Catalytically Active Species in Copper/DiPPAM-Catalyzed 1,6-Asymmetric Conjugate Addition of Dialkylzinc to Dienones A Computational Overview

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Catalytically active species in Copper/DiPPAM-Catalyzed 1,6-Asymmetric Conjugate Addition of Dialkylzinc to Dienones: a computational overview.


Abstract: Four different catalytically active species are computationally examined in order to investigate the mechanism of Cu/DiPPAM-catalyzed 1,6-conjugate addition of dialkylzinc to acyclic dienones. A DiPPAM-bridged Cu(alkyl)-Zn(acetate) bimetallic complex exhibits the best catalytic activity, which can be associated with the best balance between the stability of the dienone adduct and its activation by copper. The selectivities (regio- and enantioselectivity) associated with the retained mechanism are investigated by DFT calculations and successfully compared to experimental data, including the critical influence of the substituents within the diene on the regioselectivity and the obtained enantioselectivity for the formation of one 1,6-adduct.

Introduction

Copper-catalyzed Asymmetric Conjugate Addition (ACA) to electro-deficient substrates is an efficient method to form C-C bonds.[1-2] The 1,6-addition to α,β,γ,δ-dienone is especially challenging, as a complete regiocontrol is difficult to reach because of the presence of numerous active sites. However, 1,6-ACA has been described with a range of electrophiles, nucleophiles, metal-based catalysts, and chiral ligands families.[3-9] Mauduit et al. have developed an efficient chiral tridentate P,N,O ligand, named DiPPAM (DiPhenylPhosphinoAzoMethyline salt L1),[10] which has proved its efficiency for copper-catalyzed 1,6-ACA of dialkylzinc reagents to cyclic[5-7] and more recently to acyclic[11-13] dienones (Scheme 1). While good to excellent regioselectivity and enantioselectivity could be achieved with this catalytic system, attempts to characterize intermediates were unsuccessful and the active catalytic species has remained unidentified.

On the other hand, mechanistic investigations on conjugate addition were previously undertaken in the case lithium organocuprate as nucleophiles, resorting on kinetic[14] NMR spectroscopy[15-18] studies. The rate-determining step is the C-C bond formation as described by investigations on kinetic isotope effects and activation parameters. In addition, the formation of a π-complex between copper and C-C bond was predicted by NMR studies.[17-19,20] These data are completed by computational studies.[21-26] The mechanism comprises different steps: the formation of the lithium organocuprate, the coordination of the carbonyl compound as a π-complex, an oxidative addition to form a Cu(III) intermediate (Figure 1, a), followed by a reductive elimination corresponding to the C-C bond formation.

For Cu-catalyzed ACA, the nature of the catalytically active species becomes a major question. Whereas a Cu(II) salt is generally used as the precatalyst, a Cu(I) complex is considered to be the active species,[1] in line with NMR and EPR evidences supporting the reduction of Cu(II) to Cu(I).[27] In this context, a halide-bridged bimetallic monocuprocopper is proposed for bidentate phosphine ligand (Josiphos) when resorting to a Grignard reagent (EtMgBr) as an alkyl source (Figure 1, b).[28] A similar intermediate was more recently described within the framework of the first direct experimental detection of transmetalation intermediates in copper-catalyzed addition reaction using the monodentate phosphoramidite ligand and diethylzinc as nucleophile.[29] Nevertheless, another bimetallic intermediate was detected in the latter study, this time exhibiting two Cu centers and three phosphine ligands. Two Cu centers are also present in the [Zn(μ-X)Cu(μ-X)CuR] trimetallic structure proposed as a catalytically active species (Figure 1, c) from a computational point of view by Calhorda et al. In this case, intermetallic bridge X can be a variety of suitable ligand, like an acetate (or thiophene carboxylate, triflate, ...).[30]

Scheme 1. Cu(OTf)2/DiPPAM L efficiently catalyzed 1,6-ACA of dialkylzinc reagents to cyclic and acyclic α,β,γ,δ-dienones.

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Supporting information for this article is given via a link at the end of
Having these features in mind, our group has recently proposed a mechanism for Cu-catalyzed ACA of dialkylic zinc to dienones using anionic and chiral ligands as a bridge between the Cu and Zn centers.\cite{31,32} This model was found to be applicable to a variety of ligands (Figure 2, a), as both DiPPAM L or hydroxylalkyl N-Heterocyclic Carbene ligands (NHC), and to different electrophiles (cyclic and acyclic dienones with various substituents). The relevance of this catalytic active species was supported by the good agreement with selectivity between experimental observations and calculations. Indeed, it was used to rationalize the effect of the nature of the substituent at C=C position in substrate on the regioselectivity towards 1,4- or 1,6-conjugate addition,\cite{31} evidencing the possibility for an electron-rich substituent (methyl-imidazole for instance) to establish an interaction with the electro-deficient copper. The same model also allowed to reproduce and analyze the enantioselectivity of the ACA, which was proposed to originate from a stabilizing π-stacking network in the π-complex.\cite{32} Nevertheless, no experimental or computational evidences were available to support the nature of the postulated intermediates.

In this paper, we aim at determining the origin of the catalytic activity through comparison of various reaction mechanisms. In a first part, the origin of the regio- and stereo-control is determined for ACA of ZnEt$_2$ to cyclic α,β,γ,δ-diene-1,4 with a variety of ligands as a bridge between the Cu and Zn centers.\cite{31,32} Two dienones were considered which differ by the groups at terminal position (R$^1$) and at C=O function (R$^2$). When the reaction was performed at room temperature with 1a, very good regioselectivity (98:2) with good yield (70%) was obtained in favor of the 1,6-product with a large enantiomeric excess (92%). When the positions of the methyl and phenyl groups were exchanged (1b), very different results were obtained as both yield (30%), regioselectivity (30:70) and enantioselectivity (53% ee) were found to be moderate. We thus undertook a systematic study of the reaction path in 1a to better determine the origin of the excellent selectivities.

### Results and Discussion

#### Regio- and enantio-selectivity in acyclic ketones.

The copper-catalyzed asymmetric addition of ZnEt$_2$ to (3E,5E)-trideca-3,5-dien-2-one (1) had previously been experimentally investigated using L-DiPPAM L (Table 1).\cite{11} Two dienones were investigated using L-DiPPAM L and DiPPAM for instance) to establish an interaction with the electro-deficient copper. The same model allowed to reproduce and analyze the enantioselectivity of the ACA, which was proposed to originate from a stabilizing π-stacking network in the π-complex.\cite{32} Nevertheless, no experimental or computational evidences were available to support the nature of the postulated intermediates.

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#### Table 1. CuDiPPAM-catalyzed enantio-selective 1,6-addition of ZnEt$_2$ to linear dienones.\cite{11}

<table>
<thead>
<tr>
<th>Dienone</th>
<th>R$^1$/R$^2$</th>
<th>2/3 ratio</th>
<th>Yield$^4$ [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me/Ph</td>
<td>98:2</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td>1b</td>
<td>Ph/Me</td>
<td>30:70</td>
<td>37</td>
<td>53$^4$</td>
</tr>
</tbody>
</table>

*For the 1,4-adduct
Similarly to our previous studies as well as in the study reported by Nakamura et al.,[33] the C-C bond formation step takes place in a bimetallic species (Figure 3 and Table S1, for detailed geometrical parameters in SI), in which DIOPAM ligand is the only bridge between Cu and Zn centers. As Zn(II) is coordinated to the carboxylate arm and an alkyl chain, whereas Cu(I) is bonded to the phosphine site and another alkyl chain, this heterobimetallic species is formally composed of two neutral metal centers. Bonding of the electrophile (1a) at the Zn(II) center through one of the carbonyl lone pair is referred to I₀. An additional binding is observed as the C=C bond of 1a comes into interaction through a π-bond with the Cu(I) center, resulting in intermediate I₄ when 1,4-addition is examined, and I₆ in the case of 1,6-conjugate addition. I₄ and I₆ intermediates are in equilibrium as they are isoergic, with an exchange between the two structures exhibiting a Gibbs free energy equal to 13 kcal.mol⁻¹ which proved to be lower than the C-C bond formation step. In contrast, I₆ is found to be significantly destabilized (ΔrG = + 7.2 kcal.mol⁻¹) and its formation is disfavored (TS₄ higher than C-C bond formation in TS₆₄). The C-C bond formation profile (in red for 1,4- and in blue for 1,6-conjugate addition in Figure 3) clearly suggests that the most favorable pathway is the 1,6-conjugate addition from both thermodynamic (as the enolate product P₆ is more stable than P₄ by 7.2 kcal.mol⁻¹) and kinetic (as TS₆₄ is lower than TS₄₆) points of view. It is in line with previous theoretical studies for addition of Me group at the terminal C=C bond of penta-2,4-dienal in a cuprate aggregate model.[34] This can be associated to the loss of conjugation during the 1,4-addition, which is already well advanced in TS₄₆, as highlighted by the evolution of the C₉=C₈ bond length along the 1,4-addition pathway (1.36 Å in I₄, lengthened to 1.42 Å through formation of the π-adduct in I₄, quasi-single with 1.47 Å in TS₆₄ compared to 1.53 Å for the C₈=C₇ single bond in the product P₄). These conjugation effects fully justify the strong difference observed between 1a to 1b. In 1b, in the case of 1,6-addition, the C-C bond formation fully breaks the conjugation of the phenyl group with the π system whereas, in the 1,4-addition, conjugation of the terminal C=C bond with Ph is kept. Conjugation is thus proposed to be the factor tuning regioselectivity between 1a and 1b, in parallel to the already observed ligand effects (reported for BINAP)[11] or to the additional substrate-catalyst interaction (reported for Acyl-N-methylimidazole).[35] This is confirmed by computations on a simple model including only electronic effects in 1a and 1b (see Tables S2-S4 in SI).

Figure 3. DFT calculations on the regioselectivity of the copper-catalyzed addition of diethylzinc to α,β,γ,δ-unsaturated dienone 1a (R¹=Me ; R²=Ph): Gibbs free energy (in kcal.mol⁻¹) profile of the C-C bond formation steps relative to separated Cu(L-DIOPAM), ZnEt₂ and 1a.
We next investigate the origin of the enantioselectivity of the 1,6-addition to dienone 1a using the previously reported results showing that it is possible to predict the experimentally formed enantiomer from the stability of adduct I6.[35] Such an approach proved efficient in the case of cyclic dienone in agreement with the VCD and X-ray data,[32] provided an adapted computational level (dispersion correction was added to DFT calculations, see Computational Details) and an adapted docking procedure are used. Indeed, it appeared necessary to envision not only the two potential docking sides of the C=C double bond, but also all possible conformations relative to the C(0)-Cα and Cβ-Cγ bonds, as the most stable structure of the free ketone is not necessarily the one preferred in the bimetallic π-complex. In the case of acyclic ketones, a similar study was thus undertaken, which required investigation of a larger number of conformers as both C(0)-Cα and Cβ-Cγ single bonds can afford both s-cis and s-trans conformations (Figure 4).

![Figure 4](image-url)

Figure 4. Eight possible structures computed for I6 with L = L-(S)-DiPPAM and acyclic dienone 1a in the various conformations of the C-C single bonds. Structures on the left yield the S enantiomer and those on the right lead to the R. Energies (in kcal mol⁻¹) are given with respect to structure (a).

Eight structures of the π-complex I6 were computed, corresponding to the two docking sides for the four possible conformations of the substrate, introduced in Figure 4 and noted CT, TT, TC and CC. These structures are expected to be in fast equilibrium, considering the high C-C bond formation barriers compared to the coordination/coordination of the ketone to the bimetallic complex reported above. The CT conformer is the most stable for the free dienone (by 1.3 kcal.mol⁻¹ compared to the TT analogue). This preference is conserved in I6 intermediates. The most stable arrangement calculated is affiliated with the formation of the S-enantiomer (structure (a) in Figure 4) and this strong (> 4 kcal.mol⁻¹) preference is conserved when adding entropic contributions (See SI, Figure S1). An NCI analysis, given in Figure 5, allows determination of the origin of this preference thanks to the observation of two characteristic non-bonding isosurfaces. This conformer seems to be stabilized by CH-π interaction between the C-H bond of tert-butyl group and a phenyl group of diphenylphosphino moiety. A second π-π interaction is observed between C=C bond of substrate and imine group of DiPPAM ligand. This network of CH-π interactions (in SI, Figure S2) is similar to that obtained in the intermediate with cyclic dienone.[32] As conclusion, the enantioselectivity of the addition is controlled by two main non-covalent interactions, one ensuring the folding of the DiPPAM ligand (CH-π interaction) and one associated with the docking of the ketone and related to the interaction of its unsaturated π system with the C=N bond of DiPPAM.

An experimental derivatization was initiated to confirm the enantioselectivity obtained from DFT calculations. In order to access to the absolute configuration of 2a obtained from Cu/L-DiPPAM catalyzed 1,6-ACA to 1a, the former was converted to the known ester 4[36] following a slightly modified described procedure (Scheme 2 and Experimental Section).[37]

![Scheme 2](image-url)

Scheme 2. Experimental process to determine the absolute configuration of 2a.
The literature reported an $S$ absolute configuration with a positive rotation ($[\alpha]_D^{20} = +10.0$ (c 1.0, CHCl$_3$))\textsuperscript{[38]} In our case, compound 4 obtained from 2a have the same sign, confirming $S$ is the major enantiomer for 2a. The evaluated value for $[\alpha]_D^{21} = +6.0$ (c 1.0, CHCl$_3$) is consistent with 85% ee obtained for 2a. Thus, a (S) configuration can be assigned to compound 2a, in accordance to the calculated data.

**Alternative mechanisms.**

The mechanism proposed above, based on the similarity with previous studies,\textsuperscript{[21-28]} nicely confronts to experimental selectivity data (regio- and enantio-selectivity). It nevertheless relies on a catalytically active species (bimetallic Cu-Zn complex of DiPPAM) which could not be characterized through experimental analysis. We thus decided to undertake theoretical mechanistic investigations of the 1,6-addition pathway to understand the electronic factors governing the formation and activation with this catalytic intermediate. This interpretative part of the theoretical study was carried out using models compounds including all electronic effects but minimizing steric ones: ZnMe$_2$ is reacted in the presence of a copper (I) complex and a model of DiPPAM ligand (M), for which the tert-butyl group as well as the phenyl group at the phosphine are replaced by hydrogen atoms. This small model provides similar result to the full one in the case of the addition to 1a (Figure S3 and Table S5).

Three alternative mechanisms are envisioned for the 1,6-conjugate addition. The first one (going through intermediate J, Figure 6) is deduced from direct interaction of the ZnMe$_2$ with a preformed Cu(M) complex without methyl transfer from Zn to Cu. Cu is thus bonded to the phosphine chain of the DiPPAM whereas ZnMe$_2$ interacts with the carboxylate arm. The second one (K in Figure 6) is similar to I$_0$ except for the exchange of the Cu and Zn binding sites. The last one is obtained from I$_0$ through decoordination of the ZnMe$^+$ center from the carboxylate arm of the DiPPAM to form a separated ion pair (L in Figure 6).

Detailed studies of the energetics and structural features associated to these three mechanisms are next reported. (Figure 7, complete data in SI, Tables SS-S6). In order to better characterize the docking of the dienone in the intermediates given in Figure 5, the associated Cu-Zn bimetallic complexes have also been optimized (Figure 8).

**Mechanism through J.** The docking of the carbonyl compound to Cu(M) forms intermediate noted I$_0$ in Figure 7, b. As expected, no interaction of Zn center with C=C bond could be obtained.\textsuperscript{[38]} In this case, Cu plays the role of Lewis acid while Zn acts as a Me donor. The sole coordination energy of the C=O bond to copper in I$_0$ can be evaluated relative to C$_2$ to -6.6 kcal mol$^{-1}$. In contrast, substrate binding to I$_0$ forms a coordination of the C=O to Zn and of the C=C to copper, leading to an overall interaction energy computed with respect to C$_0$ of -11.1 kcal mol$^{-1}$. It is found to be the quasi-additive contribution of the sole coordination of the C=O to Zn in I$_0$ ($\Delta$E = -6.6 kcal mol$^{-1}$ with respect to C$_0$) and of the binding of the double bond to Cu (-3.9 kcal mol$^{-1}$ for binding of ethylene to (Me)Cu(M)).\textsuperscript{[39]} Intermediate I$_0$ allows thus both a good coordination of the C=O to the metal center and a significant coordination of the $\pi$ system to Cu. Let us nevertheless notice that the strong binding of the carbonyl compound in I$_6$ is associated with a large entropic loss compared to I$_0$, for which more degrees of freedom of the carbonyl chain are kept. As a consequence, similar Gibbs energies with respect to separated reactants were found for I$_0$ and I$_6$ (7.2 kcal mol$^{-1}$). Discrimination between these two mechanisms thus originated from kinetic factors. The activation barrier in the non-transmetalated mechanism is equal to 27.2 kcal mol$^{-1}$ relative to I$_0$, so that TS$_J$ is significantly higher than TS$_{CuMe}$ (in Figure 7, a. associated with 17.5 kcal mol$^{-1}$ barrier). TS$_J$ is found to be a little more reactant-like, as evidenced from the shorter C$_2$ bond (1.403 Å in TS$_J$ in comparison with 1.466 in TS$_{CuMe}$), in line with the strongest exothermicity of the reaction and the Hammond postulate. This structural feature is in fact associated with absence of activation of the C$_2$ bond in I$_6$ (1.345 Å, which is similar to the free electrophile) as expected in absence of interaction between the metal center and the double bond. We can thus propose that this mechanism, in which I$_0$ is a non transmetalated species, is not effective because i) copper cannot act as an efficient Lewis acid and ii) there is no activation of the C=C bond in I$_6$.

![Figure 6. Proposed alternative intermediates. [Zn] refers to Zn(II) coordinated to explicit solvent molecules (taken as OMe).](https://example.com/figure6.png)

![Figure 8. Optimized intermediates without docking of dienone (energies are given relative to the separated reactants Cu(M) + ZnMe$_2$).](https://example.com/figure8.png)
Mechanism through K. As the docking of the carbonyl compound takes place in a transmetalated species (only one alkyl group on Zn), the roles of the two metal centers in \( \text{I}_K \) are very similar to those in \( \text{I}_6 \): Cu is a C=C bond activator and Me donor while Zn, coordinated to the carbonyl compound, acts as a Lewis acid. The docking of the substrate in \( \text{I}_K \) is also similar to that stated in \( \text{I}_6 \), with the coordination of C=O to Zn and C=C bond to Cu. Nevertheless, due to the exchange of the bonding environment in \( \text{I}_6 \) and \( \text{I}_K \), the \( \text{C}_\gamma=\text{C}_\delta \) bond distance (1.421 Å) is longer in \( \text{K} \) than that obtained in \( \text{I}_6 \) (1.410 Å) suggesting that the coordination of Cu to the carboxylate arm of \( \text{M} \) increases its activating potential, in line with an anionic cuprate formal charge and thus a cuprate character in this intermediate. Consistently, the \( \text{C}-\text{C} \) bond formation exhibits a lower activation barrier with respect to the docking intermediate (15.7 kcal. mol\(^{-1}\) in Figure 7, c compared to 17.5 kcal. mol\(^{-1}\) calculated above). Increasing the cuprate character and Lewis acidity favor kinetically the step of \( \text{C}-\text{C} \) bond forming (\( \text{TS}_K \)). Consequently, the decrease of the activation barrier between \( \text{I}_K \) and \( \text{TS}_K \) is lost by the destabilization of the adduct \( \text{I}_K \), already evidenced in the bimetallic catalyst \( \text{C}_K \).

Mechanism through L. The activation at stake in reaction path \( \text{K} \) relies on the synergetic double activation of the carbonyl compound by a Lewis acidic cation and a strong back donation of the electron rich copper center toward the C=C double bond.\(^{[26]} \) To obtain the best of this effect, an “extreme” mechanism was thus searched using a ZnR\(^+\) entity as an activating cation and docking the C=C double bond to the \([\text{Cu(M)}\text{R}]^+ \) cuprate. The resulting docking intermediate is noted \( \text{I}_L \) in Figure 7, d. Intermediate \( \text{I}_L \) has a tetracoordinated geometry, in which the copper center is bonded to the phosphine and carboxylate groups of the ligand (\( \text{M} \)), to a methyl, and to the \( \text{C}_\delta \) terminal atom of substrate according to a short Cu-\( \text{C}_\delta \) distance of 2.017 Å. The square planar geometry of Cu and the pyramidalization of \( \text{C}_\delta \) in \( \text{I}_L \) confirms a strong back-donation of copper toward the dienone and thus a Cu(III) nature of the intermediate. The efficiency of this electron transfer in activating the electrophile is confirmed by the small activation barrier for C-
C bond formation (6.4 kcal.mol⁻¹), which is found to be 9.3 kcal.mol⁻¹ lower than the smallest found up to now, in the case of mechanism K. Nevertheless, intermediate L is very high in energy relative to L₂ (+31.3 kcal.mol⁻¹), as could be expected from the decoordination of the Zn center from the DIPPMAM ligand. Considering that this is associated to a very strong Lewis acidity of the ZnMe⁺ entity and that the reaction takes place experimentally in ethereal solvent, an explicitly solvated model must be used to counterbalance this decooordination. Two molecules of dimethylether, as a model of solvent, namely MeTHF, are added to the ZnMe⁺ moiety and decrease the energies of L, TS₁ and P₁ by 10 kcal.mol⁻¹ with respect to their analogues in gas phase (See SI, Table S7). Addition of single point implicit solvation to the latest model does not change the conclusions and mechanism through L remains higher than in our proposed mechanism (See SI, Table S7).

As a conclusion, we have examined four bimetallic mechanisms, using either Zn (mechanism J) or Cu as a nucleophilic center. The absence of C=C activation in the former increases significantly its activation barrier and disfavors this pathway. The three nucleophilic-Cu mechanisms differ by an increasing cuprate character, which is associated with lowering of activation barrier. Nevertheless, associated intermediates are at the same time destabilized. It thus appears that the preferred reaction pathway results from an equilibrium between the stability of the adduct and the activation of the substrate.

**Conclusions**

In this paper, the Cu-Zn bimetallic pathway and the resulting selectivity (regio- and enantioselectivity) of the Cu-catalyzed conjugate addition reaction of dialkylzinc to acyclic dienones are investigated by DFT calculations. The 1,6-addition is the kinetically and thermodynamically favored step, unless the conjugation of the α-β-γ-δ-diene chain is altered by a terminal phenyl group. Furthermore, the retained bimetallic model allows the theoretical prediction of the absolute configuration, which was confirmed experimentally by converting a 1,6-adduct formed in the Cu/L-DIPPMAM catalyzed ACA into a known chiral product. As this bimetallic mechanism seems general and proved compatible with different ligands (DIPPMAM and NHC ligands) and various substrate types (cyclic and acyclic with different substituents), different competing pathways are considered to understand the factors that govern the mechanism. This confirms not only that the copper has to be a C=C bond activator and an alkyl donor while zinc plays the role of a Lewis acid which stabilizes the enolate during the C-C bond formation step but also that the C=C bond activation lowers that activation barrier of the C-C bond formation step. However, developing a strong Lewis acidity toward Zn and electronically enriching Cu appears energetically costly. As a consequence, the catalytic pathway appears as a balance between the stable neutral bimetallic complex and the activating ion-pair formation.

**Experimental Section**

**Experimental Details.** Compound 4 was prepared according to a slightly modified described procedure.⁴³ Compound 2a (164.5 mg, 0.815 mmol, 85% ee) was dissolved along with K₂CO₃ (56 mg, 0.407 mmol) in a mixture of t-BuOH (40 mL) and distilled water (9 mL). A solution of K₂CO₃ (56 mg, 0.407 mmol), NaIO₄ (732.1 mg, 3.423 mmol) and KMnO₄ (32.2 mg, 0.204 mmol) in distilled water (31 mL) was added and the mixture was stirred at rt for 16 h. The reaction media was acidified to pH = 2 by adding HCl (1N) and then stirred another 6 h. Afterwards, Na₂S₂O₅ was added until disappearance of the reddish color. The mixture was extracted with Et₂O (100 mL) and the aqueous layer was removed. The organic layer was extracted with a 1M KCl aqueous solution (100 mL) and after separation, the pH of the aqueous layer was lowered to 1 by a carefully addition of concentrated HCl (strong gas release). Finally, the aqueous layer was extracted with Et₂O (3x100 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure (20°C, 520 mbar). The crude mixture, containing both carboxylic acids formed in this step, was directly used in the next step.

The phenylidiazomethane in toluene solution was obtained according to Biffis' procedure.⁴⁵ To the mixture of the two carboxylic acids previously obtained was added 13 mL (2 equiv.) of the phenylidiazomethane solution and the red mixture was stirred at rt for 16 h (persistence of the reddish color after this time). The mixture was concentrated under reduced pressure and purified by silica gel chromatography using a deposit solid (pentane/EtOAc:100/0 to 80/20 Snap ultra 10g, Biotage puriflash). Many purifications were performed in order to obtain a fraction of 4 having an acceptable purity (25 mg; 16% yield over 2 steps, slightly yellow oil). [α]D²⁷ = +6.0 (c 1.0, CHCl₃).

**Computational Details.** The calculations were carried out with the Gaussian09 package.⁴¹ All geometries and frequencies were obtained using the Density Functional Theory (DFT) with the hybrid B3PW91 functional.⁴²,⁴³ This method is believed to be appropriate despite the bimetallic character of the studied complexes since both Cu(I) and Zn(II) centers are d¹⁰ closed-shell and are never in direct interaction. The copper, zinc metals and phosphorous were represented with the quasi-relativistic SDD ECP⁴⁴,⁴⁵ completed by the associated basis-set⁴⁶,⁴⁷ A 6-31G(d,p) basis set was used for all other atoms (H, C, N, O, P).³⁴,⁴⁷ Geometry optimizations were performed without any constraint and the nature of the extrema (minima and transition state) were verified by analytical calculations of frequencies. In addition, the connections between the transition state and minima were verified by carrying out a small displacement along the reaction coordinate in each direction and optimizing geometry starting from these structures. The Gibbs free energies were calculated assuming an ideal gas, unscaled harmonic frequencies, and the rigid rotor approximation in the standard conditions (P = 1 atm and T = 298 K). Dispersion effects were examined for the complete system with the hybrid B3PW91-D3 corrected functional.⁴⁸ A single point evaluation was carried out on all the stationary points of the 1,4 and 1,6 reaction pathways (see S.I. Table S8) and confirmed that dispersion effects don’t alter our conclusions. For the enantioselectivity aspects, geometry optimizations were directly carried out including dispersion. To illustrate weak interactions, Non Covalent interactions were obtained using NCIPLLOT code.⁵¹,⁵² For alternative mechanisms part, copper and zinc metals were represented with the quasi-relativistic SDD ECP⁴⁴,⁴⁵ completed by the associated basis-set.⁴⁶ A 6-31+G(d,p) basis set was used for all other atoms (H, C, N, O, P).³⁴,⁴⁷ In addition, Density-based Solvation Model (SMD)³⁸ was used as it is considered as a good method to calculate the free energy of solvation ΔG°w for neutral and ionic molecules in solvent (mean unsigned errors of 1 kcal.mol⁻¹ for neutral molecules). SMD Single point calculations (THF is used) are given in the solvent molecule (Me₂O instead of MeTHF) as a supermolecule, was used as the second method of solvation model.

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Copper/DiPPAM-catalyzed 1,6-Asymmetric Conjugate Addition (ACA) of dialkylzinc to acyclic dienones pathway is demonstrated to originate from a balance between the activating potential of the two Cu and Zn centers and the stability of the bimetallic complex. The retained mechanism is supported by the experimentally observed regio- and enantioselectivities.