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# Asymmetric Cooperative Catalysis in a Three-Component Reaction: Mechanism and Origin of Enantio- and Diastereoselectivities

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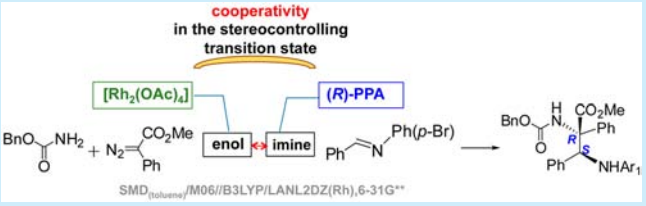
Supporting Information

**ABSTRACT:** Mechanistic insights gained through density functional theory (DFT M06 and B3LYP) computations on a three-component cooperative asymmetric catalytic reaction between a diazo ester, a carbamate, and an imine, catalyzed by dirhodium acetate and chiral phosphoric acid (Brønsted acid), are presented. The addition of the dirhodium-bound enol to the imine yielding an $\alpha,\beta$-diamino ester is energetically more preferred over a potentially competitive protonation of the same enol leading to an $\alpha$-amino ester.

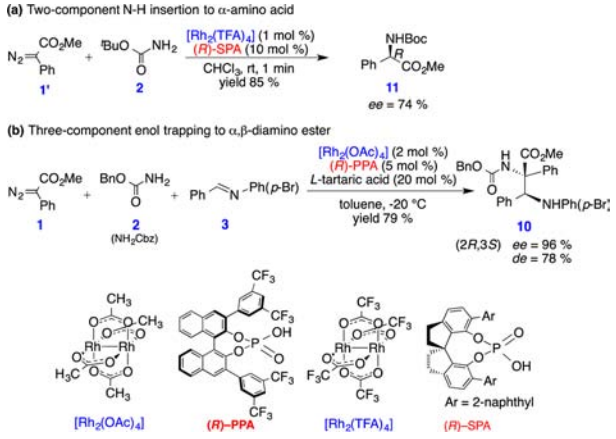



A large number of interesting examples that evolved recently make use of multiple catalysts in one-pot reaction conditions.[1] The individual catalysts chosen in such endeavors have generally been the ones that were well-established candidates as a single catalyst for a given transformation. One of these combinations in cooperative dual catalysis relies on the use of a traditional transition-metal catalyst in conjunction with an organocatalyst. Although such metallo−organo cooperative protocols are in an early stage of development, the approach has already offered access to complex target molecules.[2] A good number of cooperative asymmetric catalytic methods offer a high degree of stereocontrol.[3]

Among the richly diverse group of transition-metal catalysts, dirhodium acetates personify a robust subset that exploits the tunable reactivity of dirhodium carbenoids.[4] Dirhodium carbenoids can be suitably intercepted with a whole gamut of nucleophiles to synthesize several useful target molecules.[5] Quite expectedly, dirhodium carbenoids are now employed under cooperative dual catalytic one-pot conditions with other organocatalysts such as phosphoric acids.[6] In a recent study, Zhou and co-workers have utilized a dual catalytic combination of dirhodium tetra(fluoro)acetate and (*R*)-spinolphosphoric acid in an asymmetric amination reaction between methyl diazo ester (carbenoid precursor) and *tert*-butyl carbamate ($BocNH_2$).[7] In this two-component reaction, as shown in Scheme 1a, the initial adduct formed as a result of carbene insertion into the N−H bond is enantioselectively protonated to yield an $\alpha$-amino ester as the final product with high enantioselectivities. An enantioselective protonation of a dirhodium-bound enol is reported as the key step in the formation of the observed enantiomer.[8]

Quite intriguing is the question of whether the enol (or the generally proposed enolate or even a zwitterionic intermediate) could suitably be made to react with another electrophile such as an imine prior to the protonation event. The reaction could be then steered to proceed in a three-component manner. Such modifications can open up valuable protocols toward more diverse and densely functionalized products.

**Scheme 1. Cooperative Catalysis by $[Rh_2(OAc)_4]$ and Chiral Brønsted Acid in (a) Two-Component N−H Insertion (ref 7) and (b) Three-Component Enol Trapping Reactions (ref 9)**




In an exquisite demonstration, Hu and co-workers showed that dirhodium acetate and chiral phosphoric acid cooperativity can indeed be utilized in a three-component reaction.[9] The reaction, as shown in Scheme 1b, catalyzed by achiral dirhodium acetate and a chiral phosphoric acid, offers a way to combine diazo esters, carbamates, and imines. It provides access to biologically important $\alpha$-substituted $\alpha,\beta$-diamio esters in high enantio- and diastereoselectivities.[10] As with several other cooperative catalytic reactions, mechanistic clarity such as the timing of action as well as the mode of participation of each of the catalysts continues to remain vague.

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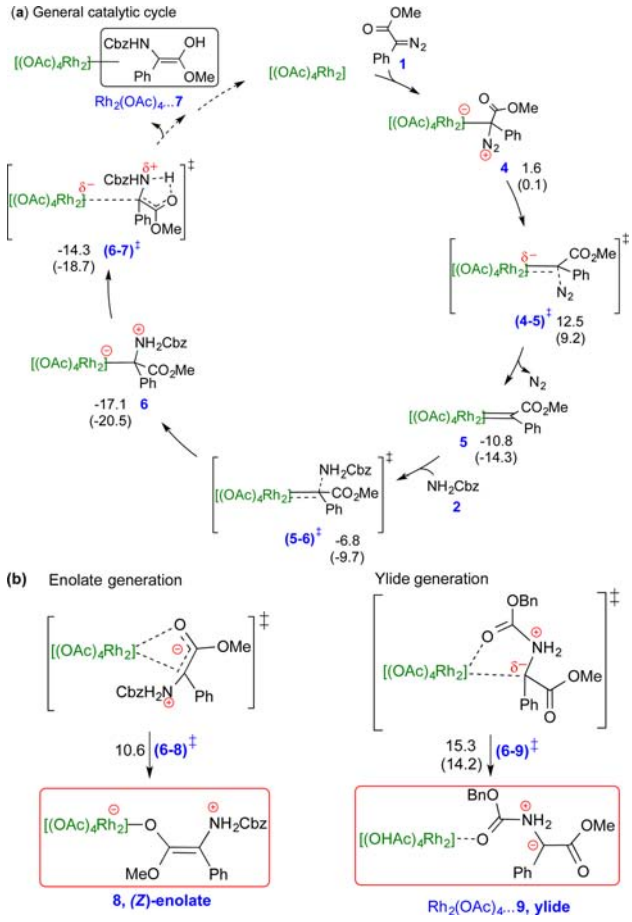
In the conventional mechanism involving dirhodium acetates, the diazo compound is considered to first react with the catalyst to produce a dirhodium carbenoid intermediate. The addition of the nucleophile (carbamate $BnOCONH_2$═$CbzNH_2$)) to the dirhodium carbenoid then produces an important intermediate, which can either be protonated by the chiral phosphoric acid or it can react with the imine (PhHC═N(*p*-Br)Ar). A few vital mechanistic questions are the origin of (i) preferential formation a three-component coupling product with the imine, as opposed to a two-component N−H insertion product, (ii) high degree of *syn* diastereoselectivity as well as the enantioselectivity in favor of the (2*R*,3*S*) product. In keeping with our recent efforts toward understanding the mechanism and stereoselectivity in cooperative asymmetric catalysis,[11] we decided to examine this three-component asymmetric cooperative catalytic reaction by using transition state (TS) modeling at the $SMD_{(toluene)}$/M06//$SMD_{(toluene)}$/B3LYP/def2-TZVP(Rh),6-31G** level of theory.[12] We employ the relative Gibbs free energies, inclusive of thermal and entropic corrections from the gas phase, for our discussion.

The important elementary steps in the mechanism involve (a) the formation of a dirhodium carbenoid (**5**) between the catalyst and the substrate diazo ester, (b) the nucleophilic addition of the carbamate on the carbenoid to produce a zwitterionic intermediate (**6**), and (c) subsequent conversion of **6** to an enol intermediate (**7**) (Scheme 2a). In concert with the earlier reports on the rate-determining step, the TS for the nitrogen extrusion $(\mathbf{4}-\mathbf{5})^{‡}$ leading to the dirhodium carbenoid is found to be of the highest energy.[13] While the mechanistic features are found to be broadly similar to the literature reports, a few interesting variations deserve attention at this juncture. For instance, the zwitterionic intermediate **6** is usually considered to undergo a change of coordination to give an O-(*Z*)-enolate **8**[6a,b,7,9,14] or even convert itself to an ylide **9**.[15] The TS energies, as summarized in Scheme 2b, conspicuously suggest that the formation of **8** and **9** has higher energy demands, and hence, the most favorable pathway should be regarded as an intramolecular proton transfer to give an (*E*)-enol intermediate **7** (Scheme 2a).[16]

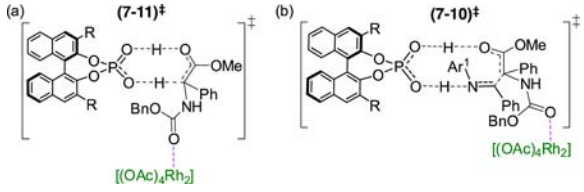
In view of the energetic advantage toward the formation of the (*E*)-enol intermediate, the ensuing steps of the reaction are expected to depend on the reactivity of this species. There could be two major pathways **7** can now follow. It can either react with the electrophilic imine or undergo a protonation to another product without the participation of the imine. In the former case, the electrophilicity of the imine can be enhanced by Brønsted acid activation by the phosphoric acid. The reaction of the activated imine with the amino enol, as shown in Scheme 3, is the vital step that controls the stereochemical outcome of the reaction. In this three-component pathway, the trapping of the imine by the amino enol intermediate (**7**) would result in the formation of the *α*,*β*-diamino ester (**10**) with two new chiral carbon atoms. On the other hand, if the phosphoric acid protonates the amino enol intermediate at the phenyl bearing *α*-carbon atom, the resulting product will then be an *α*-amino ester (**11**). Interestingly, enantioselective formation of *α*-amino esters have earlier been noted under similar reaction conditions.[7] Hence, a comparison of the computed energetics is undertaken to establish the relative preference between protonation (effectively leading to an N−H insertion product) and imine trapping, as these could result in potentially competitive pathways.

**Scheme 2. (a) Catalytic Cycle for the $[Rh_2(OAc)_4]$ Catalyzed Reaction between $PhC(N_2)CO_2Me$ and $BnOCONH_2$. (b) Generation of Enolate (8) and Ylide (9)[a]**




[a]The relative free energies (in kcal/mol) with respect to the separated reactants, respectively, at the $SMD_{(toluene)}$/M06//$SMD_{(toluene)}$B3LYP/def2-TZVP(Rh),6-31G** and the $SMD_{(toluene)}$/M06//B3LYP/LANL2DZ(Rh),6-31G** Levels of Theory are given in and out of parentheses.

**Scheme 3. Stereocontrolling Transition States for (a) N−H Insertion and (b) Imine Trapping Reactions**




The relative free energies of the TSs for the N−H insertion ($(\mathbf{7}-\mathbf{11})^{‡}$) and imine trapping ($(\mathbf{7}-\mathbf{10})^{‡}$) are provided in Table 1. Two types of TSs, without a bound dirhodium (designated as type I) and when the dirhodium is bound to the carbonyl oxygen of the Cbz group of the substrate (type II), are considered. The type-II TSs are generally of lower energy, suggesting that dirhodium binding to the substrate is preferred.[17] We have employed activation strain analysis to examine the role of distortion of catalysts and reactants in the stereocontrolling TSs.[18] The type-I *re-re*-$(\mathbf{7}-\mathbf{10})^{‡}$ is found to be more distorted (~17 and 42 kcal/mol, respectively, for (*R*)-PPA and enol) than the corresponding TS in type II. The difference in the distortion



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**Table 1. Relative Free Energies (in kcal/mol) of the Stereocontrolling Transition States Obtained at the $SMD_{(toluene)}$/M06//B3LYP/LANL2DZ(Rh),6-31G** Level of Theory with Respect to the Separated Reactants for (a) Protonation of Amino Enol and (b) Reaction with Imine**

| entry | type of TS/addition [a] | I | II [c] | stereo-isomer [e] |
|---|---|---|---|---|
| | **(a) N-H insertion [b]** | | | |
| 1 | ***re*-(7-11')$^{\ddagger}$** | -13.4 [-6.9] | -11.6 (-15.8) [-5.1] | *S* |
| 2 | ***si*-(7-11)$^{\ddagger}$** | -16.2 [-8.6] | -18.6 (-23.1) [-10.2] | *R* |
| | **(b) Imine trapping** | | | |
| 3 | ***re-re*-(7-10)$^{\ddagger}$** | -14.1 | -21.6 (-25.8) | 2*R*,3*S* |
| 4 | ***si-si*-(7-10')$^{\ddagger}$** | -15.7 | -16.7 (-19.1) | 2*S*,3*R* |
| 5 | ***re-si*-(7-10")$^{\ddagger}$** | -15.8 | -14.7 (-19.9) | 2*R*,3*R* |
| 6 | ***si-re*-(7-10"')$^{\ddagger}$** | -18.9 | -18.7 (-) [d] | 2*S*,3*S* |

[a]Type-I refers to the reaction of a free enol without the dirhodium acetate whereas type-II is a Cbz-bound dirhodium acetate. [b]The relative Gibbs free energies of transition states in the presence of a bound imine are provided in square brackets. [c]The relative Gibbs free energies obtained at the $SMD_{(toluene)}$M06//$SMD_{(toluene)}$B3LYP/def2-TZVP(Rh),6-31G** level of theory is in parentheses. [d]Could not be located even after repeated attempts. [e]Experimental major stereoisomer for imine trapping is 2*R*,3*S* (*ee* = 96%, *de* = 78%). In a related experiment, the N−H insertion product with *R* configuration is observed (*ee* = 74%) (ref 7). The prochiral notations respectively represent the enol and the imine in the C−C bond formation.

between type-I and type-II TSs is lesser in the case of other stereochemical modes of addition.[17] The more important aspect is to note that the most preferred TS for the reaction of the amino enol with the activated imine (***re-re*-(7−10)$^{\ddagger}$**) is significantly lower than that for the enantioselective protonation (***si*-(7−11)$^{\ddagger}$**).

It is also likely that the reactant imine could remain passively bound to the catalyst in the N−H insertion TSs, although it may not participate in the reaction. A more interesting comparison between the N−H insertion and imine trapping pathways would be consider the role of passive imine in the latter pathway. We note that the N−H insertion TSs (**(7−11)$^{\ddagger}$**), when the imine interacts with (*R*)-PPA, are of higher energies than the TSs for the imine trapping (**(7−10)$^{\ddagger}$**). These values are provided in square brackets in entries 1 and 2 in Table 1.[19] This prediction clearly indicates that the three-component imine-trapping pathway responsible for the formation of *α*,*β*-diamino ester is energetically more preferred over a two-component protonation route.

It can be gleaned from Table 1 (entry 6) that the lowest energy type-I TS in the three-component reaction belongs to the *si-re* mode of addition. This results in an incorrect prediction of the configuration of the new chiral carbon atom in the product. Interestingly, within type-II TSs, the *re-re* mode is the most preferred one (entry 3). This *re-re* stereochemical mode of C−C bond formation between the amino enol and the imine corresponds to 2*R*,3*S* configuration of the product, consistent with the experimental observation.[9] In other words, the correct stereochemical outcome could be reproduced only with dirhodium acetate binding to the substrate (via type-II TS). We note that the computed de (∼99%) is higher than the experimental value (78%). The role of dirhodium acetate, as noted here, is a significant insight relating to the emerging group of multicatalytic reactions wherein the question of whether both catalysts are involved in the stereocontrolling step of a reaction or not, has not been adequately addressed. In the present reaction, the stereocontrolling step enjoys the participation of both dirhodium acetate and chiral phosphoric acid catalysts, serving as an example of true cooperative dual catalysis.

In the case of the two-component product formation, the protonation at the *si*-face of the amino enol (entry 2) is found to be the most preferred mode leading to an *R* enantiomer of the *α*-amino ester (N−H insertion product). Both type-I and type-II TS models provide correct stereoselectivities. The computed sense and extent of enantioselectivity are also noted as consistent with a related set of earlier experiments conducted in the absence of an imine.[7,8]

After having identified the energetic preference for the formation of *α*,*β*-diamino ester, we have examined the factors responsible for the origin of stereoselectivity. Two new chiral carbon atoms are generated as a result of the addition of the prochiral carbon of the amino enol to that of the imine. The *re-re* mode of C−C bond formation is found to enjoy additional stabilization due to a number of favorable interactions between the substituents of the axially chiral (*R*)-phosphoric acid and the reactants (both imine and enol).[20] The activation strain analysis of the enantiocontrolling TSs ***re-re*-(7−10)$^{\ddagger}$** and ***si-si*-(7−10′)$^{\ddagger}$** revealed a larger distortion (∼27 kcal/mol) in the higher energy *si-si* mode of addition.[21] The geometric distortion is primarily located on the catalysts (*R*)-PPA (7 kcal/mol) and dirhodium-bound enol (7) (22 kcal/mol). To convey these vital geometric distortions, distortion coordinates $\omega_1$, $\omega_2$, and $\omega_3$ as shown in Figure 1, are chosen. The larger distortions of both (*R*)-PPA and enol in the higher energy TS are quite evident. Thus, the relative distortion of the chiral phosphoric acid (*R*)-PPA and the dirhodium-bound enol (7) plays a vital role toward influencing the energy ordering of the stereocontrolling TSs. The interaction energy noted in ***re-re*-(7−10)$^{\ddagger}$** is lower than those in the other TSs, suggesting that the destabilization due to fragment distortions overwhelms the stabilization provided by improved interactions in *si-si*, *re-si*, and *si-re* TSs. The lower energy TSs reported herein are obtained through conformational search by varying the critical dihedral $\omega_3$. The range of $\omega_3$ appears to remain rather narrow, as the initial guess geometries with larger deviations converged to the lowest energy TS or failed to optimize to a TS geometry.

We have also examined whether the coordination of a second ligand on the other end of the dirhodium carbenoid (also known as diaxial coordination) in the stereocontrolling step. The relative energy differences between stereocontrolling TSs suggested similar trends and hence predicted a similar stereochemical outcome in the imine trapping pathway, as noted without the diaxial coordination.[22]

In conclusion, the mechanistic investigations on a dual catalytic three-component reaction involving $[Rh_2(OAc)_4]$ and a chiral phosphoric acid suggest a cooperative participation of both catalysts in the stereocontrolling step of the reaction. The reactant diazoester is activated in the form of dirhodium carbenoid while the imine enjoys Brønsted acid activation. Comparison of relative Gibbs free energies revealed a preference for enol trapping process wherein it reacts with an activated imine (three-component reaction) rather than undergoing a potentially competitive protonation of the enol to furnish an N−H insertion product (two-component reaction).



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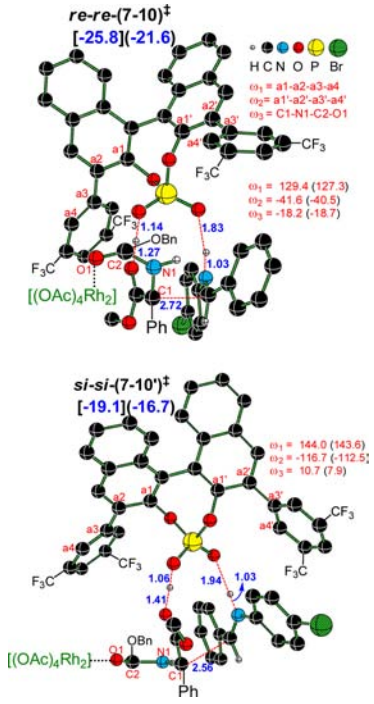


**Figure 1.** Optimized geometries of the stereocontrolling C−C bond formation and relay proton transfer TSs in the imine-trapping process. The values in square brackets and parentheses are, respectively, the relative Gibbs free energies obtained at the $SMD_{(toluene)}$/M06//$SMD_{(toluene)}$B3LYP/def2-TZVP(Rh),6-31G** and $SMD_{(toluene)}$/M06//B3LYP/LanL2DZ(Rh),6-31G** levels of theory. The distances and angles are, respectively, in angstroms and degrees. Only select hydrogens are shown.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01765.

Optimized geometries and additional schemes, figures, and tables (PDF)

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### Notes

The authors declare no competing financial interest.

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(14) The TS for the formation of (*E*)-enolate is only 25.2 kcal/mol higher in energy. See Figure S1.

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(16) (a) A relay proton transfer pathway promoted by L-tartaric acid is noted to be of higher energy. See Figure S1.. (b) The TS for the formation of *Z*-enol through a relay proton transfer enabled by the phosphoric acid is found to be of 8.1 kcal/mol higher energy. SeeScheme S1..

(17) Type-II TSs enjoy an enthalpic advantage over Type-I TSs due to the interaction of $[Rh_2(OAc)_4]$ with (a) the substrate and with (b) *R*-PPA. See Table S1. Details of the distortion analysis are provided in Table S2.

(18) (a) In activation strain analysis, the activation barrier ($\Delta E^{\ddagger}$) is partitioned into (i) destabilizing distortion of the reactants ($\Delta E^{\ddagger}_{d}$) with respect to their ground-state geometries and that in the TSs and (ii) the stabilizing interaction energy between such distorted reactants ($\Delta E^{\ddagger}_{i}$) as seen in the TS geometry [$\Delta E^{\ddagger} = \Delta E^{\ddagger}_{d} + \Delta E^{\ddagger}_{i}$]. (b) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12664. (c) Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114. (d) Diefenbach, A.; Bickelhaupt, F. M. *J. Phys. Chem. A* **2004**, *108*, 8460. (e) Fernández, I.; Bickelhaupt, F. M. *Chem. Soc. Rev.* **2014**, *43*, 4953.

(19) See Figure S4.

(20) The $-CF_3$ groups of the aryl substituents on both the arms of the chiral phosphoric acid hold the imine and enol in the chiral pocket in ***re-re*-(7−10)$^{\ddagger}$** through various weak interactions. More details are provided in Figure S5.

(21) (a) The distortions of 18.9 and 18.7 kcal/mol, respectively, were noticed in the other diastereomeric TSs ***re-si*-(7−10″)$^{\ddagger}$** and ***si-re*-(7−10‴)$^{\ddagger}$**.. (b) All diasteromeric TSs are provided in Figure S6. For more details, see Figures S7 and S8 and Table S3..

(22) See Table S4.



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