Computational Chemistry

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Mechanism and Stereocontrol: Enantioselective Addition of Pyrrole to Ketenes Using Planar-Chiral Organocatalysts**

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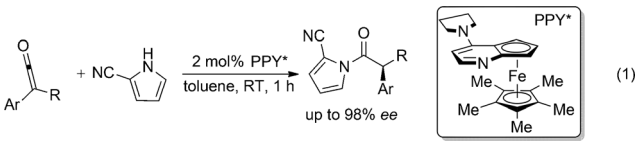
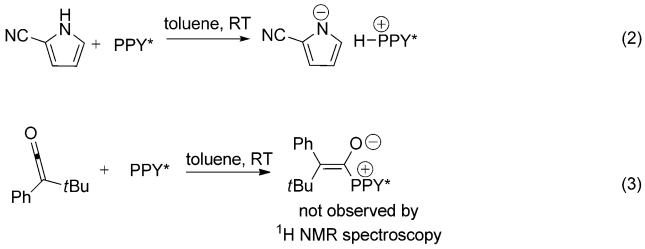
The number and variety of asymmetric transformations involving ketenes catalyzed by the planar-chiral 4-(pyrrolidino) pyridine (PPY*) are remarkable.[1] Yet, the exact mechanism and origin of stereoselectivity in this entire series of reactions have so far remained elusive. Herein we reveal the first detailed computational study of the enantioselective coupling of ketenes and pyrroles using a planar-chiral organocatalyst [Eq. (1)].[1s] We have discovered that the resting state is a chiral Brønsted acid complex, while the rate-determining step (RDS) involves a chiral base (PPY* enolate). We have also discovered structural features of the catalyst that effect catalysis and stereocontrol through a combination of stabilizing CH···O interactions and stereoelectronic effects.



(1)

PPY* forms an ion pair with 2-cyanopyrrole [Eq. (2)], but does not react with the ketene [Eq. (3)].[1s] Addition of the potassium salt of the cyanopyrrole to phenyl *tert*-butyl ketene results in an enolate complex that readily protonates to give the product [Eq. (4)]. Competition experiments with N-deuterated cyanopyrrole revealed a prominent normal primary kinetic isotope effect [$k_H/k_D \approx 5$, Eq. (5)].



(2)

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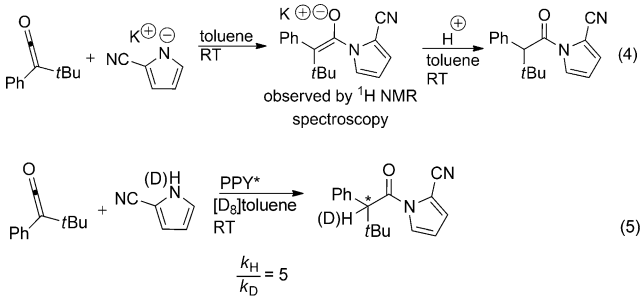


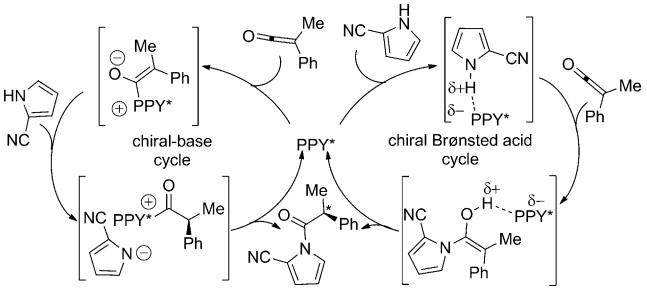
(4)

(5)

$\frac{k_H}{k_D} = 5$

The mechanism and origins of stereoselectivity of this reaction were studied using calculations at the SCS-MP2[2]/def2-∞[3]//B3LYP[4]/6-31G* level of theory.[5–8] Single-point solvation corrections were computed with a polarizable continuum model (PCM)[9] at B3LYP/6-31 + G** with UFF radii[10] for toluene.[6b] This method correctly reproduces the exergonicity of the catalyst resting state and the experimentally observed stereoselectivity.[11] The experimental substrates used were PPY*, 2-cyanopyrrole, and phenyl methyl ketene. Manual, exhaustive conformational searches were performed to ensure all relevant intermediates and transition structures were located.

Two mechanisms are possible (Scheme 1): The PPY* can serve as a chiral proton source to stereoselectively protonate the pyrrole ketene enolate (chiral Brønsted acid mechanism). In the original report, the chiral Brønsted acid mechanism, which was based on ^{1}H NMR experiments, was proposed [Eqs. (2)–(4)].[1s]



Scheme 1. The two possible mechanisms for the title reaction

The computed reaction coordinate for the chiral Brønsted acid mechanism is shown in Figure 1 a. The overall reaction is exergonic by 10.5 kcal mol^{-1} and the 2-cyanopyrrole/PPY* complex is the resting state. The addition of ketene to pyrrole is the RDS ($\Delta G^{\ddagger} = 23.4$ kcal mol^{-1}), and the stereoselective protonation ($\Delta G^{\ddagger} = 10.2$ kcal mol^{-1}) of the resultant pyrrole

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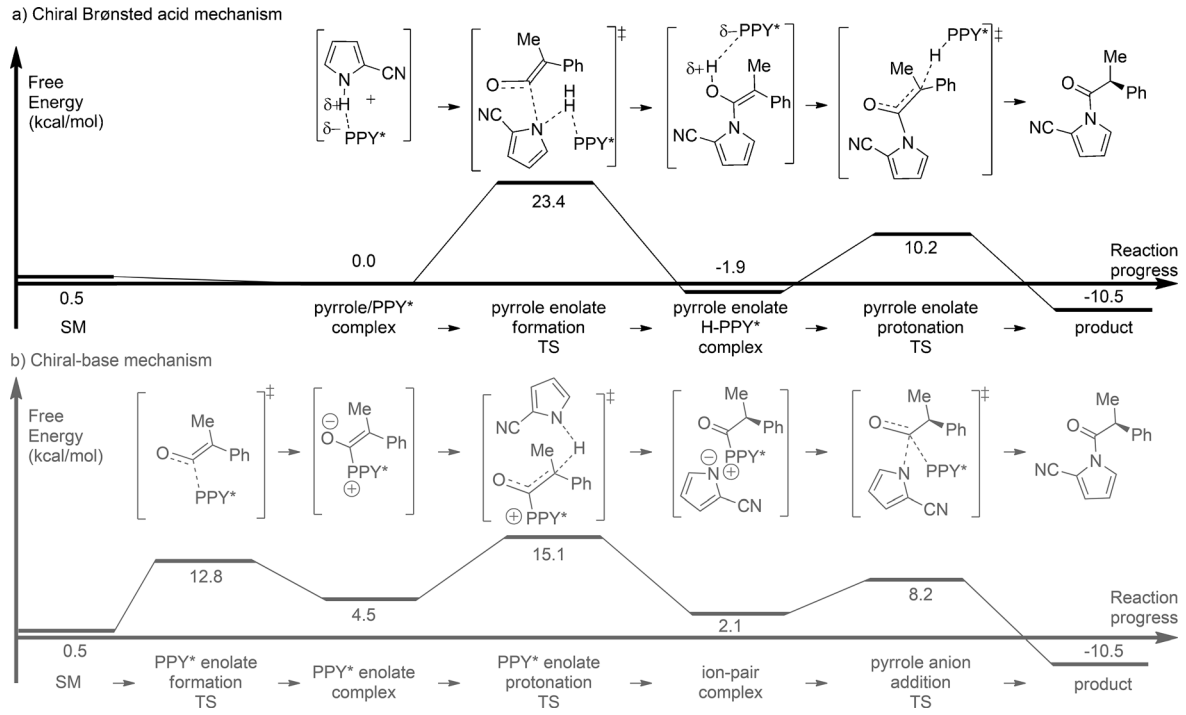

Figure 1. Reaction coordinate diagrams for the PPY*-catalyzed addition of 2 cyanopyrrole to phenyl methyl ketene: a) Chiral Brønsted acid mechanism. b) Chiral-base mechanism. The chiral-base mechanism is energetically more favored than the chiral Brønsted acid mechanism by 8.3 kcal mol^{-1}. This is a Curtin–Hammett mechanistic scenario—the resting state is the pyrrole/PPY* chiral Brønsted acid complex, while the rate-determining step of the reaction is the protonation of the PPY* enolate (chiral-base) complex. Energies are in kcal mol^{-1}. All energies and thermal corrections are from SCS-MP2/def2-∞//B3LYP/6-31G* with PCM solvation corrections for toluene.

enolate by the chiral Brønsted acid, $^{+}$H-PPY*, leads to the product.

The free energy span[12] of the chiral Brønsted acid mechanism is reasonable (23.4 kcal mol^{-1}) compared to the estimated upper limit of the experimental barrier, 22 kcal mol^{-1}.[13,11] However, the computed primary kinetic isotope effect ($k_H/k_D = 1{:}1$) is not in agreement with the experimental data [$k_H/k_D \approx 5$, Eq. (5)].[14] The analogous process corresponding to the KIE experiment involving the phenyl *tert*-butyl ketene was also computed, and this also showed the same inconsistency ($k_H/k_D = 1{:}1$).

These KIE discrepancies led us to consider the chiral-base mechanism (Scheme 1; left side). The corresponding reaction coordinate is shown in Figure 1 b. The catalytic cycle starts with the addition of PPY* to the ketene to form the PPY* enolate (chiral base) complex ($\Delta G^{\ddagger} = 12.8$, $\Delta G = 4.5$ kcal mol^{-1}). This endergonicity is consistent with the inability to observe this complex by ^{1}H NMR spectroscopy. Stereoselective protonation of this chiral enolate by 2-cyanopyrrole is rate- and stereo-determining, ($\Delta G^{\ddagger} = 15.1$ kcal mol^{-1}) and leads to the acyl PPY* complex. Acyl transfer to the pyrrole anion ($\Delta G^{\ddagger} = 8.2$ kcal mol^{-1}) liberates the product and regenerates the catalyst.

The free-energy span[12] of the chiral-base mechanism is lower by more than 8 kcal mol^{-1} compared to that of the chiral Brønsted acid mechanism. Moreover, the computed primary KIE ($k_H/k_D = 5{:}1$) is in agreement with the experimental data [$k_H/k_D \approx 5$, Eq. (5)]. The KIE involving phenyl *tert*-butyl ketene is also identical to the experimental data ($k_H/k_D = 5{:}1$). These results reveal that the chiral-base mechanism is most likely to be operative.

The origins of stereoselectivity for this reaction have also been studied. The computed enantioselectivity for the coupling between 2-cyanopyrrole and phenyl methyl ketene is 0.9 kcal mol^{-1}, which is in good agreement with the experimentally observed selectivity of 1.3 kcal mol^{-1}. There are a total of eight possible transition structures (TSs) for the stereoselective protonation of the PPY* enolate, and all have been computed. The four most stable and representative TSs are shown in Figure 2. The *E*/*Z* describes the enolate alkene stereochemistry and the *R*/*S* describes the chirality of the new stereocenter. **TS-*ES*** leads to the formation of the experimentally observed major product while **TS-*ER*** leads to the minor.

To effect stereocontrol in this reaction, the conformation and configuration (*E*/*Z*) of the PPY* enolate as well as the *re*/*si* facial approach of the cyanopyrrole must be controlled.

All ketene/PPY* structures have the enolate oxygen atom sandwiched between the rings of the PPY* (Figure 2). These conformations are more stable than the nonsandwiched conformations because of the presence of stabilizing CH···O interactions between the anionic enolate oxygen atom and the hydrogen atoms of the rings of the PPY* catalyst.[11,15,16] The ground state (*E*)- and (*Z*)-PPY*-ketene enolates are equally stable ($\Delta\Delta G = 0.3$ kcal mol^{-1}, Figure 2). TSs involving *E* enolates are always more stable than those involving *Z* enolates by about 1–3 kcal mol^{-1}. The *E*-enolate TSs are consistently earlier (shorter pyrrole N–H bonds), and exhibit smaller

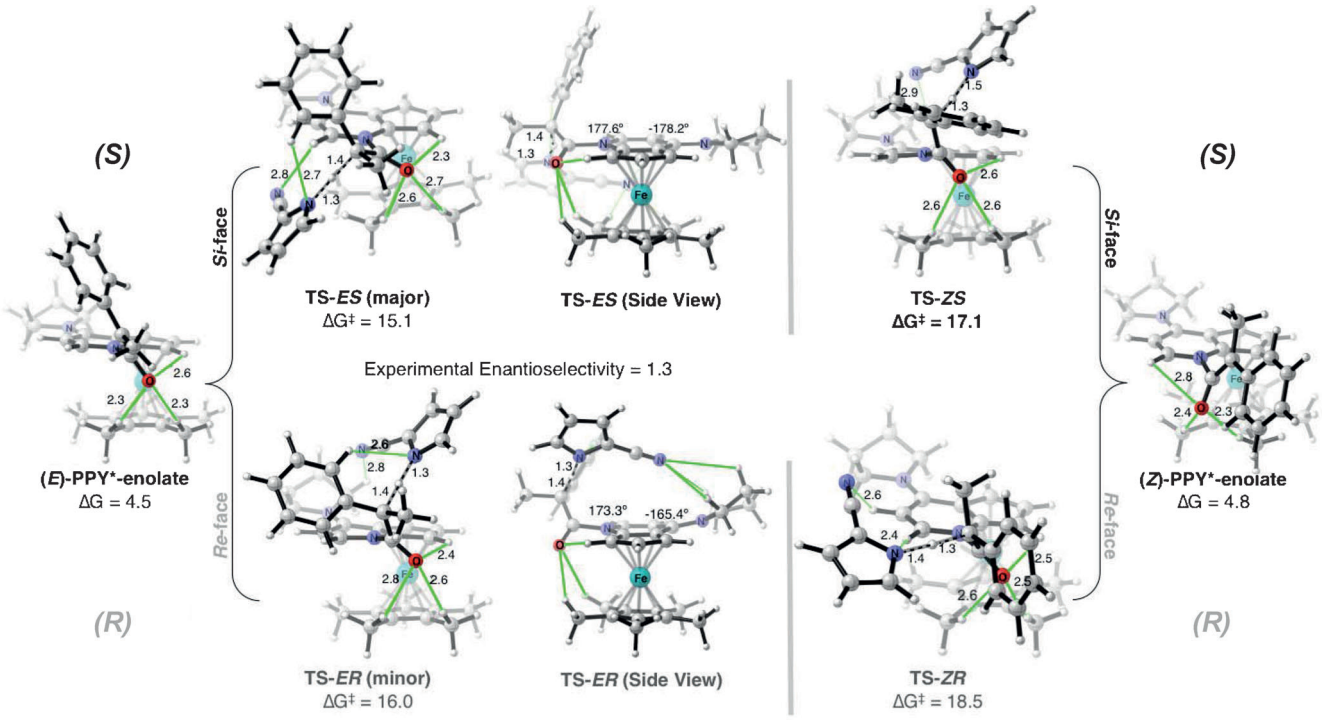

Figure 2. The two PPY* ketene enolates and the corresponding four most stable protonation transition states in the chiral-base mechanism are shown. The *E*/*Z* describes the enolate alkene stereochemistry and the *R*/*S* describes the chirality of the new stereocenter. (*Z*)-PPY*-enolate TSs (right-hand side) are destabilized compared to the analogous (*E*)-PPY*-enolate TSs (left-hand side) because of conjugative neutralization of the enolate reactivity by the Ph. **TS-*ES*** is favored over **TS-*ER*** because of distortions in the catalyst structure necessary to maintain stabilizing CH···O interactions. This is evident in the side view of the two transition states and in the distortion energies of the enolates. Thin grey lines indicate stabilizing CH···O interactions. Grey bonds with dotted line indicate breaking/forming bonds. Energies are in kcal mol^{-1} and distances in Å. All geometries, energies and thermal corrections are from SCS-MP2/def2-∞//B3LYP/6-31G* with PCM solvation corrections for toluene.[19]

pyrrole distortions by about 2–18 kcal mol^{-1} (Figure 1).[11,17] The diminished reactivity of the *Z* enolate stems from stereoelectronic effects.[11,18] In the *Z*-enolate TSs, the enolate reactivity is diminished by conjugation with the ketene Ph substituent. This is in contrast to the *E*-enolate TSs, where the Ph is orthogonal to the enolate π system, and the reactivity remains optimal.

The enantioselectivity of this reaction is ultimately determined by the *re* or *si* approach of the pyrrole to the *E* enolate (**TS-*ER*** and **TS-*ES***, Figure 2). The *re* face of the *E* enolate is more sterically accessible, and yet the pyrrole approach to the *si* face is energetically favored. Upon closer inspection, it is clear that the pyrrolidine of the PPY* in the less favored *re*-face attack (**TS-*ER***) is distorted to stabilize the negative charge of the approaching pyrrole through CH···O interactions (Side View, Figure 2). This is in contrast to the *si*-face attack (**TS-*ES***), wherein the pyrrole is sandwiched between the rings of the PPY* and requires minimal geometric distortion to maintain the stabilizing CH···O contacts. Consistent with these observations, the PPY* ketene enolate is less distorted in the **TS-*ES*** than in the **TS-*ER*** by 6 kcal mol^{-1}.[17]

In conclusion, we have used high-accuracy computational methods to perform an energetically and conformationally exhaustive elucidation of the mechanism and stereocontrol of the addition of pyrroles to ketenes using the planar-chiral 4-(pyrrolidino) pyridine (PPY*) as a catalyst. The computed energies and KIE evidence show that the chiral-base mechanism is operative. The catalyst controls the enantioselectivity through a combination of stereoelectronic effects and CH···O interactions. The former differentiates the *E*/*Z*-catalyst enolates in the transition states, while the latter is responsible for the generation of the all-important PPY* enolate and control of the facial selectivity of the protonation. The themes revealed herein are key to understanding most, if not all, reactions involving ketenes catalyzed by these planar chiral organocatalysts.

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[14] We considered the possibility that the 2-cyanopyrrole tautomer may participate in this reaction. However, the analogous barrier for the pyrrole tautomer was found to be 36.4 kcal mol^{-1} with a KIE of 1:1, which are nearly identical and equally unlikely as the nontautomer mechanism.

[15] These CH···O are weaker than the analogous hydrogen bonds, yet the magnitudes of these interactions have been found to be significant. To verify and quantify their role in this reaction, the CH···O complexes between a hemi-methylated ferrocene and an acetaldehyde enolate or a cyanopyrrole anion were computed. Both complexes exhibited significant electrostatic stabilization arising from CH···O ($\Delta H_{\text{complexation}} < -3.4$ and -2.8 kcal mol^{-1}) in toluene.

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