Chiral Brønsted acid-catalyzed asymmetric allyl(propargyl)boration reaction of *ortho*-alkynyl benzaldehydes: synthetic applications and factors governing the enantioselectivity

Elsa Rodríguez,[a] Matthew N. Grayson,[b] Amparo Asensio,[a] Pablo Barrio,[a] K. N. Houk*[b] and Santos Fustero*[a],[c]*

[a] Departamento de Química Orgánica, Universidad de Valencia, Av. Vicente Andrés Estellés s/n E-46100 Burjassot, Spain

[b] Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

[c] Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain

ABSTRACT. Chiral Brønsted acid-catalyzed allyl(propargyl)boration of *ortho*-alkynyl benzaldehydes gives rise to ω-alkynyl homoallylic(homopropargylic)alcohols that can be further transformed to complex molecular scaffolds via subsequent hydroalkoxylation, ring-closing enyne metathesis (RCEYM) or intramolecular Pauson-Khand reaction (PKR). Optimizations of each

two-step transformation is reported. A strong dependence between enantioselectivities and the nature of the substitution at the alkynyl moiety is observed, showcasing that the triple bond is not merely a spectator in this transformation. Density functional theory (DFT) calculations (M06-2X/6-311+G(d,p)−IEFPCM//B3LYP/6-31G(d)) show that this dependence is the result of the steric and electronic properties of the alkyne substituent.

KEYWORDS. chiral Brønsted acids; organocatalysis; asymmetric allylboration; diversity-oriented synthesis; DFT calculations.

INTRODUCTION

The discovery of new chemical entities for drug discovery has received a great deal of attention during the last few decades. This is mainly due to the necessity to cover the broadest possible portion of chemical space in order to maximize the likelihood of finding suitable drug candidates. In this context, Diversity Oriented Synthesis (DOS) has emerged as a powerful tool to obtain the maximum structural variability from simple starting materials.[1,2] In this sense, the reliable construction of plurifunctional molecules, which can be engaged predictably in different reaction pathways by the careful choice of the appropriate catalyst, allows the rapid construction of molecular complexity.[3] Chiral (poly)cyclic alcohols and derivatives are widespread substructures both in natural products and pharmaceuticals.[4] Among the existing methods for the asymmetric synthesis of alcohols, the chiral Brønsted acid-catalyzed allylboration of aldehydes[5] displays some salient features: 1) high level of enantiocontrol; 2) wide substrate scope; 3) functional group compatibility; 4) feasibility of combination with transition metal catalysts in binary systems (*vide infra*). In addition, the resulting homoallylic alcohols possess a double bond capable of participating in a variety of transition metal catalyzed transformations. The versatility of this

methodology contrasts with the drawbacks associated with other stereoselective allylation protocols, such as the use of stoichiometric chiral auxiliaries, difficult to prepare or unstable allylation reagents or complex catalytic systems. In 2013, we reported an efficient entry to enantioenriched benzo-fused cyclic homoallylic alcohols by a tandem chiral Brønsted acid-catalyzed allylboration / RCM process on aldehydes bearing an olefin appendage on an appropriate position performed under orthogonal relay catalysis conditions (see Figure 1).[6]

In view of the need for new efficient strategies for the synthesis of cyclic chiral alcohols,[7] the use of other *ortho*-functionalized benzaldehydes is described herein, thus expanding the molecular complexity accessible from 2-bromobenzaldehyde, a simple and readily available starting material. Herein, we report the first highly enantioselective allylation of 2-alkynylbenzaldehydes. Thus, a whole array of unprecedented polyfunctionalized homoallylic alcohols and their divergent synthetic applicability is described in this study for the first time. In addition, DFT calculations have been used to elucidate the origins of stereocontrol. The results of this theoretical study have shown that the triple bond is not merely a spectator during the allylboration reaction but it plays an active role dictating the final stereochemical outcome. As disclosed below, the sterically undemanding ethynyl group destabilizes the TSs leading to the major product yielding poor enantioselectivities, while the introduction of an aromatic ring at the terminal position of the alkyne overwhelms this negative effect through a favorable π-stacking interaction.

RESULTS AND DISCUSSION

Preliminary results. Continuing with our interest in the chiral Brønsted acid-catalyzed allylboration reaction,[6] we envisioned that the introduction of an alkynyl substituent at the *ortho*-position of the benzaldehyde would give rise to versatile enynes **3** in an enantiomerically enriched

manner. These densely functionalized chiral alcohols would in turn become appropriate substrates for selected transition metal-catalyzed transformations (intramolecular Pauson-Khand reaction PKR, ring-closing enyne metathesis RCEYM, intramolecular hydroamination HA) aimed at obtaining a small library of structurally diverse molecules in two steps (Figure 1).

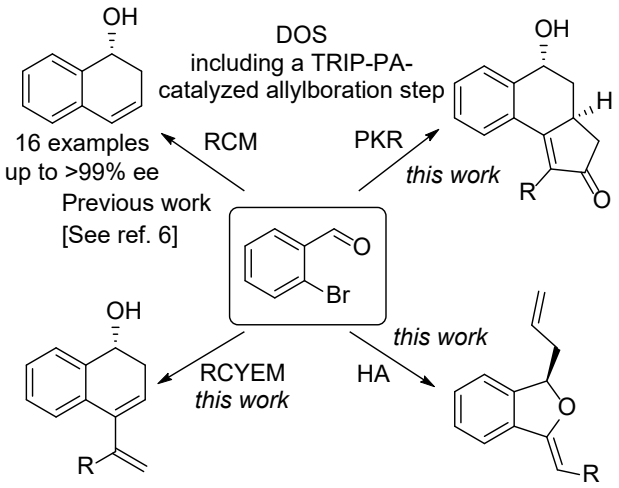


Figure 1. DOS strategy.

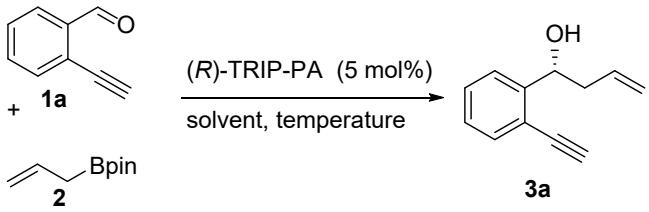
In our recent studies,[6,8] we observed a strong dependence of the enantioselectivity on the steric bulk of the *ortho*-substituent. Specifically, the enantiomeric excess of the (*R*)-TRIP-PA catalyzed allylboration dropped from 99% to 82%, from *ortho*-vinyl to *ortho*-allylbenzaldehyde. We also observed that substrates bearing substitution at both *ortho* positions suffered from moderate enantiomeric excess when compared to any other substitution pattern in *ortho*-vinylbenzaldehydes (92-99% ee vs 65% ee). Recently, the dependence of the enantioselectivity on the substitution at the *ortho*-position has been studied by Kotora and co-workers.[9] However, no rationale for the observed differences in selectivity was given.

In view of these results, *ortho*-ethynylbenzaldehyde **1a** was anticipated to perform in the 90 % ee range given the low steric demand of the ethynyl group.[10,11] To our surprise, a poor 52% ee was

obtained upon subjecting **1a** to the optimized conditions for allylboration described in reference 5 (Table 1, entry 1). In view of this result, we carried out an optimization of the reaction conditions, the results of which are summarized in Table 1.

A decrease in the reaction temperature to -78 ºC results in a minor improvement in the chemical yield accompanied by a noticeable drop in enantioselectivity (Table 1, entry 2). The use of DCM instead of toluene gave rise to a noticeable increase in chemical yield but similar enantiomeric excess (Table 1 entries 3, 4). The use of other solvents did not lead to any improvement neither in chemical yield nor enantioselectivity (Table 1, entries 5-8).

Table 1. (*R*)-TRIP-PA catalyzed allylboration of *ortho*-ethynylbenzaldehyde.

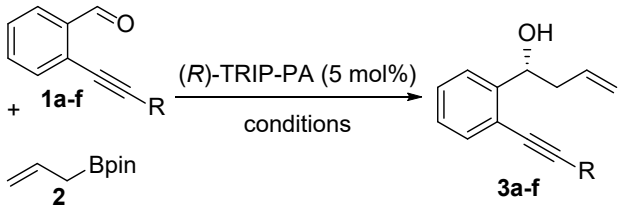


Entry	Solvent	Temp (ºC)	Yield (%)	ee (%)
1	Toluene	-30	61	52
2	Toluene	-78	68	40
3	DCM	-30	91	62
4	DCM	-78	70	65
5[a]	Cyclohexane	-30	11	24
6	Cyclopentane	-30	68	13
7	F_8-toluene	-30	38	38
8	F_3-toluene	-30	58	12

[a] 4 Å MS were used as additive

Optimization. Next, we turned our attention to the influence of the substituent at the triple bond on the enantioselectivity of the process under the best two sets of reaction conditions obtained for **1a**: Toluene -30 ºC and DCM -30 ºC (Table 2).

Table 2. Influence of the substitution at the triple bond on the (*R*)-TRIP-PA catalyzed allylboration of *ortho*-alkynylbenzaldehydes.



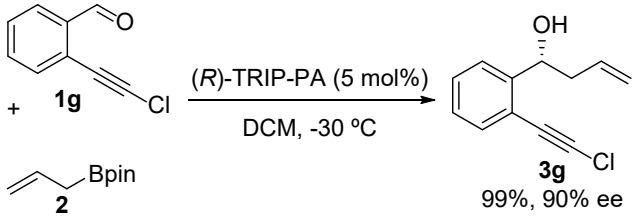
Entry	**1**	R	Conditions[a]	Yield (%)	ee (%)
1	**1a**	H	A	61	52
2	**1a**	H	B	91	62
3	**1b**	Bu	A	78	79
4	**1b**	Bu	B	40	78
5	**1c**	Cy	A	30	28
6	**1c**	Cy	B	98	76
7	**1d**	Ph	A	90	74
8	**1d**	Ph	B	99	90
9	**1e**	TMS	A	80	37
10	**1e**	TMS	B	99	53
11	**1f**	TIPS	A	83	7
12	**1f**	TIPS	B	91	5

[a] Conditions A: Toluene, -30 ºC; conditions B: DCM, -30 ºC.

From this table an interesting preliminary conclusion can be drawn: under conditions A, a rough correlation between steric hindrance and ee can be obtained with **1a** and **1d**, the only substrates that deviate from this trend. Hence, increasing substituent size (estimated by their corresponding

A-values)[11] H (0 kcal/mol) < Bu (≈1.80 kcal/mol)[12] < Cy (2.2 kcal/mol) ≈ TMS (2.5 kcal/mol) ≈ Ph (2.8 kcal/mol) < TIPS[13] results in a drop in enantioselectivity (Table 2). In an attempt to provide a rationale for the abnormal position of the terminal and phenyl substituted alkynyl moieties, we speculated that the acidity of the acetylenic proton may disrupt the highly ordered transition state proposed for this transformation by H-bond formation, giving rise to the unexpected low selectivity,[14] and that the relatively high enantioselectivity obtained for the phenyl substituent may be attributed to π-stacking with the binaphthyl backbone of the catalyst. Our DFT study supports this π-stacking hypothesis (*vide infra*).

In an attempt to provide some evidence for the H-bond forming ability of the acetylenic proton being responsible for the low *ee* observed for **1a**, we prepared the corresponding chloroacetylene **1g**,[15] which was in turn subjected to (*R*)-TRIP-PA catalyzed allylboration under optimized conditions B (Scheme 1). **3g** was obtained in excellent yield and high ee (90%). Subsequent DFT calculations suggested that higher ee should be obtained in the allylboration of **1g** relative to **1a** which we propose is the result of favorable interactions between the aldehyde oxygen and the local dipole induced by chlorine which would stabilize the *Re* TS (*vide infra*).

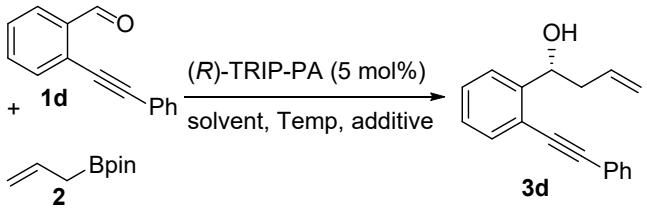


Scheme 1. (*R*)-TRIP-PA catalyzed allylboration of **1g**.

A further optimization was undertaken for phenyl substituted substrate **1d** (Table 3). A decrease of the reaction temperature to -78 ºC resulted in a substantial drop in chemical yield, while the

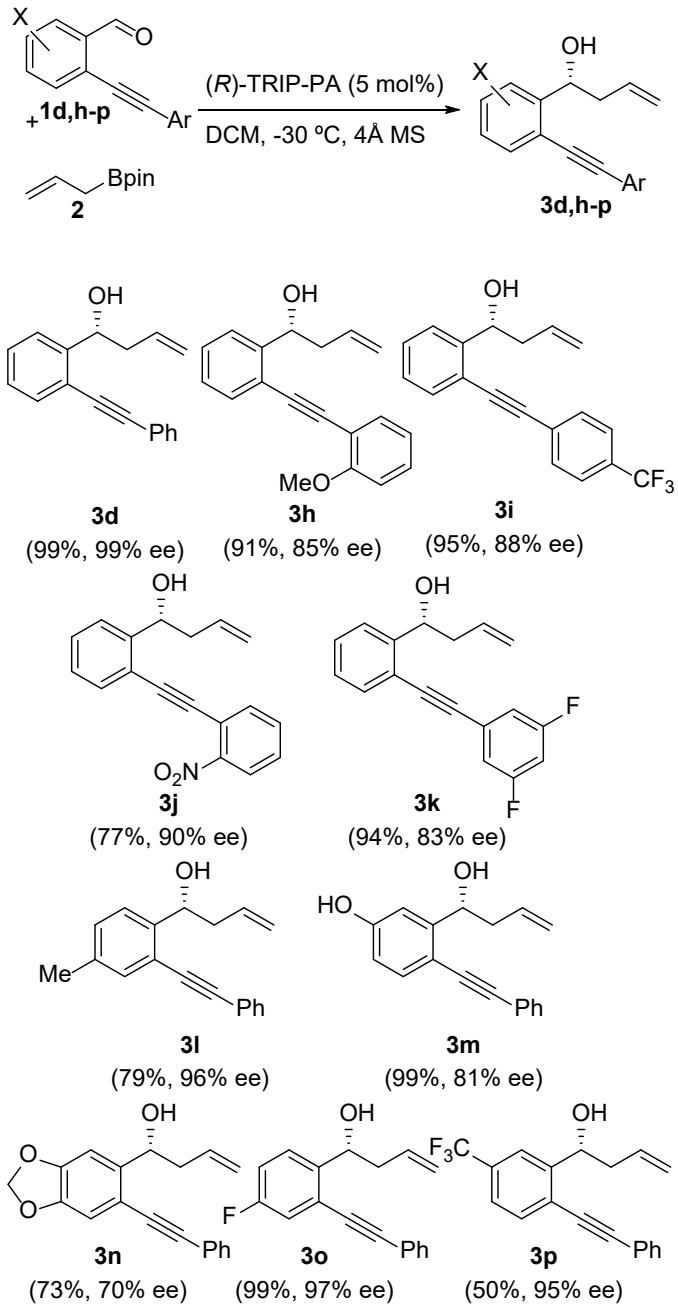
enantioselectivity also decreased (Table 3, entry 3). Increasing the temperature to 25 ºC also diminished the enantioselectivity (Table 3, entry 4). However, the addition of 4Å molecular sieves resulted in a dramatic improvement in enantiomeric excess without any erosion of the excellent 99% yield (Table 3, entry 5).

Table 3. Optimization of the reaction conditions for substrate **1d**.



Entry	Solvent	Temp (ºC)	Additive	Yield (%)	ee (%)
1	Toluene	-30	-	90	74
2	DCM	-30	-	99	90
3	DCM	-78	-	65	86
4	DCM	25	-	95	84
5	DCM	-30	4 Å MS	99	99

Scope and synthetic applicability. The scope of this transformation was studied under the optimized conditions obtained for **1d** with a variety of aryl-substituted 2-alkynylbenzaldehydes (Scheme 2).

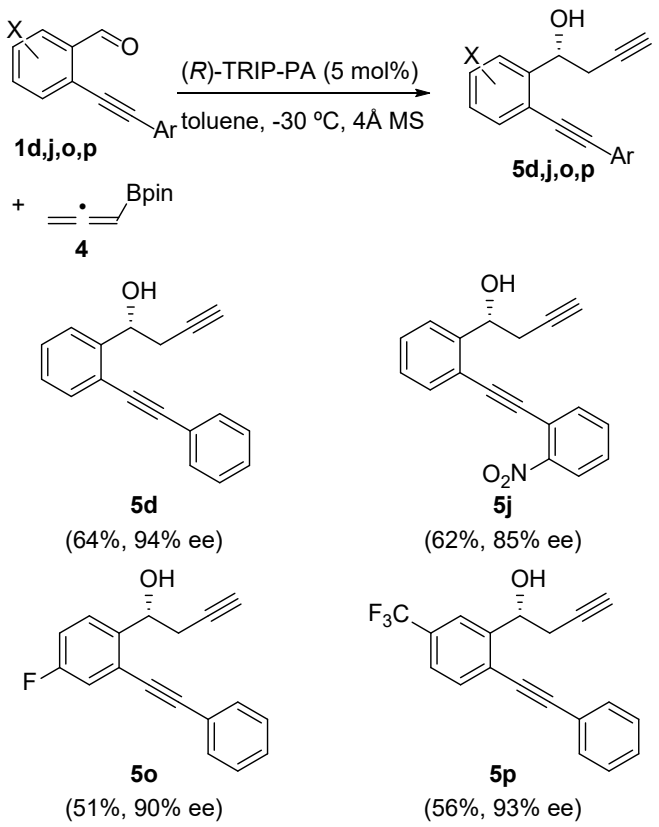


Scheme 2. Scope and limitations of the (*R*)-TRIP-PA catalyzed allylboration of *ortho*-alkynylbenzaldehydes.

Substitution at the terminal alkynyl position with either electron-donating (**3h**), electron-withdrawing (**3i,j**) or halogen groups (**3k**) at the *ortho* (**3h,j**), *meta* (**3k**) or *para* position (**3i**) is

tolerated although it results in a drop in enantiomeric excess (83-90% ee). On the other hand, the introduction of a weak electron-donating substituent on the spacer aryl ring maintains the enantiomeric excess (**3l**), while increasing the electron-donating ability of the substituent starts to damage enantioselectivity (**3m,n**). Electron-withdrawing groups and halogens on this aromatic ring do not hamper the elevated enantioselectivity (**3o,p**).

In order to further diversify our library of highly functionalized chiral alcohols, the asymmetric propargylboration of *o*-alkynyl benzaldehyde derivatives was studied.[14b,16] After a thorough optimization, we identified toluene, -30 ºC, 4Å MS as the optimum reaction conditions.[17] A similar dependence of enantioselectivity with substitution at the alkyne moiety was observed, with aromatic substitution giving rise to the best enantioselectivities.[18] A selection of *o*-alkynyl benzaldehyde derivatives (**1d,j,o,p**) were subjected to the optimized conditions affording a small library of chiral propargyl diyne alcohols **5d,j,o,p** (Scheme 3).

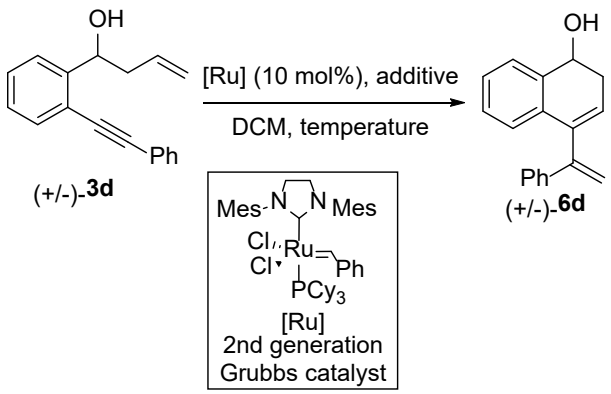


Scheme 3. Scope and limitations of the (*R*)-TRIP-PA catalyzed propargylation reaction.

Again, substitution at both aromatic rings is tolerated although slightly lower enantioselectivities are obtained in comparison with the allylboration.

Products **3d,h-p** and **5d,j,o,p** present three functional groups amenable for a wide range of intramolecular transformations. In recent years, we studied suitably *o*-functionalized benzaldehydes and the *tert*-butylsulfinyl imines derived from them as versatile starting materials in the context of DOS.[6,19] One of the most useful transformations is the ring–closing enyne metathesis (RCEYM) on derivatives **3d,h-p**. Hence, several reaction conditions were assayed on substrate **3d** (Table 4).

Table 4. Optimization of the RCEYM process.



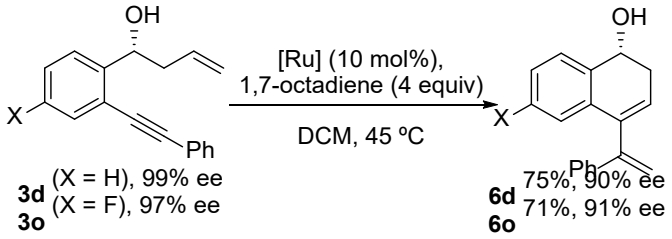
Entry	Temp (ºC)	addit.	Time (h)	**6d** (%)[a]
1	rt	-	24	10
2	40	-	12	20
3	45	ethylene	24	47
4[b]	40	1,7-octadiene	24	41[c]
5[b]	**45**	**1,7-octadiene**	**16**	**76**[d]
6[b]	90 (MW)	1,7-octadiene	3	57

[a] Isolated yield. [b] 4 equivalents of the additive were used. [c] Reflux. [d] Sealed tube.

As a starting point for our optimization, we took the reaction conditions reported in the literature on closely related substrates (2nd generation Grubbs catalyst, dichloromethane).[20] The reaction carried out at room temperature only afforded minor amounts of the metathesis product (Table 4, entry 1). Increasing the reaction temperature improved the reactivity but still an unsatisfactory yield was obtained (Table 4, entry 2). The beneficial effect of ethylene in RCEYM processes has been known for more than fifteen years.[21] Consequently, the reaction carried out under an atmosphere of ethylene displays higher performance (Table 4, entry 3). Recently, our group reported the use of 1,7-octadiene as a useful ethylene surrogate in RCEYM / Diels-Alder tandem processes.[22] The use of 1,7-octadiene as an additive gave rise to similar results when performed under positive pressure of nitrogen (Table 4, entry 4) but in a sealed tube, the product was formed

in an optimized 76% yield (Table 4, entry 5). Finally, the use of microwave irradiation did not produce any improvement (Table 4, entry 6).

The optimized reaction conditions were then applied to the enantiomerically enriched substrates **3d,o** affording the desired products in good yield albeit in somewhat diminished enantiomeric excess (Scheme 4).[23]



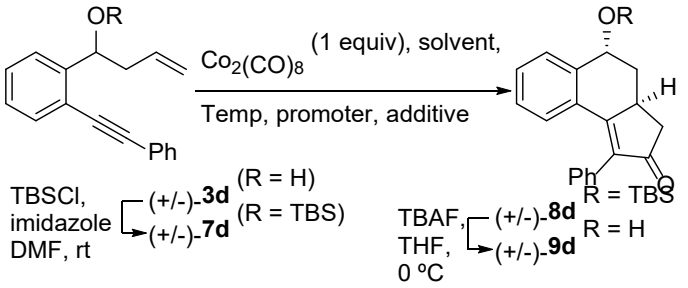
Scheme 4. RCEYM on enantiomerically enriched substrates **3d,o**.

In order to extend the scope of accessible backbones from model substrate **3d** in the context of DOS, the intramolecular Pauson-Khand reaction (PKR) of this 1,6-enyne was explored in turn.[24,25]

In our first approach, the PKR was carried out under stoichiometric conditions using DMSO as the promoter in toluene at 80 ºC, affording the desired product **9d** in good yield and moderate diastereoselectivity (Table 5, entry 1). Aiming to improve the diastereomeric ratio, the reaction was carried out at room temperature using NMO as the promoter (Table 5, entry 2). Under these conditions, the diastereoselectivity was improved to 9:1 without loss of chemical yield. Then, the reaction was carried out with a catalytic amount of $Co_2(CO)_8$ under an atmosphere of CO[26] but no conversion was observed (Table 5, entry 3). The use of molecular sieves, as CO adsorbent,[27] afforded the desired product in good yield but moderate diastereoselectivity both in toluene and DCE (Table 5, entries 4,5). Finally, the diastereoselectivity could be drastically improved (>20:1)

by using the bulky TBS protecting group for the alcohol (Table 5, entry 6), which could in turn be removed without affecting the diastereoselectivity.

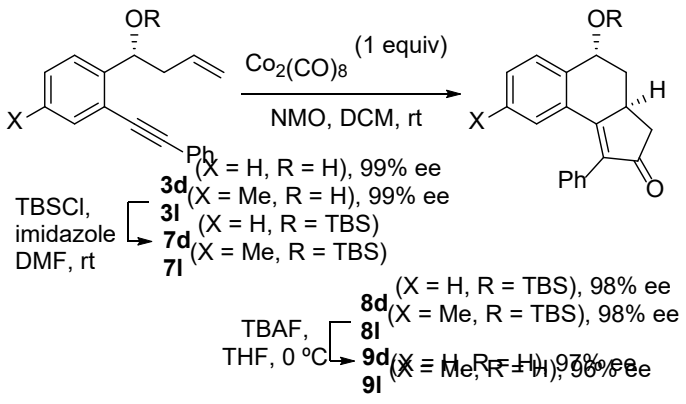
Table 5. Optimization of the intramolecular PKR



Entry	solvent	T (ºC)	prom.	R	**8d,9d** (%)	dr
1	TolH	80	DMSO	H	76	7:1
2	DCM	rt	NMO	H	78	9:1
3[a],[b]	DCE	80	CO	H	-	-
4[a],[b],[c]	TolH	65	CO	H	85	6:1
5 [a],[b],[c]	DCE	65	CO	H	76	7:1
6	DCM	rt	NMO	TBS	85	>20:1

[a] 0.2 equiv of $Co_2(CO)_8$ were used. [b] 1atm CO [c] 4Å MS used as additive

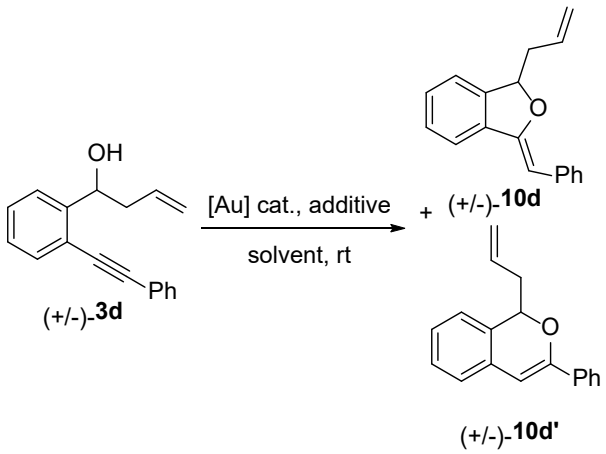
To our delight, we found that our optimized reaction conditions were applicable to the enantiomerically enriched substrates in good yield and with only minor erosion of the enantiomeric excess (Scheme 5).[28]



Scheme 5. PKR on enantiomerically enriched substrates **3d,l**.

Finally, the gold-catalyzed intramolecular hydroalkoxylation of the triple bond was investigated (Table 6).[29,30] First, aiming at a tandem hydroalkoxylation/Prins process leading to tricycles, we tried the conditions reported by Barluenga.[31] However, the new spot identified by TLC could not be isolated by column chromatography (Table 6, entry 1). On the other hand, the use of an *in situ* generated cationic gold (I) species led to the exclusive formation of the 5-*exo* cyclization product, albeit in moderate yield (Table 6, entry 2). A quantitative conversion with >20:1 selectivity towards 5-*exo* over 6-*endo* cyclization was achieved by switching to the NHC ligand IPr (Table 6, entry 3). The use of a pregenerated cationic gold (I) catalyst resulted in a significant decrease in the regioselectivity (Table 6, entry 4).

Table 6. Optimization of the intramolecular hydroalkoxylation



Entry	[Au]	Solv.	addit.	**10d** (%)	**10d'** (%)
1[a]	$AuCl_3$	MeOH	-	-[b]	-[b]
2[c],[d]	Ph_3PAuCl	DCM	AgOTf	40	-
3[c],[d]	IPrAuCl	DCM	AgOTf	95	4
4[a]	$SPhosAuNTf_2$	DCM	-	70	20

[a] 5 mol% of the gold catalyst was used. [b] Decomposition upon chromatographic purification. [c] 5 mol % of both gold and silver pre-catalyst precursors were used. [d] Substrate added to the preformed cationic gold complex.

These optimized conditions were then successfully applied to enantioenriched **3d** and propargyl derivative **5d** affording **10d** and **11d**, respectively, in moderate to excellent yield as single regioisomers and with minor loss of optical purity (Scheme 6).

Scheme 6. Gold (I)-catalyzed intramolecular hydroalkoxylation on enantiomerically enriched substrates **3d** and **5d**.

DFT Calculations. In order to investigate the mechanism of this allylboration reaction and particularly to explain the observed dependence of the enantioselectivity on the nature of the triple bond substituent, DFT calculations were performed.

Quantum mechanical calculations were performed using Gaussian 09 (Revision D.01).[32] All geometries were optimized using the B3LYP density functional,[33,34] and the 6-31G(d) basis set. Single point energies were calculated using M06-2X,[35] and the 6-311+G(d,p) basis set within the IEFPCM model.[36] The resulting energies were used to correct the gas phase energies obtained from the B3LYP calculations.[37-39] The free energy corrections were calculated using Truhlar's quasiharmonic approximation.[40] Computed structures were illustrated with CYLView.[41] The naphthyl rings of the catalyst were replaced by phenyl rings to simplify our calculations. Previous computational studies of BINOL-derived phosphoric acids showed that this truncation provides results in accord with experiment.[14] Goodman and Houk have investigated the mechanism of the BINOL-derived phosphoric acid-catalyzed allylboration and propargylboration reactions of benzaldehyde.[14] A formyl CH•••O hydrogen bond from the aldehyde CH to the phosphate oxygen controlled the stereoselectivity. This type of interaction has been shown to play a crucial role in many asymmetric reactions.[42-44] However, this mechanistic work does not explain the observed dependence of the enantioselectivity on the nature of the triple bond substituent in our allyl(propargyl)boration of *ortho*-alkynyl benzaldehydes.

To explain the low levels of ee observed in the phosphoric acid-catalyzed allylboration of **1a**, we located eight chair-like C-C bond forming TSs. These arise from the following variables: protonation site (equatorial or axial boronate oxygen), face of aldehyde attacked (*Re* or *Si*) and aldehyde conformation (A or B, Table 7). The four lowest energy TSs are shown in Figure 2. The lowest energy TS is **TS-1*Re*-B** which corresponds to Goodman's axial model and leads to the

experimentally observed product. **TS-1*Re*-B** is lower in energy than **TS-1*Re*-A** by only 0.1 and 0.3 kcal mol^{-1} in toluene and DCM respectively. This small energy difference can be rationalized in terms of two competing effects: the preferred conformation of **1a** and the strength of the formyl hydrogen bond. Aldehyde conformation A is preferred over conformation B due to unfavorable interactions between the lone pairs of the oxygen and the electron density of the alkyne in conformation B (Table 7). However, adopting conformation A in the TS disrupts the formyl hydrogen bond due to the proximity of the alkyne to the phosphate moiety thus increasing the interaction distance from from 2.24 to 2.65 Å. The hydrogen bond between the phosphoryl oxygen and the acidic terminal acetylenic proton (2.90 Å) does not compensate for this weaker formyl hydrogen bond and so **TS-1*Re*-B** and **TS-1*Re*-A** are almost identical in energy. Both **TS-1*Re*-B** and **TS-1*Si*-B** adopt aldehyde conformation B which destabilizes them relative to **TS-2*Si*-A**. **TS-1*Si*-B** is further destabilized by the proximity of the pinacol ester methyl groups to the bulky catalyst aromatic group. **TS-2*Si*-A** adopts preferred aldehyde conformation A and unlike **TS-1*Re*-A**, this does not disrupt the hydrogen bonding between the catalyst and the substrate. The small energy difference between the two *Re* TSs and **TS-2*Si*-A** leads to lower enantioselectivity in this reaction than that observed for the allylboration of benzaldehyde.

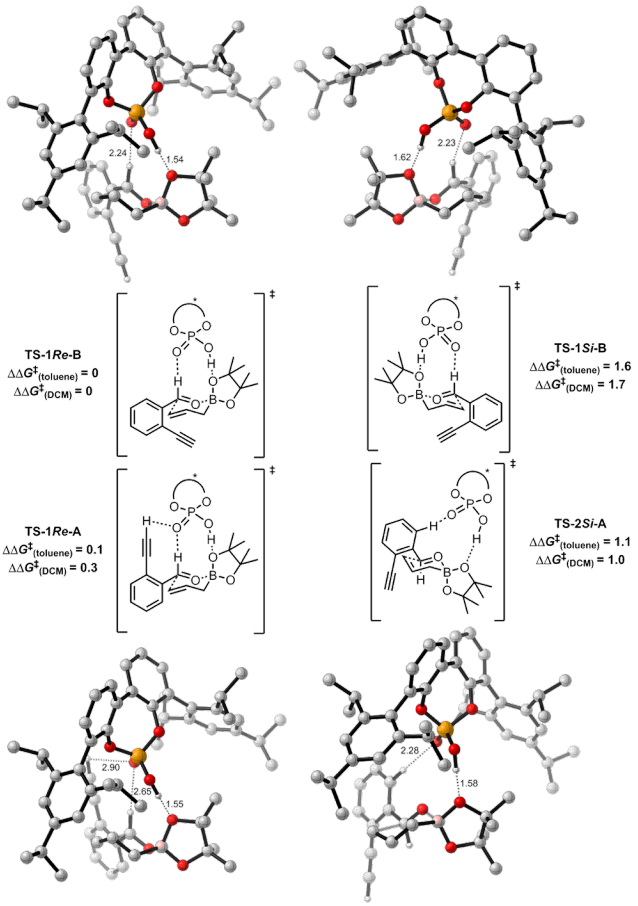
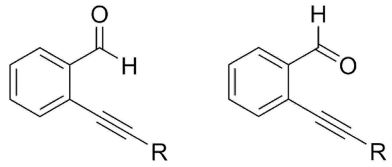


Figure 2. The four lowest energy C-C bond forming TSs for the BINOL-derived phosphoric acid-catalyzed allylboration of **1a**. M06-2X/6-311+G(d,p)−IEFPCM//B3LYP/6-31G(d). Non-critical hydrogen atoms omitted for clarity. All energies in kcal mol^{-1}.

Using this mechanistic understanding, we can analyze the observed enantioselectivity for other substrates. Experimentally, the ee observed in the allylboration of chloroacetylene **1g** is 90% (Scheme 1). **1g** is expected to reduce the unfavorability of aldehyde conformation B due to favorable interactions between the aldehyde oxygen and the local dipole induced by chlorine, stabilizing Goodman's TS-*Re*-B, leading to higher ee. Effects of this nature have been shown to be crucial in explaining the attractive interactions between anions and substituted benzenes.[45] Table 7 shows that the calculated difference between the two aldehyde conformations of **1g** is 0.4 kcal mol^{-1} lower than the difference between the conformers of **1a**, which is consistent with the

higher levels of ee seen experimentally for reaction of **1g** relative to **1a**. This energy difference is the same with both B3LYP and M06-2X methods (see Table S5). Table 7 also shows that the calculated difference between the two aldehyde conformations of **1e** are almost identical to that of **1a**, which is consistent with the similar enantioselectivity seen for the allylboration of these aldehydes. Sterics can also play a role in determining enantioselectivity. The TIPS-substituted aldehyde **1f** is expected to have similar electronic properties to **1e** but the observed ee is only 5%. Goodman's TS-*Re*-A and TS-*Re*-B would be destabilized by the proximity of the TIPS group to the chiral phosphate and boronate, respectively. However, Houk's TS-*Si*-A is not destabilized by the large TIPS group because the alkyne points into empty space, hence very low ee is observed experimentally.

Table 7. Preferred conformations of *o*-alkynyl benzaldehydes in DCM and toluene. M06-2X/6-311+G(d,p)−IEFPCM//B3LYP/6-31G(d). All energies in kcal mol^{-1}.



Conformation A Conformation B

R	Conformation A	Conformation B	
		DCM	Toluene
H (**1a**)	0	1.6	2.2
TMS (**1e**)	0	1.6	2.3
Cl (**1g**)	0	1.2	1.8

To understand the high levels of enantiocontrol seen in the allylboration of **1d**, the eight possible TSs were located. The four lowest energy TSs are shown in Figure 3. The lowest energy TS

corresponds to Goodman's axial model but, unlike the lowest energy allylboration TS of **1a**, aldehyde conformation A is adopted (**TS-3*Re*-A**). Aldehyde conformation A disrupts the formyl hydrogen bond but this is offset by favorable interactions between the phosphoryl oxygen and an aromatic CH and a CH-π interaction (2.28 Å and 3.23 Å, respectively, Figure 3). **TS-4*Si*-A** does not benefit from this CH-π interaction because the alkyne moiety points into empty space and also there is no formyl hydrogen bond in this TS. **TS-3*Si*-B** is stabilized relative to **TS-4*Si*-A** due to a favorable CH…O interaction between the equatorial boronate oxygen and a CH of the phenyl substituent (Figure 3). Therefore, **TS-3*Si*-B** and **TS-4*Si*-A** are close in energy but neither is stabilized to the same extent as **TS-3*Re*-A**, leading to higher ee in this reaction than that observed in the allylboration of **1a**.

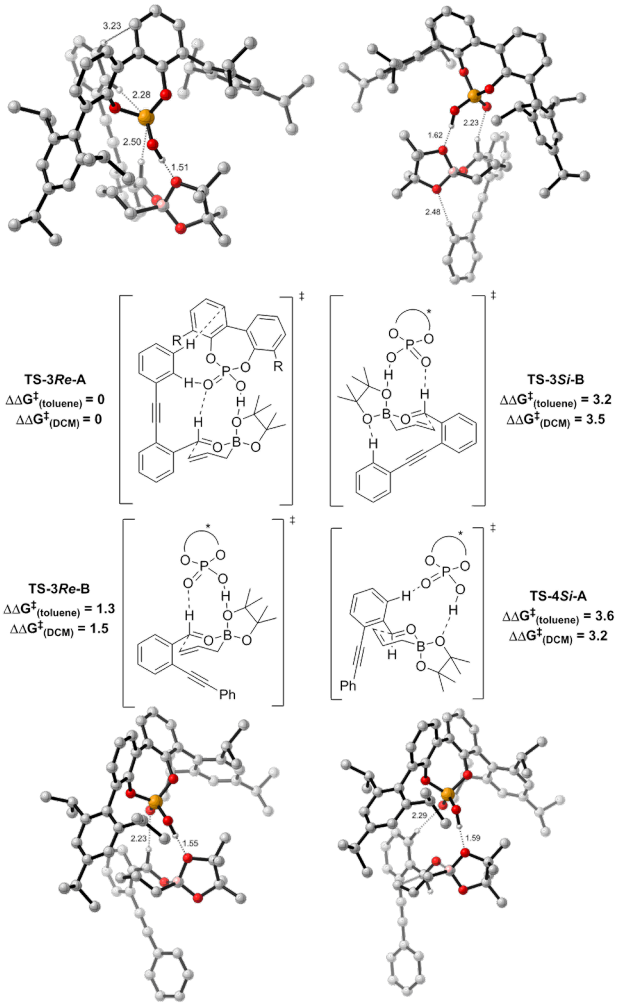


Figure 3. The four lowest energy C-C bond forming TSs for the BINOL-derived phosphoric acid-catalyzed allylboration of **1d**. M06-2X/6-311+G(d,p)−IEFPCM//B3LYP/6-31G(d). Non-critical hydrogen atoms omitted for clarity. All energies in kcal mol^{-1}.

The eight possible TSs were also located for the propargylboration of **1d**. In toluene, the two lowest energy *Re* and *Si* TSs are Goodman's TS-*Re*-A (0 kcal mol^{-1}) and TS-*Si*-B (+2.6 kcal mol^{-1}), in agreement with the results of the allylboration of **1d** in toluene.[46]

In summary, our calculations have shown that the introduction of an alkynyl substituent at the *ortho* position of benzaldehydes results in two different aldehyde conformations, conformation A and B. Conformation A is preferred over B by approximately 1.5 kcal mol^{-1}. However, adopting

conformation A in the TS disrupts the formyl CH•••O interaction, which has been shown to be crucial for high enantiocontrol, and results in diminished ee's in most cases. Only the introduction of an aromatic ring at the terminal position of the alkyne, which is able to establish additional favourable interactions under conformation A, reverses this trend achieving excellent levels of enantiocontrol.

CONCLUSIONS

In conclusion, the chiral Brønsted acid–catalyzed allyl(propargyl)boration of 2-alkynylbenzaldehyde derivatives has been studied leading to the first highly enantioselective allylation methodology for such derivatives. A strong dependence between enantioselectivities and the nature of the substitution at the alkynyl moiety was observed; only aryl–substituted substrates lead to satisfactory enantioselectivities.

The reaction conditions were further optimized for substrates of this kind and then the scope and limitations of this reaction were studied. The unprecedented densely functionalized intermediates thus obtained were then engaged in a number of synthetically interesting transformations, namely: RCEYM, PKR and intramolecular hydroalkoxylation, giving rise to an assorted library of polycyclic benzo-fused carbo- and heterocycles, difficult to obtain through known procedures.

DFT calculations showed that the high performance of the phenyl–substituted alkyne in the asymmetric allylboration reaction is the result of an interaction between the phosphoryl oxygen of the catalyst and an aromatic CH and a CH-π interaction. The dependence between enantioselectivities and the nature of the substitution at the alkynyl moiety can be understood in terms of the conformational preference of each aldehyde and the size of the substituent. All these observations showed that the *ortho*-alkynyl moiety, not only serves as a handle for follow-up

chemistry, but must be taken into consideration for the understanding of the observed stereochemical outcome.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, NMR spectra of all new compounds, HPLC chromatograms, crystallographic data for compounds **3d** and **5d**, including their CIF files; complete list of authors in the Gaussian 09 reference; Cartesian coordinates, energies, free energies (1 atm, 298 K) and number of imaginary frequencies of all stationary points and values of imaginary frequencies of all transition structures. This material is available free of charge via the Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author

*santos.fustero@uv.es

houk@chem.ucla.edu

pablo.barrio@uv.es

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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ABBREVIATIONS

RCEYM, ring-closing enyne metathesis; PKR, Pauson-Khand reaction; HA, hydroalkoxylation: DFT, density functional theory.

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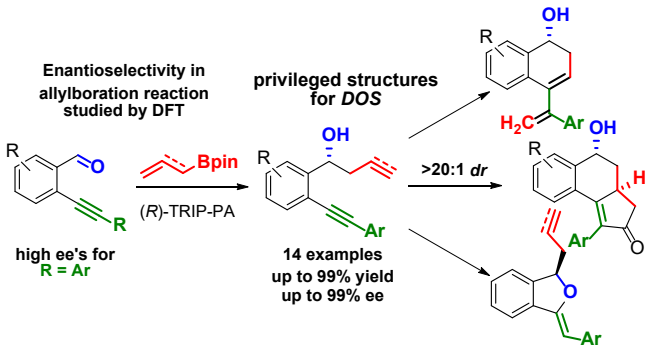

Chiral Brønsted acid-catalyzed allyl(propargyl)boration of *ortho*-alkynyl benzaldehydes gives rise to ω-alkynyl homoallylic(homopropargylic)alcohols that can be further transformed to complex molecular scaffolds via subsequent follow-up chemistry. Density functional theory (DFT) calculations show that this dependence is the result of the steric and electronic properties of the alkyne moiety.