Computational ligand design in enantio- and diastereoselective ynamide [5 + 2] cycloisomerization

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Transition metals can catalyse the stereoselective synthesis of cyclic organic molecules in a highly atom-efficient process called cycloisomerization. Many diastereoselective (substrate stereocontrol), and enantioselective (catalyst stereocontrol) cycloisomerizations have been developed. However, asymmetric cycloisomerizations where a chiral catalyst specifies the stereochemical outcome of the cyclization of a single enantiomer substrate—regardless of its inherent preference—are unknown. Here we show how a combined theoretical and experimental approach enables the design of a highly reactive rhodium catalyst for the stereoselective cycloisomerization of ynamide-vinylcyclopropanes to [5.3.0]-azabicycles. We first establish highly diastereoselective cycloisomerizations using an achiral catalyst, and then explore phosphoramidite-complexed rhodium catalysts in the enantioselective variant, where theoretical investigations uncover an unexpected reaction pathway in which the electronic structure of the phosphoramidite dramatically influences reaction rate and enantioselectivity. A marked enhancement of both is observed using the optimal theory-designed ligand, which enables double stereodifferentiating cycloisomerizations in both matched and mismatched catalyst-substrate settings.

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emand for higher efficiency, economy and selectivity in the synthesis of novel molecular scaffolds drives organic chemistry\textsuperscript{1,2}. In this context, cycloisomerizations represent ideal methods for the formation of cyclic organic molecules, as they can fulfill all of these criteria. Despite much research into transition metal-catalysed cycloisomerization\textsuperscript{3–14}, and reports where high enantioselectivity is achieved for the cyclization of prochiral substrates to enantioenriched products\textsuperscript{5,6,15–18}, this important field of synthetic methodology has neglected the development of enantiospecific diastereoselective transformations, where single enantiomer starting materials are subjected to asymmetric cycloisomerization to give specific diastereomer products (that is, double stereodifferentiation, where catalyst and substrate stereocontrol compete)\textsuperscript{7–10}. In an age where absolute control of molecular substitution and stereochemistry is paramount for applications, the realization of such processes would represent a major advance in the sustainable synthesis of precision-manufactured target molecules.

Here we describe rationally designed cycloisomerization catalysts that address these challenges. The reaction selected for this study was the $[5+2]$ cycloisomerization of ynamide-vinylcyclopropanes to [5.3.0] azabicycles ($\text{1}\rightarrow\text{2}$, Fig. 1). Although $[5+2]$ processes have a rich history in the field of alkyne-vinylcyclopropanes\textsuperscript{11–22}, the development of this process using ynamides—or indeed any asymmetric cycloisomerization of ynamide-tethered enynes—has not been explored either experimentally or theoretically\textsuperscript{23–27}. More generally, we question whether a catalyst system optimized to achieve an enantioselective cyclization ($\text{1}\rightarrow\text{2}$, Fig. 1b) can translate to a double stereodifferentiating setting ($\text{1}\rightarrow\text{3}$ or $\text{epi-3}$, Fig. 1c), particularly should the catalyst be required to overcome powerful substrate stereocontrol. Intrinsically, these studies is a combined theoretical and experimental approach to optimize catalyst design\textsuperscript{28–30}, which in the event reveals an unexpected mechanistic pathway for rhodium-catalysed $[5+2]$ carbocyclizations (Fig. 1a). This work demonstrates the powerful role of density functional level of theory (DFT) computations in understanding asymmetric catalysis, leading to quantitative computational-lead design of new, highly selective ligands.

**Results**

**Substrate synthesis and reaction optimization.** A selection of ynamide cycloisomerization substrates $\text{1}$ were readily accessed from allylic esters $\text{4}$ (Fig. 2) by an Ireland-Claisen/Curtius rearrangement/ynamide formation sequence. Substituents could be introduced at one or both of the carbon atoms on the ene-ynamide backbone, and by incorporating an enzymatic resolution into this synthesis, enantioenriched ynamides could be prepared. Ynamide formation ($\text{6}\rightarrow\text{1}$) was achieved using copper-catalysed coupling of the sulfonamide with a bromoalkyne\textsuperscript{19}, or via formation of an intermediate dichloroenamide\textsuperscript{20}. Initial screening of ruthenium\textsuperscript{14} and rhodium$\text{20,24}$ catalyst systems (Table 1) revealed that only the latter afforded high yields of azabicycle $\text{7a}$ from ynamide $\text{1a}$; using $\text{[Rh(cod)naphthalene]BF}_3$ (5 mol\% ) as the catalyst\textsuperscript{25,26}, the cycloisomerization could be effected within 3 h at room temperature, giving $\text{7a}$ in 91% yield (Entry 6).

**Substrate scope.** A variety of ynamides $\text{1a}$–$\text{s}$ were now examined in the cycloisomerization using these optimized conditions (Fig. 3). Aryl-substituted ynamides $\text{1b}$–$\text{d}$ reacted with high efficiency, and revealed a clear electronic effect on the reaction rate, with electron-deficient ynamides $\text{1b}$ and $\text{1c}$ showing reduced reaction times. Alkyl-substituted ynamides $\text{1e}$–$\text{g}$ also displayed enhanced reactivity compared with phenyl ynamide $\text{1a}$, affording the corresponding [5.3.0]-azabicycles $\text{7e}$–$\text{g}$ in excellent yields within 15 min at ambient temperature. Similar efficient reactivity was observed for the cyclization of the heteroaryl-substituted ynamides $\text{1h}$ and $\text{1i}$ to the indolyl- and pyrryl-substituted products $\text{7h}$ and $\text{7i}$. The mild conditions of the reaction are emphasized by the cyclization of the aniline-derived ynamide $\text{1j}$, which led to tricycle $\text{7j}$ in 74% yield—notably, this 1,4-diene did not undergo in situ isomerization to the indole.

Of clear interest was the level of substrate stereocontrol that might be achieved using ynamides $\text{1i}$–$\text{s}$. Excellent levels of substrate stereoinduction were observed, with products $\text{7i}$–$\text{s}$ afforded in high yield and as single diastereomers for substrates containing homoallylic stereocenters proved less favorable, with products $\text{7j}$–$\text{s}$ reacting with high enantioselectivity ($\text{dr}=12:1$) could be achieved using $\text{[Rh(cod)Cl]}_2$. These collected results are significant in the wider context of $[5+2]$ cycloisomerization, where high levels of substrate stereocontrol have previously been generally interpreted to arise from an ‘inside alkoxy effect’ from oxygen-bearing stereocenters allylic to the vinylcyclopropane\textsuperscript{37,38}. In this work, it is apparent that such stereoelectronic effects are not a prerequisite for high stereoselectivity.

![Figure 1](https://example.com/figure1.png) **Figure 1 | A reaction blueprint for enantioselective and/or double stereodifferentiating diastereoselective ynamide-vinylcyclopropane cycloisomerization.** (a) We show that mechanistic calculations are crucial in the design of an enantioselective cycloisomerization catalyst. (b) Enantioselective higher order ynamide cycloisomerization is realized. (c) Despite high levels of substrate stereocontrol, the computationally designed catalyst is able to define product stereochemistry.
Supplementary Fig. 4. (a) Employed the versatile phosphoramidite ligand L1. A preliminary screen of a range of phosphoramidite ligands revealed that L1 indeed seemed optimal for the enantioselective cycloisomerization of ynamide-vinylcyclopropane 1a, delivering product (−)-7a in excellent yield and enantioselectivity (96%, 98% ee) after just 15 min at room temperature (see Supplementary Information for assignment of absolute stereochemistry). However, forays with other substrates suggested that this ligand might not meet our expectations in more challenging settings, and we realized that any further advance would require a combined theoretical and experimental design approach.

To this end, we conducted a computational exploration of the reaction pathway, which began with investigation of the empirical model adopted by Shintani et al. to explain the enantioselectivity of vinylcyclopropane-alkyne cycloisomerization. This model (Fig. 4b) is based on an X-ray crystal structure of [Rh(1) norbornadiene]BF4 reported by Mezetti (8) (ref. 42), which reveals an η2-complexation of one of the α-methylenylamine arenes to the rhodium cation—the phosphoramidite thus acting as a bidentate ligand. The Shintani–Hayashi model docks the vinylcyclopropane-alkyne onto this ligated rhodium framework as in structure 9, such that the alkyne coordinates trans to the phosphorous atom of the phosphoramidite ligand, and the vinylcyclopropane coordinates trans to the η2-complexed arene, with an orientation that minimizes steric interactions between the cyclopropane ring and naphthyl group.

Computational study and ligand optimization. Computation, particularly at the DFT level, has emerged as a powerful tool for assessing the feasibility of mechanistic steps involved in catalysis32. Our theoretical work first explored eight possibilities for the binding of ynamide-vinylcyclopropane 1a to the [Rh(L1)]

Table 1 | Optimization of the [5 + 2] cycloisomerization reaction.

| Entry | Catalyst (mol%) | Solvent | Temp. (°C) | Time (h) | Yield (%) |
|-------|-----------------|---------|-------------|----------|-----------|
| 1     | [CpRu(MeCN)3]PF6 (10) | acetone | 50         | 20       | 72        |
| 2     | [RhCl(cod)]2 (10) | toluene | 110        | 20       | b         |
| 3     | RhCl(PPh3)3 (10) | toluene | 110        | 1        | 72        |
| 4     | [Cp2Rh]2SbF6 (10) | 1,2-dichloroethane | rt | 1.5 | 92        |
| 5     | [Cp2Rh]2SbF6 (10) | CH2Cl2 | rt | 1.5 | 94        |
| 6     | [Cp2Rh]2SbF6 (10) | CH2Cl2 | rt | 3    | 91        |

*Reactions performed at 0.1 M substrate in the solvent stated. aReaction gave a complex mixture of products.

Enantioselective cycloisomerization. In targeting an asymmetric version of the cyclization, we were mindful of the excellent asymmetric [5 + 2] Rh-catalysed cycloisomerization of alkyne-vinylcyclopropanes described by Shintani et al.39,40, which employed the versatile phosphoramidite ligand L1 (Fig. 4a)41. A preliminary screen of a range of phosphoramidite ligands L1–L4 revealed that L1 indeed seemed optimal for the enantioselective cycloisomerization of ynamide-vinylcyclopropane 1a, delivering product (−)-7a in excellent yield and enantioselectivity (96%, 98% ee) after just 15 min at room temperature (see Supplementary Information for assignment of absolute stereochemistry). However, forays with other substrates suggested that this ligand might not meet our expectations in more challenging settings, and we realized that any further advance would require a combined theoretical and experimental design approach.

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In contrast to the Shintani–Hayashi model, this suggested that the lowest energy complex of \([\text{Rh(L1)}]_a\) positions the ynamide proximal to the naphthyl ring and trans- to the arene ligand, and the vinylcyclopropane trans- to the phosphorous atom (10, Fig. 5, P-trans-ene/Up). The next lowest energy structure maintains this positional selectivity of substrate binding, but inverts its orientation (that is, P-trans-ene/Down). Next, calculations were carried out to explore the two widely accepted mechanisms for \([5 + 2]\) cycloisomerization, which initiate either with an oxidative addition into the vinylcyclopropane, followed by alkyne insertion into the resultant \(\sigma/\pi\)-allyl rhodium(III) complex 11 to give eight-membered rhodacycle 12 (vinylcyclopropane pathway), or via oxidative cycloaddition of Rh(I) with the alkyne and alkene to give rhodacyclopentene 13, followed by ring expansion into the cyclopropane to give the same intermediate 12 (metallacyclopentene pathway). Where investigations by Yu, Houk and Wender on Rh-catalysed \([5 + 2]\) cycloisomerizations suggest that oxidative addition into the vinylcyclopropane is the first step on the catalytic pathway17,21, our DFT calculations

**Figure 3 | Rhodium-catalysed ynamide \([5 + 2]\) cycloisomerization.** (a) Ynamide substituent scope. (b) Diastereoselective cycloisomerization proceeds with high levels of substrate stereoinduction. (c) High regioselectivity and diastereoselectivity is observed with a substituted cyclopropane. aReaction performed using [Rh(cod)Cl]_2 (10 mol%), toluene, 110 °C.
rhodacyclopentene formation. The character of the selectivities depicted (distances in Å). (Fig. 4) Our calculations (Fig. 5) support an alternative mode of binding of the ynamide, and an alternative reaction pathway that initiates with rhodacyclopentene formation. Re face binding of the vinylcyclopropane is favoured, with calculated structures, and activation barriers (kcal mol$^{-1}$) selectivities depicted (distances in Å). (Fig. 5) suggest that oxidative coupling of the alkene-ynamide to form metallacyclopentene 13 appears to be the preferred reaction pathway for an ynamide-vinylcyclopropane to give 12, followed by ring expansion of the cyclopropane. Notably, this mechanism has also been calculated to be the preferred pathway in ruthenium-catalysed $[5+2]$ cycloisomerization.$^{17}$ The preference for this pathway over vinylcyclopropane oxidative addition is in the range of 4–12 kcal mol$^{-1}$, depending on the orientation with which 1a binds to the [Rh(L1)] cation; notably, the transition states for both pathways favour Re-face binding of the alkene in a $P$-trans-ene/Down orientation. This sequence of steps is favoured in this intramolecular reaction due to additional stabilization of the forming Rh(III) intermediate in the oxidative coupling step by the electron-rich ynamide. The free energy profile for the catalytic cycle is exergonic by more than 40 kcal mol$^{-1}$, and product inhibition is predicted to be minimal, since the reactant preferentially binds to the catalyst by 6.2 kcal mol$^{-1}$; taken together with a turnover and selectivity determining barrier of 17.0 kcal mol$^{-1}$ for the metallacyclopentene pathway, our computations are consistent with the short reaction times observed at room temperature for the conversion of 1a–7a using L1.

The lowest energy transition state for the oxidative coupling of this metallacyclopentene pathway (TS3) is illustrated in Fig. 4c. This transition state leads to a calculated enantioselectivity for cyclization with ligand L1 of 97.9% ee ($\Delta\Delta G^{\ddagger}$Re/Si = –2.69 kcal mol$^{-1}$), which is in excellent agreement with the experimental value (R, 98% ee). The calculated enantioselectivity for phosphoramidite L4 (9.3% ee, $\Delta\Delta G^{\ddagger}$Re/Si = –0.11 kcal mol$^{-1}$) also correlates well with the poor selectivity we had already observed experimentally with this ligand (7% ee), supporting the mechanistic model, and implying that the naphthyl ring plays a crucial role—likely related (for aryl ynamides) to a stabilizing dispersive ($\pi$–$\pi$) interaction between L4 and the metalla(III) center. Together with the increased competition of trans-P-phenyl vs trans-P-nitromethyl and dearomatized phenyl substituents, this would explain the improved ee values with MeO-Ph substituents.

Figure 4 | Exploration of asymmetric ynamide $[5+2]$ cycloisomerization inspires a computation-guided ligand design. (a) A selection of phosphoramidite ligands screened reveals a strong dependence of enantioselectivity and reaction rate on amine and BINOL components’ structure and chirality, with L1 giving superior results. (b) The Shintani–Hayashi model for enantioselectivity is based on a crystal structure of [L1 Rh(norbornadiene)]$^+$. (c) Our calculations (Fig. 5) support an alternative mode of binding of the ynamide, and an alternative reaction pathway that initiates with rhodacyclopentene formation. Re face binding of the vinylcyclopropane is favoured, with calculated structures, and activation barriers (kcal mol$^{-1}$) selectivities depicted (distances in Å). (d) A transition state model is shown that identifies key ligand design parameters. (e) Variation of the electronic character of the $\eta^2$-bound arene of the phosphoramidite leads to predicted enantioselectivities for L5 ($p$-F) and L6 ($p$-OMe), and an excellent correlation of experiment and theory for L1 and L4.
Table 2 | Eight possible orientations of enynamide docking onto the L1-Rh cation are explored.

| Orientation | Metallacyclopentene Pathway | Vinlycyclopropane pathway |
|-------------|-----------------------------|--------------------------|
|             | Re-selectivity (R)           | Si-selectivity (S)        | Re-selectivity (R) | Si-selectivity (S) |
| 1           | 18.7                        | 31.3                     | 23.0              | 22.0              |
| 2           | 17.0                        | 19.7                     | 21.9              | 24.8              |
| 3           | 23.6                        | 23.9                     | 29.3              | 24.5              |
| 4           | 23.2                        | 30.7                     | 35.3              | 41.7              |

Transition state energies (SMD-ωB97XD/6-311+G(d,p)/Lanl2TZ//ωB97XD/6-31G(d)/Lanl2DZ Gibbs free energies, shown in kcal mol⁻¹) associated with each mode of binding are tabulated.

Figure 5 | Theoretical reaction analysis. Complex 10 (Re face binding) is found to be the lowest energy ground state for ynamide complexation, and transition state for oxidative coupling (metallacyclopentene pathway, see Table 2). The calculated energy profiles of the cycloisomerization for Re-face (black, bold) and Si-face (grey) substrate association via pathways initiating with metallacyclopentene formation (left), or vinylcyclopropane insertion (right) are illustrated; the former is favoured. SMD-ωB97XD/6-311+G(d,p)/Lanl2TZ//ωB97XD/6-31G(d)/Lanl2DZ Gibbs free energies are shown in kcal mol⁻¹.

The oxidative coupling (TS3) is the rate-limiting and enantioselectivity determining step in this rhodacyclopentene mechanism. As observed in the Mezetti norbornene crystal structure (Fig. 4b)¹², one of the ligand benzylamine groups acts as a 2π-electron donor (2.6–2.7 Å) in these transition states.
We hypothesized that variation of the electronic character of this η²-complexed arene could dramatically influence both the rate, and selectivity, of the reaction. Calculations on the effect of electronically-biasing methoxy and fluoro groups at the para position of these arenes suggested that decreasing the electron density on the arene (p-F, L5, Fig. 4d,e) would lead to an increase in reaction rate ($\Delta G^1_{R/S}$) and enantioselectivity ($\Delta G^1_{R/S}$) = -4.56 kcal mol⁻¹, 99.9% ee), while an electron-donating substituent (p-MeO, L6) would have the opposite effect ($\Delta G^1_{R/S}$, L6) = +0.76 kcal mol⁻¹, 96.7% ee). This computed trend in reactivity and enantioselectivity, namely L5 > L1 > L6, results from a weakened metal-arene interaction in the TS leading to the major enantiomer, which is compensated for through stronger coordination of the alkynyl and alkenyl groups (see Supplementary Information for further details and discussion). These ligand structural modifications also modulate the Lewis basicity at phosphorus, however preferential stabilization of the major enantiomeric pathway confirms that the predominant effect is not inductive in nature, but rather depends on through-space interactions involving the Rh-coordinating aryl group.

Substrate scope in the asymmetric cycloisomerization. While phosphoramidite L6 is known, (ref. 44) L5 is not, but could be readily synthesized using standard methods. Both were evaluated in the enantioselective cyclization alongside L1 and L5, showing an excellent correlation of computation and experiment for the theory-designed ligands L5 and L6. The synthesis of 7e was performed on 1 mmol scale (1.25 mol% catalyst). ¹H NMR spectroscopic monitoring of reaction progress emphasizes the rate enhancement between ligands L6, L1 and L5, also predicted theoretically. Matched double stereodifferentiating cycloisomerizations proceed with high selectivity and rate. Mismatched double stereodifferentiating cycloisomerizations proceed successfully under catalyst stereocontrol using the enantiomers of ligands L1, L5 and L6 (that is, (R,S,S)-L stereochemistry); the major diastereomer is shown. The $^a$ signifies reaction conversion, as judged by ¹H NMR spectroscopic analysis.
could be achieved on a 1 mmol scale in less than 5 min with 1.25 mol% catalyst loading. Monitoring of reaction conversion by 

1H NMR spectroscopy (in CDCl3, Fig. 6b) emphasizes the dramatic rate difference between these three ligands, with the reaction using L5 complete in under 4 min, compared with the slower cyclizations with L1 and L6 (addition of the catalyst solution to the substrate followed by NMR spectroscopic analysis necessitated a four minute delay between reaction initiation and acquisition of the first NMR spectrum. The reaction catalysed by [L5Rh] was complete by this time).

Finally, the performance of these ligands was tested against the challenge of cyclizations that proceed with high levels of substrate stereocontrol, to address the question of how a high enantioselectivity-inducing catalyst would cope with mismatched substrate-catalyst diastereoselective cyclosomerization scenarios. Three substrates were chosen for this challenge: ynamides 1l, 1q and 1r, which gave >20:1, 1.8:1 and >20:1 dr, respectively when cyclized using [Rh(cod)naphthalene][BF4] (Fig. 3). As expected, these single enantiomer substrates cyclized rapidly, and with high efficiency and selectivity, with the matched substrate-catalyst combination (that is, (S,R,R)-L5, Fig. 6c). To our delight, we found that cyclosomerization of substrate 1l using the enantiomeric catalyst system ([(S,S,S))L1] successfully overturned this powerful substrate stereoselectivity, giving 14l in up to 1:8 dr. Interestingly, it was ligand L1—and not L5—which performed optimally in this challenging situation, albeit requiring an extended reaction time. In the case of 1q, the catalyst (with either L1 or L5) was able to achieve an equivalent (reversed) level of selectivity to that achieved in the matched sense—in this instance, a modest level of inherent substrate stereocontrol being completely overturned. Finally, the most challenging setting of the reinforcing substituents in 1r proved a hurdle that could also be partly overcome, again demonstrating significant catalyst influence.

These observations may suggest that tighter substrate-Rh complexation in the case of L5 (a consequence of a slightly weaker ligand-metal interaction observed in our calculations (see Supplementary Information for details), which improves rate and enantioselectivity), enhances unfavourable (that is, mismatched) steric effects in a double stereodifferentiating setting such that it effectively increases the stereocontrolling influence of the substrate relative to that of the ligand. The most reactive/selective catalysts for enantioselective cyclizations could thus suffer from higher than expected transition state energies in diastereoselective cyclizations, where such steric effects are enhanced compared with less enantioselective catalysts (looser substrate binding); and that different considerations are therefore needed in the development of double stereodifferentiating reactions, with more ‘promiscuous’ catalysts potentially giving superior selectivity.

Discussion

In summary, the first example of an enantioselective ynamide-tethered cyclosomerization has been achieved, with a series of highly enantio- and diastereoselective cyclizations giving a range of substituted/enantiomericrich [5,3,0] azabicycles. Theoretical reaction analysis crucially influenced ligand design, leading to a catalyst system that displayed enhanced rate and enantioselectivity in the cyclosomerization. The demonstration of the first successful examples of enantiospecific diastereoselective transition metal-catalysed cyclosomerizations in a significantly mismatched substrate-catalyst environment illustrates that cyclosomerization can assemble functionalized ring systems with tuneable selectivity. These studies set the stage for the development of further computationally guided catalyst systems.

Methods

Racemic [5 + 2] cyclosomerization. To an oven-dried vial containing the ynamide vinylcyclopentane (1.0 equiv.) under Ar was added a solution of [(C6H5)2Rh(cod)][BF4] (5 mol%) in degassed CH2Cl2 (10 ml mmol of ynamide). The reaction mixture was stirred at room temperature under Ar until consumption of the ynamide was observed by thin layer chromatography (see Fig. 3 for reaction times). The reaction mixture was then concentrated, and the resulting material was purified by flash chromatography (SiO2, petroleum ether/ethyl acetate eluent) (Fig. 3).

Asymmetric [5 + 2] cyclosomerization. A solution of [RhCl(C6H5)2] (2.5 mol%), NaBARF4 (6 mol%) and phosphoramidate ligand (6 mol%) in degassed CH2Cl2 (10 ml mmol of ynamide) was stirred for 20 min under Ar. The solution was filtered (through a PTFE filter-tipped syringe) into an oven-dried vial containing ynamide vinylcyclopentane (1.0 equiv.) under Ar. The reaction mixture was stirred at room temperature under Ar until consumption of the ynamide was observed by thin layer chromatography (see Fig. 6 for reaction times). The reaction mixture was then concentrated, and the resulting material was purified by flash chromatography (SiO2, petroleum ether/ethyl acetate eluent) (Fig. 6).

Computational methods. Molecular geometries were fully optimized at the DFT theory level in Gaussian 09 (rev. D.01), using the dispersion-correctedωB97XD functional46 without symmetry constraints. The effective core potentials (ECPs) of Hay and Wadt47 with a double-ζ basis set (LANLDZ) were used for Rh, S and P, and the 6-31G(d) basis set was used for H, C, N and O(BS1). The energies were further estimated using a larger basis set (6-311+G (d, p) basis set for H, C, N, O, S and P) and triple-ζ basis set (LANL2DZ)48 for Rh (BS2) by single-point calculations, in implicit solvent CH2Cl2 treated with the SM6 universal solvation model49. The structures of the ynamide substrate and a series of phosphoramidate ligands were computed in full, while the toluenesulfonamide p-tolyl group was modelled as a methyl group in the interests of computational tractability. See Supplementary Methods for further details.

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