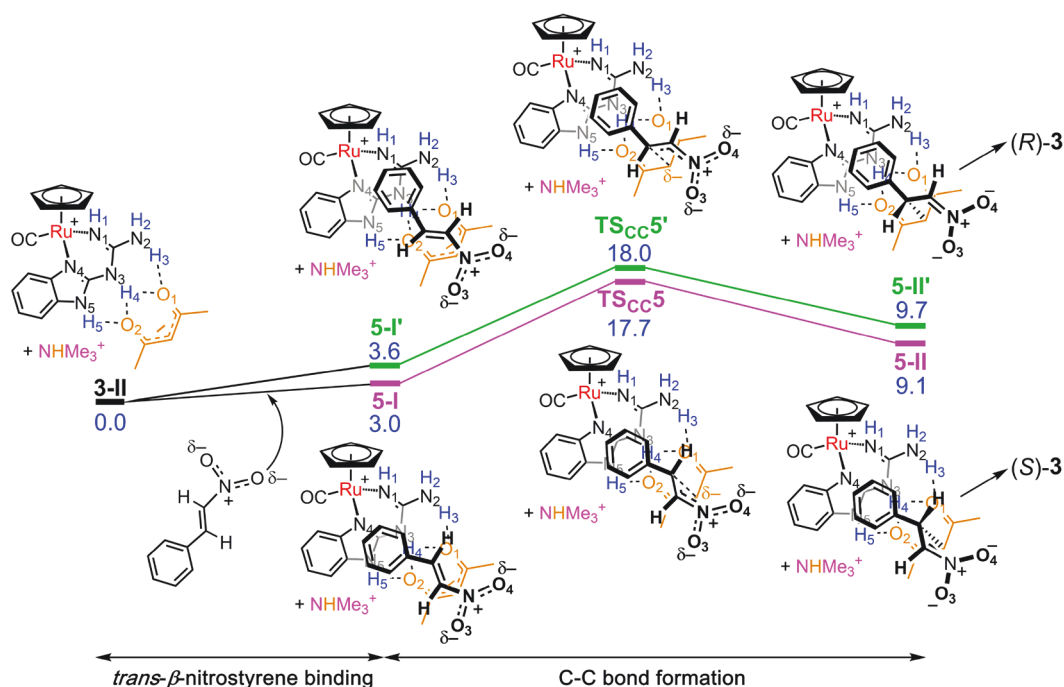


Figure 5. Relative free energy profiles ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) for species derived from $(S_{\text{Ru}})^{-1+}$, 2,4-pentanedione, NMe_3 , and *trans*- β -nitrostyrene, the last of which approaches *syn* to the cyclopentadienyl ligand. Selected distances (Å): **5-I**, $\text{H}_3\text{--O}_1$ 1.73, $\text{H}_4\text{--O}_1$ 1.91, $\text{H}_4\text{--O}_2$ 2.19, $\text{H}_5\text{--O}_2$ 1.61; **5-I'**, $\text{H}_3\text{--O}_1$ 1.75, $\text{H}_4\text{--O}_1$ 1.86, $\text{H}_4\text{--O}_2$ 2.27, $\text{H}_5\text{--O}_2$ 1.59; **TS_{CC5}**, $\text{H}_3\text{--O}_1$ 1.81, $\text{H}_4\text{--O}_1$ 1.98, $\text{H}_4\text{--O}_2$ 2.20, $\text{H}_5\text{--O}_2$ 1.69; **TS_{CC5'}**, $\text{H}_3\text{--O}_1$ 1.82, $\text{H}_4\text{--O}_1$ 1.92, $\text{H}_4\text{--O}_2$ 2.27, $\text{H}_5\text{--O}_2$ 1.70; **5-II**, $\text{H}_3\text{--O}_1$ 1.87, $\text{H}_4\text{--O}_1$ 2.01, $\text{H}_4\text{--O}_2$ 2.25, $\text{H}_5\text{--O}_2$ 1.78; **5-II'**, $\text{H}_3\text{--O}_1$ 1.90, $\text{H}_4\text{--O}_1$ 1.90, $\text{H}_4\text{--O}_2$ 2.46, $\text{H}_5\text{--O}_2$ 1.78.

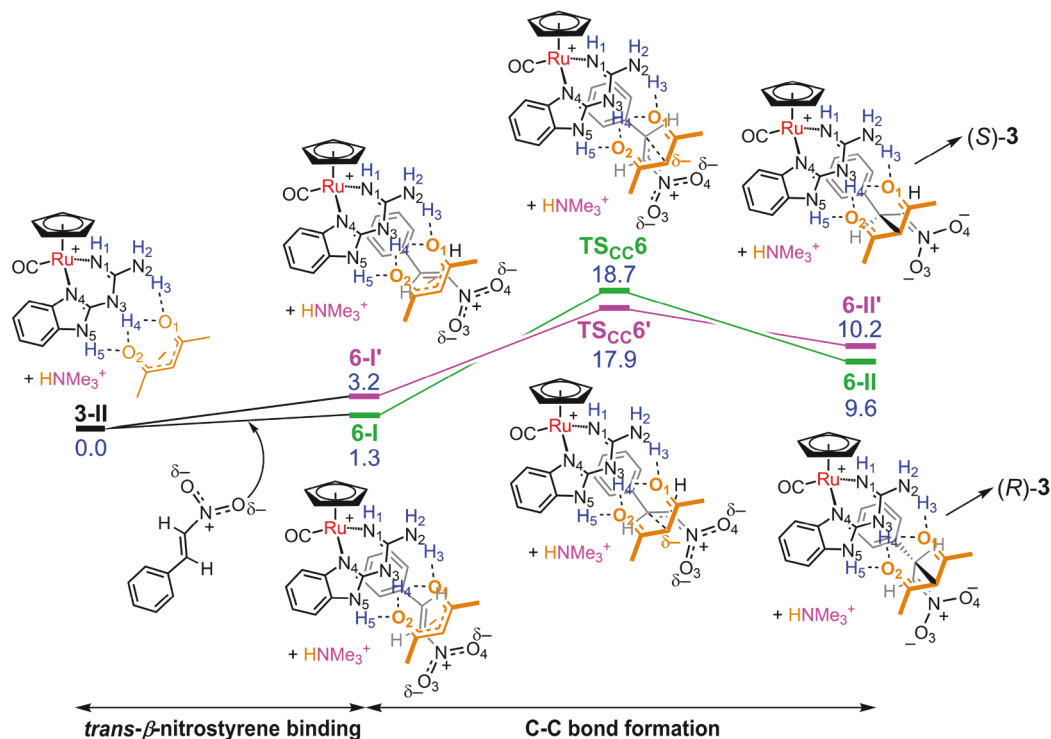


Figure 6. Relative free energy profiles ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) for species derived from $(S_{\text{Ru}})^{-1+}$, 2,4-pentanedione, NMe_3 , and *trans*- β -nitrostyrene the last of which approaches *anti* to the cyclopentadienyl ligand. Selected distances (Å): **6-I**, $\text{H}_3\text{--O}_1$ 1.72, $\text{H}_4\text{--O}_1$ 1.88, $\text{H}_4\text{--O}_2$ 2.34, $\text{H}_5\text{--O}_2$ 1.59; **6-I'**, $\text{H}_3\text{--O}_1$ 1.73, $\text{H}_4\text{--O}_1$ 1.88, $\text{H}_4\text{--O}_2$ 2.37, $\text{H}_5\text{--O}_2$ 1.58; **TS_{CC6}**, $\text{H}_3\text{--O}_1$ 1.77, $\text{H}_4\text{--O}_1$ 1.93, $\text{H}_4\text{--O}_2$ 2.41, $\text{H}_5\text{--O}_2$ 1.67; **TS_{CC6'}**, $\text{H}_3\text{--O}_1$ 1.76, $\text{H}_4\text{--O}_1$ 1.99, $\text{H}_4\text{--O}_2$ 2.28, $\text{H}_5\text{--O}_2$ 1.68; **6-II**, $\text{H}_3\text{--O}_1$ 1.84, $\text{H}_4\text{--O}_1$ 1.97, $\text{H}_4\text{--O}_2$ 2.47, $\text{H}_5\text{--O}_2$ 1.75; **6-II'**, $\text{H}_3\text{--O}_1$ 1.84, $\text{H}_4\text{--O}_1$ 1.97, $\text{H}_4\text{--O}_2$ 2.46, $\text{H}_5\text{--O}_2$ 1.76.

negatively charged $\text{C}=\text{N}^+(\text{O}^-)_2$ moieties and positively charged ruthenium fragments and are 9.1–10.2 kcal/mol less

stable than the educts. However, the energies plummet dramatically upon proton transfer from the protonated base

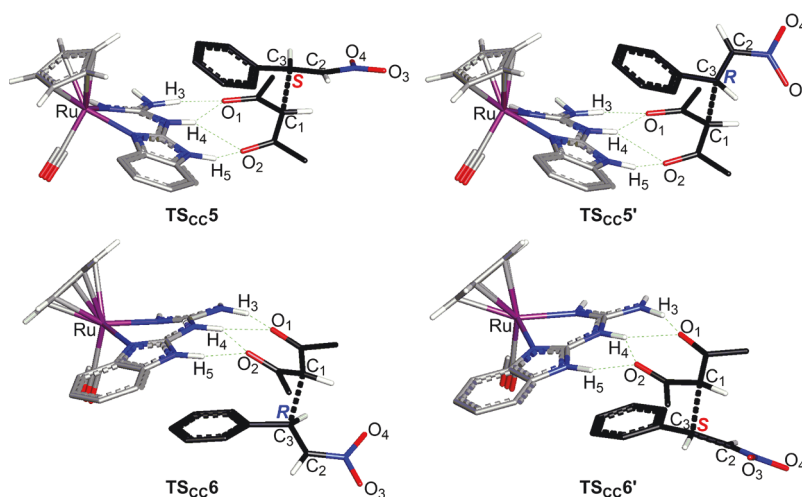


Figure 7. Alternative views of the transition states in Figures 5 and 6. Additional distances (Å): **5-I**/**TS_{cc5}**/**5-II**, C₁–C₃ 3.30/2.08/1.62; **5-I'**/**TS_{cc5'}**/**5-II'**, C₁–C₃ 3.15/2.07/1.62; **6-I**/**TS_{cc6}**/**6-II**, C₁–C₃ 3.33/2.07/1.62; **6-I'**/**TS_{cc6'}**/**6-II'**, C₁–C₃ 3.38/2.07/1.62.

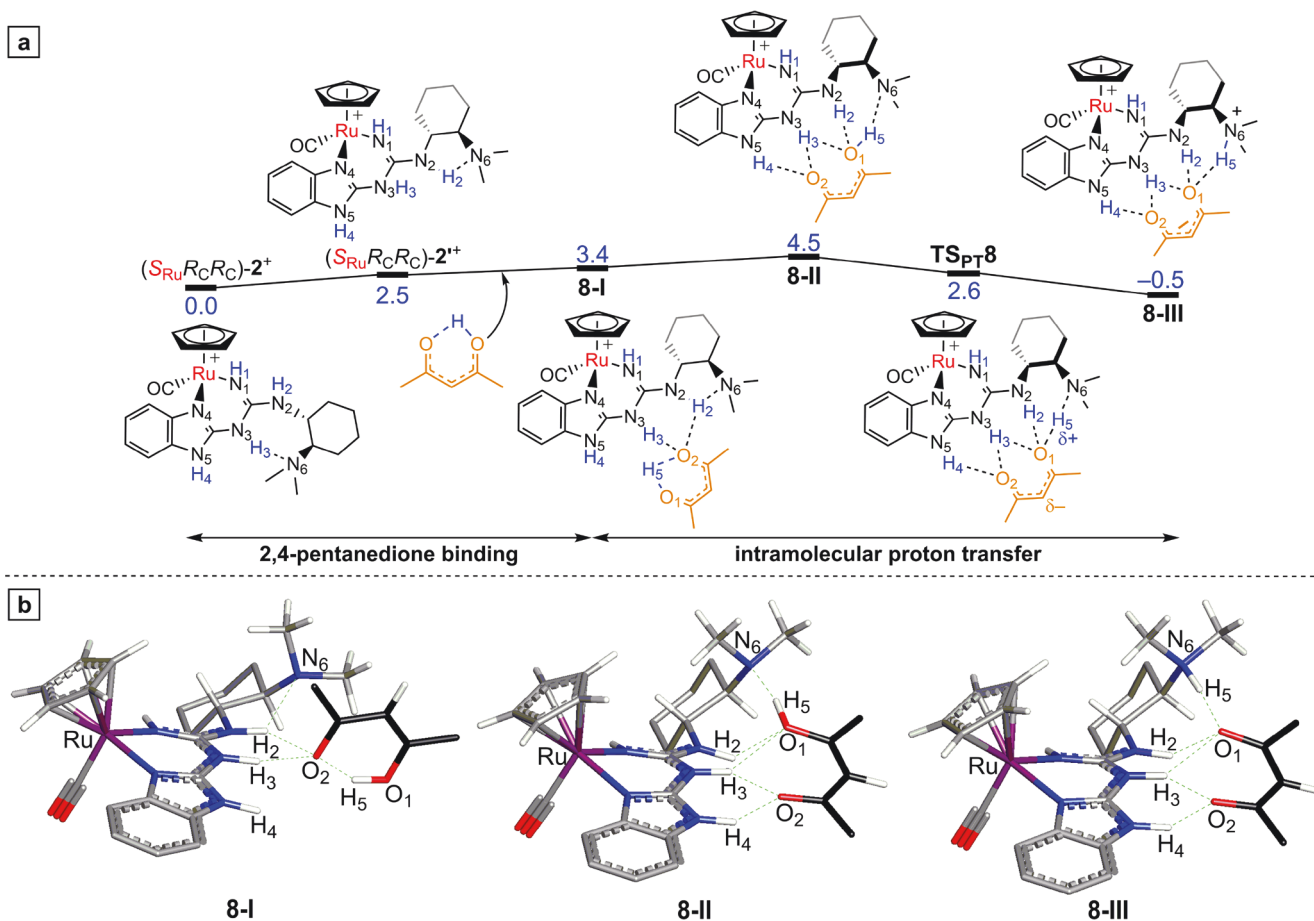


Figure 8. (a) Relative free energy profile ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) for binding of the enol of 2,4-pentanedione to $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+$ and subsequent intramolecular O/N proton transfer. (b) Optimized geometries of **8-I**, **8-II**, and **8-III**. Selected distances (Å): $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+$, H₃–N₆ 1.58; $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+$, H₂–N₆ 2.12; **8-I**, H₂–O₂ 2.18, H₂–N₆ 2.23, H₃–O₂ 1.78, H₅–O₁ 1.00, H₅–O₂ 1.61; **8-II**, H₂–O₁ 2.06, H₃–O₁ 2.40, H₃–O₂ 1.85, H₄–O₂ 1.87, H₅–O₁ 1.04, H₅–N₆ 1.59; **TS_{PT8}**, H₂–O₁ 1.99, H₃–O₁ 2.45, H₃–O₂ 1.82, H₄–O₂ 1.86, H₅–O₁ 1.13, H₅–N₆ 1.40; **8-III**, H₂–O₁ 1.82, H₃–O₁ 2.41, H₃–O₂ 1.81, H₄–O₂ 1.79, H₅–O₁ 1.63, H₅–N₆ 1.07.

HNMe₃⁺ to the C=N⁺(–O[–])₂ moiety. Importantly, **5-II** and **6-II'** lead to (*S*)-**3**, whereas **5-II'** and **6-II** lead to (*R*)-**3** (all initially hydrogen bonded).

With reference to the lowest energy precursor **2-I** (Figures 2 and 3), the energy barriers associated with **TS_{cc5}**, **TS_{cc5'}**,

TS_{cc6}, and **TS_{cc6'}** are 18.0 (17.7 + 0.3), 18.3 (18.0 + 0.3), 19.0 (18.7 + 0.3), and 18.2 (17.9 + 0.3) kcal/mol, respectively. These values are quite close and are within commonly accepted “computational experimental error”. In any case, those with activation energies of 18.0 and 18.2 kcal/mol lead

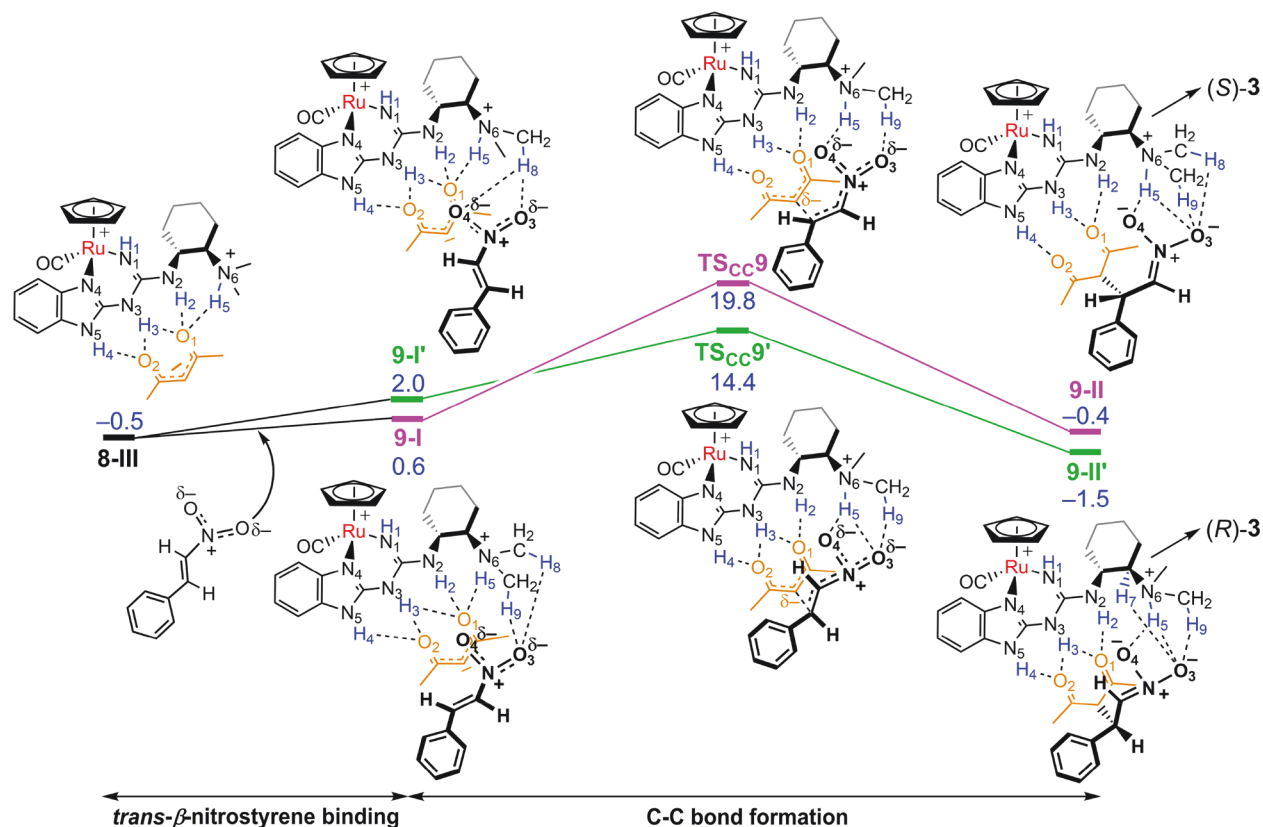


Figure 9. Relative free energy profiles ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) for species derived from $(S_{\text{Ru}}R_C R_C)\text{-}2^+$, 2,4-pentanedione, and *trans*- β -nitrostyrene, the last of which approaches *syn* to the cyclopentadienyl ligand. Selected distances ($\text{\AA}$): **9-I**, $\text{H}_2\text{-O}_1$ 1.88, $\text{H}_3\text{-O}_1$ 2.26, $\text{H}_3\text{-O}_2$ 1.79, $\text{H}_4\text{-O}_2$ 1.80, $\text{H}_5\text{-O}_1$ 1.70, $\text{H}_5\text{-O}_3$ 2.85, $\text{H}_5\text{-O}_4$ 3.42, $\text{H}_8\text{-O}_3$ 2.43, $\text{H}_9\text{-O}_3$ 2.48; **9-I'**, $\text{H}_2\text{-O}_1$ 1.85, $\text{H}_3\text{-O}_1$ 2.31, $\text{H}_3\text{-O}_2$ 1.78, $\text{H}_4\text{-O}_2$ 1.79, $\text{H}_5\text{-O}_1$ 1.70, $\text{H}_5\text{-O}_3$ 2.92, $\text{H}_5\text{-O}_4$ 3.52, $\text{H}_8\text{-O}_3$ 2.57, $\text{H}_8\text{-O}_4$ 2.61; **TS_{CC}9**, $\text{H}_2\text{-O}_1$ 1.85, $\text{H}_3\text{-O}_1$ 1.77, $\text{H}_4\text{-O}_2$ 1.72, $\text{H}_5\text{-O}_3$ 2.79, $\text{H}_5\text{-O}_4$ 1.76, $\text{H}_9\text{-O}_3$ 2.33; **TS_{CC}9'**, $\text{H}_2\text{-O}_1$ 1.71, $\text{H}_3\text{-O}_1$ 1.92, $\text{H}_3\text{-O}_2$ 2.34, $\text{H}_4\text{-O}_2$ 1.68, $\text{H}_5\text{-O}_3$ 2.39, $\text{H}_5\text{-O}_4$ 1.73, $\text{H}_9\text{-O}_3$ 2.63; **9-II**, $\text{H}_2\text{-O}_1$ 2.07, $\text{H}_3\text{-O}_1$ 1.83, $\text{H}_4\text{-O}_2$ 1.85, $\text{H}_5\text{-O}_3$ 2.60, $\text{H}_5\text{-O}_4$ 1.59, $\text{H}_8\text{-O}_3$ 2.51, $\text{H}_9\text{-O}_3$ 2.28; **9-II'**, $\text{H}_2\text{-O}_1$ 1.82, $\text{H}_3\text{-O}_1$ 2.13, $\text{H}_3\text{-O}_2$ 2.25, $\text{H}_4\text{-O}_2$ 1.84, $\text{H}_5\text{-O}_3$ 2.33, $\text{H}_5\text{-O}_4$ 1.57, $\text{H}_7\text{-O}_3$ 2.56, $\text{H}_9\text{-O}_3$ 2.51.

to (S)-3 and those with activation energies of 18.3 and 19.0 kcal/mol to (R)-3. Hence, little or no enantioselectivity would be expected. A reviewer remarked that this outcome (in contrast to those for $(S_{\text{Ru}}R_C R_C)\text{-}$ and $(R_{\text{Ru}}R_C R_C)\text{-}2^+\text{PF}_6^-$ below) remains experimentally unverified due to the unavailability of enantiopure 1^+ . However, the pentaphenylcyclopentadienyl analogue has, as described in the following paper,^{5c} been isolated in enantiopure form and catalyzes the addition of diethyl malonate to *trans*- β -nitrostyrene in a paltry 3% ee.

Alternative views of the transition states that focus on the *syn/anti* approaches of the nitroalkene to the GBI/enolate plane are provided in Figure 7. Some higher energy transition states in which $(S_{\text{Ru}})\text{-}1^+$ is hydrogen-bonded to both the enolate and *trans*- β -nitrostyrene are depicted in Figures s2–s5 in the Supporting Information.

$(S_{\text{Ru}}R_C R_C)\text{-}2^+\text{PF}_6^-$: Binding of Educts. The additional GBI substituent and functionality in this complex and its diastereomer provide motifs similar to those in the widely employed bifunctional thiourea based hydrogen bond donor catalysts.^{2b,8b,26} In contrast to the results with 1^+PF_6^- in the previous paper,²² initial computations established that ion pairs in which the PF_6^- is solvent separated are comparable in energy to those where it hydrogen bonds to the cation (Figures s7–s10 in the Supporting Information). Nonetheless, the mechanism of Scheme 2 was probed with $(S_{\text{Ru}}R_C R_C)\text{-}2^+$, incorporating a hydrogen bond between the $:\text{NMe}_2$ lone pair

and the central NH of the triad that was observed crystallographically ($\text{N}_3\text{H}_3\cdots\text{N}_6$, 1.58 $\text{\AA}$; Figure 8a).^{5b}

In a step that ultimately aids substrate binding, the hydrogen bond in $(S_{\text{Ru}}R_C R_C)\text{-}2^+$ was replaced by one involving the proximal NH of the triad ($\text{N}_2\text{H}_2\cdots\text{N}_6$, 2.12 $\text{\AA}$), giving $(S_{\text{Ru}}R_C R_C)\text{-}2'^+$ (Figure 8a). This rearrangement is 2.5 kcal/mol uphill, consistent with the presumably lower strength of the longer hydrogen bond. The new bond is in fact observed in crystal structures that contain the diastereomeric cation $(S_{\text{Ru}}R_C R_C)\text{-}2'^+$.^{5b} The addition of both 2,4-pentanedione and *trans*- β -nitrostyrene to $(S_{\text{Ru}}R_C R_C)\text{-}2'^+$ was then examined. In contrast to the sequence with monofunctional $(S_{\text{Ru}})\text{-}1^+$, the $:\text{NMe}_2$ group of $(S_{\text{Ru}}R_C R_C)\text{-}2'^+$ enables deprotonation of 2,4-pentanedione by the catalyst. This parallels results from a computational study involving the interaction of 2,4-pentanedione with a similarly functionalized thiourea.²⁷

Thus, a series of three energy minima, 8-I, 8-II, and 8-III, ensue as depicted in Figure 8a. The first features a cyclic enol ligand, in which the more weakly hydrogen bonded oxygen atom²⁴ interacts with two NH groups of the triad. In the second, the cyclic enol has isomerized to an acyclic enol, with the two oxygen atoms hydrogen bonding to all three NH groups of the triad; the OH group serves as a hydrogen bond donor to the $:\text{NMe}_2$ moiety. In the third, the hydrogen atom derived from the OH group covalently bonds to the $:\text{NMe}_2$ moiety while maintaining a hydrogen-bonding interaction with the oxygen atom. This species (8-III), the first with a

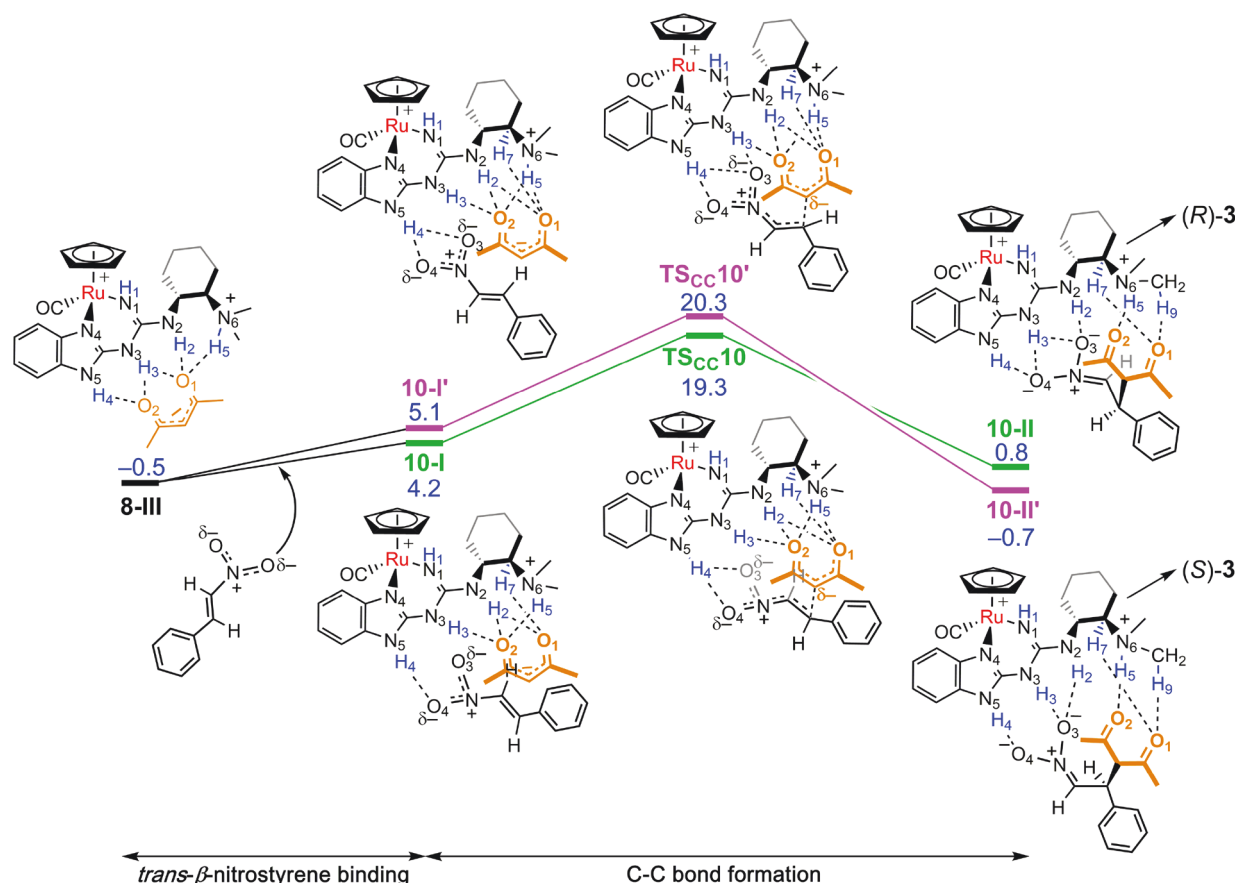


Figure 10. Relative free energy profiles ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) for species derived from $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+$, 2,4-pentanedione, and *trans*- β -nitrostyrene, the last of which approaches *anti* to the cyclopentadienyl ligand. Selected distances ($\text{\AA}$): **10-I**, H_2-O_1 1.79, H_2-O_2 2.44, H_3-O_2 1.78, H_4-O_3 2.65, H_4-O_4 1.90, H_5-O_2 1.69, H_7-O_1 2.27; **10-I'**, H_2-O_1 1.81, H_2-O_2 2.51, H_3-O_2 1.72, H_4-O_3 2.57, H_4-O_4 1.92, H_5-O_1 2.50, H_5-O_2 1.70, H_7-O_1 2.27; **TS_{cc}10**, H_2-O_1 2.04, H_2-O_2 2.41, H_3-O_2 1.84, H_4-O_3 2.49, H_4-O_4 1.78, H_5-O_1 2.49, H_5-O_2 1.82, H_7-O_1 2.21; **TS_{cc}10'**, H_2-O_1 2.00, H_2-O_2 2.54, H_3-O_2 2.59, H_3-O_3 1.82, H_4-O_3 2.41, H_4-O_4 1.79, H_5-O_1 2.49, H_5-O_2 1.72, H_7-O_1 2.19; **10-II**, H_2-O_3 1.74, H_3-O_3 2.44, H_3-O_4 1.58, H_4-O_4 2.61, H_5-O_2 1.80, H_7-O_1 2.52, H_9-O_1 2.33; **10-II'**, H_2-O_3 2.09, H_3-O_3 1.56, H_4-O_4 1.74, H_5-O_2 1.76, H_7-O_1 2.39, H_9-O_1 2.34.

deprotonated dione ligand, is downhill from the educts by -0.5 kcal/mol. Hence, 0.5 kcal/mol must be added to the $\Delta G(\text{CH}_2\text{Cl}_2)$ value of any subsequently derived transition state to obtain a free energy of activation (such intermediates were not encountered with the diastereomeric catalyst; see below).

Alternative representations of **8-I**, **8-II**, and **8-III** are provided in Figure 8b. These emphasize the increasing elevation of the $:\text{NMe}_2$ group above the GBI plane, achieved by simply rotating about the cyclohexyl- $\text{NH}(\text{C}_{\text{sp}^2})$ bond. They also illustrate the deviation of the plane of the enol or enolate from the GBI plane. Some higher energy structures in which the $:\text{NMe}_2$ group is rotated below the plane are shown in Figure s11 in the Supporting Information.

The rate-determining step in Figure 8 is the conversion of **8-II** to **8-III**. The structure of the transition state, which involves $\text{O}\cdots\text{H}\cdots\text{N}$ proton transfer, is shown as **TS_{PT}8**. The overall energy barrier is only 2.6 kcal/mol. Although the free energy of **TS_{PT}8** is lower than that of **8-II**, the electronic energy of **TS_{PT}8** is slightly higher (-15.3 vs -15.6 kcal/mol; Table s16 in the Supporting Information), a trend that has ample precedent.²⁸ In any case, the energy barrier is much less than that for $(S_{\text{Ru}})-1^+$ and the external base NMe_3 in Figure 3.

Some readers may have noted the use of 2,4-pentanedione in Figures 2 and 3 but the cyclic enol tautomer in Figure 8a.²⁴ As shown in Figure s12 in the Supporting Information, replacing

the enol ligand by the dione in Figure 8a affords significantly higher energy adducts. The binding of *trans*- β -nitrostyrene to $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+$ was also examined (Figures s13–s15 in the Supporting Information). However, the most stable adducts were 4.7 – 5.0 kcal/mol uphill, in comparison to a maximum of 4.5 kcal/mol for all of the species on the reaction coordinate in Figure 8, including transition states.

$(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+$: Carbon–Carbon Bond Formation. Interactions of **8-III** and *trans*- β -nitrostyrene were probed computationally as for **3-II** above. As in Figure 5, those involving approaches *syn* to the cyclopentadienyl ligand were considered first. As shown by **9-I** and **9-I'** in Figure 9, the most favorable initial adducts exhibited 2-fold hydrogen bonding between one or both oxygen atoms of the nitro group, and $\text{NCH}_2\text{-H}$ linkages from one or both *N*-methyl groups. The $\text{NCH}_2\text{H}\cdots\text{O}$ distances (2.43 – 2.61 $\text{\AA}$) were considerably longer than most of the $\text{NH}\cdots\text{O}$ hydrogen bonds noted above. In **9-I**, the $\text{C}_{\text{re}}=\text{C}_{\text{si}}\text{Ph}$ face is interacting with the enolate moiety, and in **9-I'** the $\text{C}_{\text{si}}=\text{C}_{\text{re}}\text{Ph}$ face is interacting. Hence, opposite enantiomers of **3** should result.

Quite different structures were computed when *trans*- β -nitrostyrene was restricted to approaching *anti* to the cyclopentadienyl ligand. As shown by **10-I** and **10-I'** in Figure 10, the nitro groups now interact with the opposite terminus of the substituted GBI ligand, hydrogen bonding to the NH

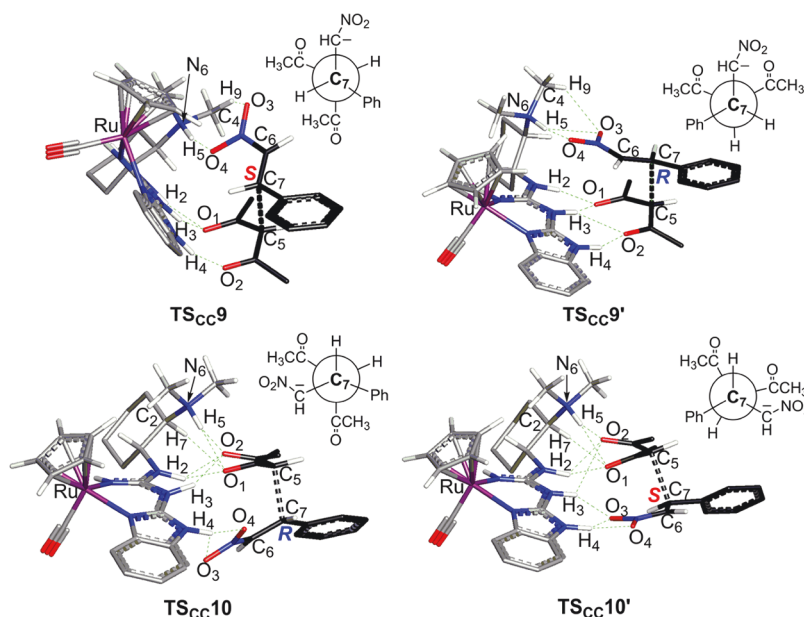


Figure 11. Alternative views of the transition states in Figures 9 and 10. Additional distances (Å): 9-I/TS_{CC}9/9-II, C₅–C₇ 3.79/2.27/1.57; 9-I'/TS_{CC}9'/9-II', C₅–C₇ 3.34/2.25/1.59; 10-I/TS_{CC}10/10-II, C₅–C₇ 3.21/2.14/1.58; 10-I'/TS_{CC}10'/10-II', C₅–C₇ 3.90/2.24/1.57. H–C₅–C₇–H torsion angle (deg): TS_{CC}9, 176.9; TS_{CC}9', 55.4; TS_{CC}10, 63.5; TS_{CC}10', 143.2.

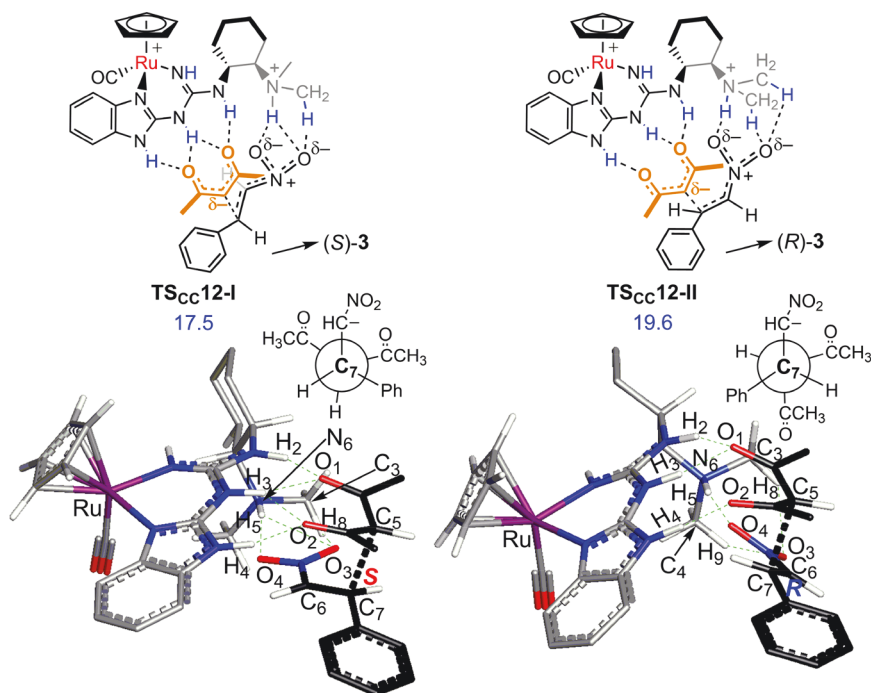


Figure 12. Additional transition states and $\Delta G(\text{CH}_2\text{Cl}_2)$ values (kcal/mol) calculated from the starting materials for Figures 9 and 10. Selected distances (Å): TS_{CC}12-I, H₂–O₁ 1.78, H₃–O₁ 1.79, H₃–O₂ 2.59, H₄–O₂ 1.69, H₅–O₃ 2.57, H₅–O₄ 1.77, H₈–O₃ 2.50, C₅–C₇ 2.23; TS_{CC}12-II, H₂–O₁ 1.87, H₃–O₁ 1.71, H₄–O₂ 1.67, H₅–O₃ 2.80, H₅–O₄ 1.79, H₈–O₃ 2.34, H₉–O₃ 2.38, C₅–C₇ 2.24. H–C₅–C₇–H torsion angle (deg): TS_{CC}12-I, 47.4; TS_{CC}12-II, 175.6.

group of the N₅–H₄ linkage. The enolate ligands maintain one hydrogen bond with the central N₃–H₃ linkage but otherwise slither over, generating multiple hydrogen bonds with the 1,2-diaminocyclohexane ring. In 10-I, the C_{si}=C_{re}Ph face is interacting with the enolate moiety, and in 10-I' the C_{re}=C_{si}Ph face is interacting.

Transition states could be located for each for the four initial adducts in Figures 9 and 10 and are designated TS_{CC}9, TS_{CC}9', TS_{CC}10, and TS_{CC}10'. Alternative views are presented

in Figure 11, together with Newman projections down the newly forming carbon–carbon bonds (C₇–C₅ or O₂NCH(Ph)HC–CH(COCH₃)₂). These constitute the rate-determining steps and afford 9-II, 9-II', 10-II, and 10-II', which are hydrogen-bonded adducts of the product 3. To obtain activation energies, 0.5 kcal/mol must be added to the $\Delta G(\text{CH}_2\text{Cl}_2)$ values in Figures 9 and 10, reflecting the energy of the global minimum 8-III (–0.5 kcal/mol). This gives 20.3 (TS_{CC}9; 19.8 + 0.5), 14.9 (TS_{CC}9'; 14.4 + 0.5), 19.8 (TS_{CC}10;

19.3 + 0.5), and 20.8 (TS_{CC}10'; 20.3 + 0.5) kcal/mol. Given the considerably lower activation energy for TS_{CC}9', it should be the dominant reaction channel and indeed leads to (R)-3 in agreement with experiment.

Additional comparisons are provided by the Newman projections in Figure 11. For example, the C₇–C₅ substituents in the highest energy species TS_{CC}10' are nearly eclipsed (X–C₇–C₅–Y torsion angles for synperiplanar X/Y: 27, 26, 15°), whereas those in the other transition states are staggered. In terms of factors favoring TS_{CC}9' over TS_{CC}9, both the enolate and NO₂ oxygen atoms are more extensively hydrogen bonded in the former. Although comparisons of TS_{CC}9' with TS_{CC}10 and TS_{CC}10' are more challenging due to the lower structural homology, transition states in which the NO₂ oxygen atoms no longer bind to the HNMe₂⁺ moiety always exhibit higher activation energies.

Eight additional transition states derived from (S_{Ru}R_CR_C)-2⁺ could be located, as depicted in Figures s16, s17, s19, and s20 in the Supporting Information. For the two shown in Figure 12, TS_{CC}12-I and TS_{CC}12-II, the ΔG(CH₂Cl₂) values (17.5 and 19.6 kcal/mol) also represent activation energies, as there are no intermediates like 8-III with energies lower than those of the educts. These constitute the only other transition states with activation energies lower than the highest energy in Figures 9–11 (TS_{CC}10', 20.3 + 0.5 kcal/mol). The second, TS_{CC}12-II, leads to (R)-3 and shares several features with TS_{CC}9 but involves the opposite C_{si}=C_{re}Ph enantioface of *trans*-β-nitrostyrene and addition *anti* to the cyclopentadienyl ligand. Since it has a much higher activation energy in comparison to TS_{CC}9' (14.4 + 0.5 kcal/mol), the dominant channel to (R)-3, it is not further analyzed.

The activation energy for TS_{CC}12-I (17.5 kcal/mol) renders it the most favorable channel to (S)-3. Here, the C_{re}=C_{si}Ph face of *trans*-β-nitrostyrene adds from a direction *anti* to the cyclopentadienyl ligand, as opposed to the C_{si}=C_{re}Ph face adding *syn* as in TS_{CC}9'. The lower activation energy for TS_{CC}9' versus TS_{CC}12-I appears to be due to a number of factors. The hydrogen-bonding motifs are similar, but the distances involving the NO₂ oxygen atoms and HNMe₂⁺ moiety in TS_{CC}9' are generally shorter (1.73 vs 1.77 Å; 2.39 vs 2.57 Å; 2.63 vs 2.50 Å). The shortest O⋯HNMe₂ linkage in TS_{CC}9' exhibits a higher degree of linearity (164.9° vs 156.4°). Also, the H–C₇–C₅–H torsion angle of TS_{CC}9' indicates a more staggered arrangement of substituents (55.4° vs 47.4°).

Furthermore, the 1,2-diaminocyclohexane rings adopt much different conformations in TS_{CC}9' and TS_{CC}12-I. To help gauge this effect, the substrates and the metal fragment were removed to give the free substituted GBI ligands and their :NMe₂-protonated forms. As illustrated in Figure 13, the conformations differ by a ca. 180° rotation about the cyclohexyl–NH(C_{sp}²) bond. That in TS_{CC}12-I (B) is 1.2–1.6 kcal/mol less stable than that in TS_{CC}9' (A). This can be ascribed to interactions involving two axial C–H groups of the cyclohexane ring and the C=NH substituent of the NH group. The stability difference increases to 2.1 kcal/mol when the substrates are added.²⁹

In any case, from a computational standpoint, the high enantioselectivities for the additions of 1,3-dicarbonyl compounds to *trans*-β-nitrostyrene catalyzed by (S_{Ru}R_CR_C)-2⁺PF₆[−] in Schemes 1 and 2 largely derive from two competing transition states with a 2.6 kcal/mol difference in free energies. This agrees well with the >99:1 to 92:8 product enantiomer ratios.

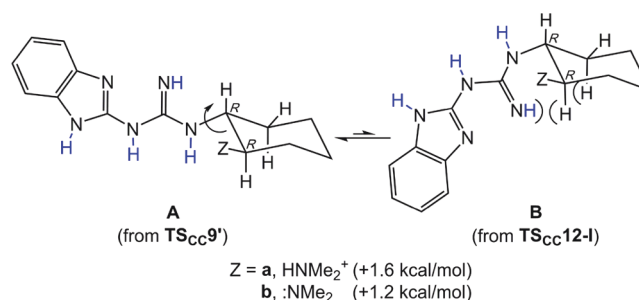


Figure 13. Differences in electronic energies for GBI ligands excised from the transition states TS_{CC}9' and TS_{CC}12-I.

(R_{Ru}R_CR_C)-2⁺: Carbon–Carbon Bond Formation. Given the comparable enantioselectivities and identical product configurations obtained with the diastereomeric catalysts (S_{Ru}R_CR_C)- and (R_{Ru}R_CR_C)-2⁺PF₆[−] (Schemes 1 and 2), it would not be surprising to compute similar sets of transition states. The former complex can be converted to the latter by simply exchanging the positions of the cyclopentadienyl and carbonyl ligands. Both ligands are remote from the sites where the catalyst and educts interact, as well as the 1,2-diaminocyclohexane moiety. There are no van der Waals contacts in any of the structures computed above or in the crystal structures.^{5b}

Accordingly, through similar procedures, the transition states and ΔG(CH₂Cl₂) values depicted in Figure 14 were computed. In this series, the latter are equivalent to the free energies of activation. There are four transition states, TS_{CC}13-I through TS_{CC}13-IV, corresponding to those in Figures 8–10, and two more, TS_{CC}13-V and TS_{CC}13-VI, corresponding to those in Figure 12. The complete reaction coordinates are illustrated in Figures s22–s30 in the Supporting Information. Now the HNMe₂⁺ units of the 1,2-diaminocyclohexane moieties are *anti* as opposed to *syn* to the cyclopentadienyl ligands for TS_{CC}13-I through TS_{CC}13-IV, and *syn* as opposed to *anti* for TS_{CC}13-V and TS_{CC}13-VI. This is a logical consequence of the “cyclopentadienyl/carbonyl flip” noted in the preceding paragraph.

Here, the lowest energy transition state, TS_{CC}13-II, leads to the major product enantiomer, (R)-3 (addition of the C_{si}=C_{re}Ph face *anti* to the cyclopentadienyl ligand). It features exactly the same grouping of hydrogen bonds as was found for the lowest energy transition state derived from the diastereomer (S_{Ru}R_CR_C)-2⁺ in Figures 8–10 (TS_{CC}9'). Their relative energies (15.1 vs 14.9 kcal/mol) represent the cost of the “cyclopentadienyl/carbonyl flip”. The two lowest energy transition states that lead to the minor product enantiomer, (S)-3, are analogous to those in Figures 8–10 (TS_{CC}13-V, comparable to TS_{CC}12-I (17.2 vs 17.5 kcal/mol) and involving addition of the C_{re}=C_{si}Ph face *syn* to the cyclopentadienyl ligand; TS_{CC}13-I, comparable to TS_{CC}9 (18.4 vs 20.3 kcal/mol) and involving addition of the C_{re}=C_{si}Ph face *anti* to the cyclopentadienyl ligand). In any case, the high enantioselectivities obtained with (R_{Ru}R_CR_C)-2⁺PF₆[−] in Schemes 1 and 2 largely derive from two competing transition states with a computed 2.1 kcal/mol difference in activation energies (TS_{CC}13-II and TS_{CC}13-V).

DISCUSSION

The data in Figures 5 and 6 show that enantiopure 1⁺PF₆[−] would be expected to catalyze additions of 1,3-dicarbonyl

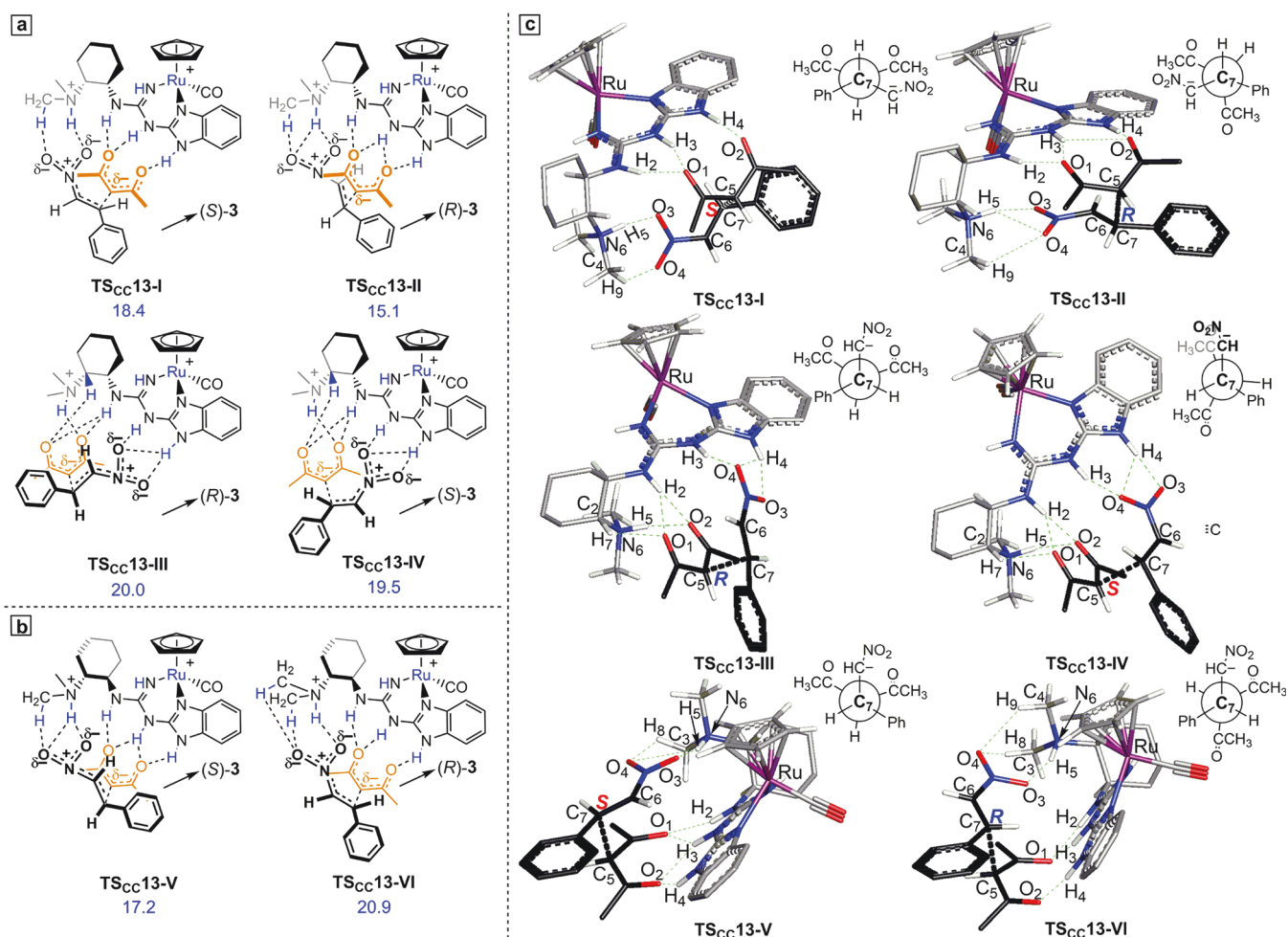


Figure 14. Relative free energies ($\Delta G(\text{CH}_2\text{Cl}_2)$, kcal/mol) of additional transition states for species derived from $(R_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+$, 2,4-pentanedione, and *trans*- β -nitrostyrene with the HNMe_2^+ moiety (a) *anti* or (b) *syn* to the cyclopentadienyl ligand. (c) Optimized geometries of the transition states. Selected distances (Å): TS_{CC13-I}, H₂–O₁ 1.87, H₃–O₁ 1.73, H₄–O₂ 1.68, H₅–O₃ 1.76, H₉–O₄ 2.27, C₅–C₇ 2.24; TS_{CC13-II}, H₂–O₁ 1.78, H₃–O₁ 1.79, H₃–O₂ 2.61, H₄–O₂ 1.68, H₅–O₃ 1.75, H₅–O₄ 2.50, H₉–O₄ 2.49, C₅–C₇ 2.24; TS_{CC13-III}, H₂–O₁ 1.96, H₂–O₂ 2.53, H₃–O₄ 1.79, H₄–O₃ 1.83, H₄–O₄ 2.53, H₅–O₂ 1.70, H₇–O₁ 2.22, C₅–C₇ 2.24; TS_{CC13-IV}, H₂–O₁ 1.89, H₂–O₂ 2.52, H₃–O₄ 1.77, H₄–O₃ 1.74, H₄–O₄ 2.50, H₅–O₂ 1.72, H₇–O₁ 2.23, C₅–C₇ 2.22; TS_{CC13-V}, H₂–O₁ 1.78, H₃–O₁ 2.26, H₃–O₂ 1.97, H₄–O₂ 1.75, H₅–O₃ 1.72, H₅–O₄ 2.57, H₈–O₄ 2.50, C₅–C₇ 2.25; TS_{CC13-VI}, H₂–O₁ 1.86, H₃–O₁ 1.73, H₄–O₂ 1.68, H₅–O₃ 1.78, H₈–O₄ 2.42, H₉–O₄ 2.37, C₅–C₇ 2.25. H–C₅–C₇–H torsion angle (deg): TS_{CC13-I}, 174.5; TS_{CC13-II}, 48.1; TS_{CC13-III}, 71.1; TS_{CC13-IV}, 134.4; TS_{CC13-V}, 49.7; TS_{CC13-VI}, 175.3.

compounds to *trans*- β -nitrostyrene or related nitroalkenes with little or no enantioselectivity. It was not possible to test this experimentally, due to our inability to resolve racemic 1^+PF_6^- . However, the conclusion makes intuitive sense, given the appreciable distance between the ruthenium stereocenter and the locus of reaction on the remote side of the GBI ligand and is buttressed by data for the enantiopure pentaphenylcyclopentadienyl analogue in the following paper.^{5c} Accordingly, the carbon stereocenters and added functionality in $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-$ and $(R_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+\text{PF}_6^-$ play critical roles in achieving highly enantioselective catalysis.

What are these critical roles? Given the close relationships of the transition states for the diastereomeric catalysts (*vide supra*), only $(S_{\text{Ru}}R_{\text{C}}R_{\text{C}})-2^+\text{PF}_6^-$ is treated here. For some stereoselective processes, one can point to a dominant interaction or causative feature, whereas in other cases a number of smaller factors come into play. The activation energies for the most favorable transition states leading to the addition product (*R*)-3 (major enantiomer) and (*S*)-3, TS_{CC9'}, and TS_{CC12-I} (Figures 9, 10, and 12) differ by 2.6 kcal/mol (14.4 + 0.5 vs 17.5 kcal/mol). As framed in the

Results, the energy difference appears to derive from a combination of factors.

In both cases, a Brønsted acidic HNMe_2^+ moiety (attached to one of the carbon stereocenters) is generated by deprotonation of the 1,3-dicarbonyl compound. This in turn mediates the introduction of the nitrostyrene via hydrogen bonding. In TS_{CC9'}, the conformation of the cyclohexane ring places the HNMe_2^+ moiety above the plane of the GBI ligand, whereas in TS_{CC12-I} it is below. In the first case, the $\text{C}_{\text{si}}=\text{C}_{\text{re}}\text{Ph}$ nitrostyrene face is attacked from a direction *syn* to the cyclopentadienyl ligand (Figures 9 and 11), and in the second the $\text{C}_{\text{re}}=\text{C}_{\text{si}}\text{Ph}$ face is attacked from a direction *anti* to the cyclopentadienyl ligand (Figure 12).

Factors noted above include the shorter lengths and more linear angles associated with key hydrogen bonds in TS_{CC9'} and more staggered torsion angles. However, roughly half of the difference in activation energies appears to derive from unfavorable steric interactions involving two axial C–H groups of the 1,2-diaminocyclohexane moiety of TS_{CC12-I} (Figure 13). One can then propose that, in order for TS_{CC12-I} to generate the hydrogen-bonding interactions necessary to

activate the substrates and effect catalysis, it is necessary to introduce some destabilizing strain involving one of the cyclohexane ring substituents, raising the energy relative to **TS_{CC}9'**.

Since the ruthenium configuration has virtually no influence upon the product configurations and ee values, one can question whether the metal stereocenter is needed at all. In this context, parallel reactions have been conducted with the free ligand (*R_CR_C*)-GBI-CH(CH₂)₄CHNMe₂, which corresponds to **A-b** in Figure 13.^{5b} These give much lower rates and enantioselectivities, with an average ee value of 34% for the substrates in Scheme 1. We have speculated that the ability of ruthenium to “preorganize” GBI ligands via chelation into geometrically well defined NH triads is a critical aspect of this difference.

Some other chiral catalysts for additions of 1,3-dicarbonyl compounds to nitroalkenes merit note. For example, Take-moto developed the bifunctional thiourea based species **14** shown in Figure 15.^{8b,26} This bears an obvious relationship to

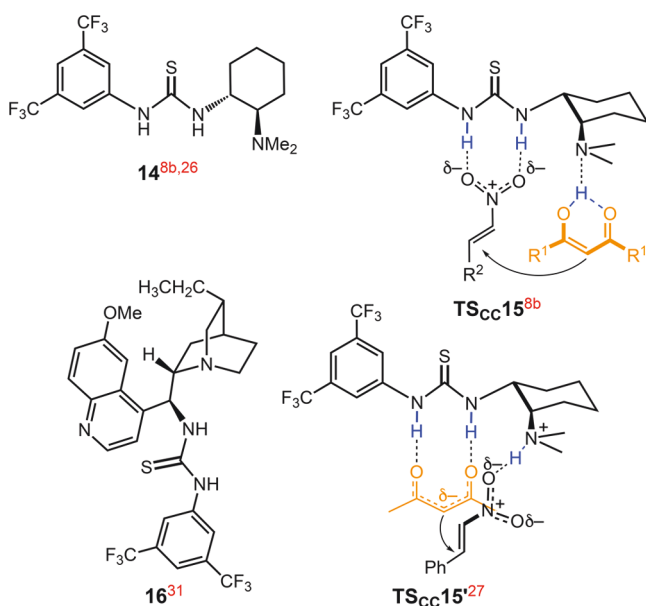


Figure 15. Other relevant bifunctional hydrogen bond donor catalysts and transition state assemblies.

(*S_{Ru}R_CR_C*)- and (*R_{Ru}R_CR_C*)-**2**⁺PF₆[−], and he has proposed the transition state assembly shown in **TS_{CC}15**, which has garnered support in some computational studies.³⁰ Many groups have subsequently developed related bifunctional catalysts,^{2d} and we single one out by Soós (**16**)³¹ as he later collaborated with Pápai in computational papers.²⁷ Their DFT calculations implicated the assembly **TS_{CC}15'** for the Takemoto system. This bears a marked conceptual relationship to our transition states **TS_{CC}9'** (Figure 9) and **TS_{CC}13-II** (Figure 14). The Pápai model has received strong support from additional studies,³² and related transition states have been calculated for other types of addition reactions.³³

In conclusion, the chiral cation **1**⁺ and 2,4-pentanedione readily associate via NH⋯O hydrogen bonds, but an external base NR₃ is required to generate an enolate. The *trans*-β-nitrostyrene then associates with the enolate in a π/π motif, but there is little selectivity with respect to the C=CPh or enolate π face, leading to racemic addition products. In

contrast, following the initial bonding of the dione to the diastereomeric cations (*S_{Ru}R_CR_C*)-**2**⁺ and (*R_{Ru}R_CR_C*)-**2**⁺, a proton is rapidly transferred to the internal :NMe₂ moiety, giving an enolate and a Brønsted acidic HNMe₂⁺ moiety. The latter, which is attached to a carbon stereocenter, mediates the introduction of the nitrostyrene such that in the rate-determining carbon–carbon bond forming step, the proximal π face of the enolate attacks the C_{si}=C_{re}Ph face. This leads to an addition product with an *R* configuration. Thus, the carbon stereocenters in the catalyst control the product configuration, in agreement with Schemes 1 and 2. These findings suggest a number of strategies for further optimizing the rates and enantioselectivities associated with this catalyst family. These are offered as speculations in the following paper, which details an alternative empirical experimental approach.^{5c}

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.organomet.0c00072>.

Free energy profiles, optimization geometries, computational details, verification of the gas- and solution-phase optimization, and tables of energies (PDF)

Optimized structure files (XYZ)

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Notes

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