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Asymmetric Catalysis

Catalytic Asymmetric Synthesis of Alkynyl Aziridines: Both Enantiomers of *cis*-Aziridines from One Enantiomer of the Catalyst

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Abstract: Alkynyl aziridines can be obtained from the catalytic asymmetric aziridination (AZ reaction) of alkynyl imines with diazo compounds in high yields and high asymmetric inductions mediated by a chiral boroxinate or BOROX catalyst. In contrast to the AZ reaction with aryl- and alkyl-substituted imines, alkynyl imines react to give *cis*-substituted aziridines with both diazo esters and diazo acetamides. Remarkably, however, the two diazo compounds give different enantiomers of the *cis*-aziridine from the same enantiomer of the catalyst. Theoretical considerations of the possible transition states for the enantiogenic step reveal that the switch in enantiomers results from a switch from *Si*-face to *Re*-face addition to the imine, which in turn is related to a switch from reaction with an *E*-imine in the former and a *Z*-isomer of the imine in the latter.

The chemistry of alkynyl aziridines has only been explored in any serious way in the last ten years or so.[1] Synthetic applications have included conjugate ring opening,[2,3] direct ring-opening at the propargylic carbon,[4–7] domino cyclization/ring expansions,[8] isomerization to pyrroles,[9] gold-catalyzed rearrangements,[10] and palladium- and indium-mediated alkylative reductive opening.[11] Many of these reactions have been employed in the synthesis of natural products including the ustiloxins,[6c–f] mitomycin C,[12] phomopsin B,[6b] saxitoxinol,[5c] lysergic acid,[11c] lysergol,[11c] isolysergol,[11c] and saxitoxin.[5b]

Previous syntheses of alkynyl aziridines encompass a cornucopia of methods including reaction of guanidinium ylides with aldehydes[13] and sulfonium ylides with imines.[14] Early methods include dehydrohalogenantion of α-bromoalkenyl aziridines[15] and nitrene addition to alkenes.[16] A popular method has been the addition of alkynyl organometallics to α-chloroimines[17] and to α-epoxy imines.[18] Access to alkynyl aziridines can be reliably realized by the ring closure of ω-haloallenyl methyl amines.[19] An attractive approach to the synthesis of alkynyl aziridines is the addition of γ-haloallenyl zinc reagents to imines.[20] There is also the straightforward option of ring-closure of a β-aminoalcohol which was employed after a base-promoted aza-Darzen reaction failed.[12a] A very effective method has been reported involving a Brønsted acid catalyzed addition of a diazo compound with an alkynyl imine.[12b] With all of the options at ones avail, there are nonetheless, a paucity of catalytic asymmetric methods. While there are a number of reports of chiral catalysts used in the preparation of alkynyl aziridines from the addition of a nitrene unit to an alkene, the scope is severely underdeveloped since all reports describe a single substrate, 1-phenyl-3-buten-1-yne.[21]

We have developed an asymmetric catalytic synthesis of aziridines from the reaction of imines and diazo compounds.[22–25] The chiral core of the catalyst for these reactions are the vaulted biaryl ligands VAPOL and VANOL.[26] The catalyst has been identified as the boroxinate **4** or **5** which is assembled in situ from the ligand and $B(OPh)_3$ only upon addition of the imine substrate (Scheme 1).[25b,27] The catalytic asymmetric aziridination is general for a variety of imine substrates providing access to aziridines with electron-rich and electron poor aryl and heteroaryl substituents as well as 1°, 2°, and 3° alkyl substituents bearing a range of functional groups. High yields, diastereoselectivity and enantioselectivity can be achieved with both *cis*- and *trans*-aziridines; the former with diazoacetates[22] and the latter with diazoacetamides.[28] The (*S*)-VANOL- or (*S*)-VAPOL-derived catalysts will deliver *cis*-aziridines via addition to the *Si*-face of the imine and *trans*-aziridines via *Re*-face addition to the imine. The present study finds that the same reaction with alkynyl imines with the same antipode of the catalyst gives *cis*-aziridines with both diazoacetates and diazoacetamides, but as opposite enantiomers (Scheme 1). The results of computational studies suggests that this enantiomeric switch is due to the preferred reaction of the *E*-isomer of the imine with diazoacetates and the *Z*-isomer of the imine with diazoacetamides.

Our initial finding was that the success of this catalytic asymmetric aziridination reaction did not translate to imines from alkynyl aldehydes. For example, the reaction of the imine **13a**

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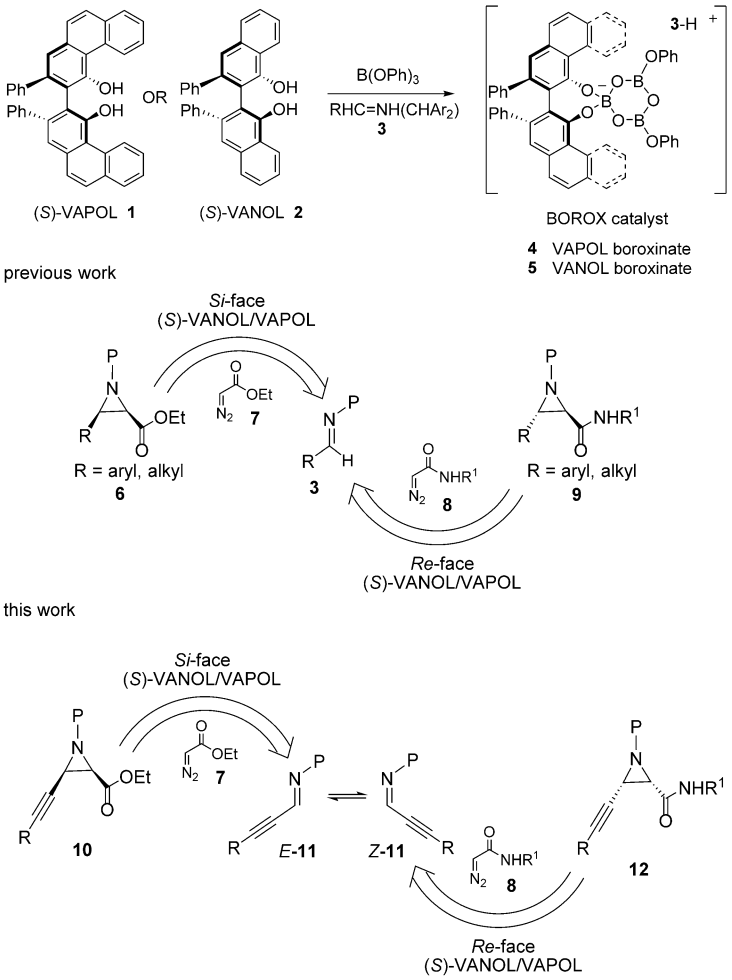


Scheme 1. Vaulted biaryl boroxinate catalysts in the aziridnation of imines.

with ethyl diazoacetate **7** gives the alkynyl aziridine **16a** in excellent yield, but with an optical purity of only 32% *ee* (Table 1, entry 1). This was surprising since we have examined a significant number of benzhydryl imines derived from aryl and aliphatic aldehydes and found that the asymmetric inductions are all in the range of 77–94% *ee*.[22b,c] Subsequent optimization studies with various substituted diaryl methyl imines from aryl and aliphahtic aldehydes, identified the MEDAM group as the optimal N-substituent for the catalytic asymmetric aziridination giving 91–99% *ee* over all substrates examined[22d] followed closely by the BUDAM group which gave 78–99% *ee* over the same set of substrates.

The optimization of the catalytic asymmetric aziridination of alkynyl imines commenced with a survey of the effect of the changes in the N-substituent in the imine and changes in the ligand in the BOROX catalyst and the results are summarized in Table 1. We did not expect much difference in the asymmetric inductions for the reaction of alkynyl imines with VANOL- and VAPOL-derived catalysts since we had observed essentially no difference (ca. 1–2% *ee*) between VANOL and VAPOL in the aziridinations of alkyl and aryl imines with either benzhydryl,[22c] MEDAM[22d] or BUDAM[22d] imines. Thus it was slightly surprising that the asymmetric induction for the reaction of the benzhydryl imine **13a** dropped from 32% *ee* for the VAPOL catalyst to 21% *ee* for the VANOL catalyst (Table 1, entries 1 and 2). As expected the asymmetric induction was better for the MEDAM imine **14a** for both the VAPOL and VANOL catalyst but the increase was modest at best (40–44% *ee*, entries 4 and 5). The big surprise was the finding that a dramatic increase in induction was realized with the BUDAM imine **15a**. The aziridine **18a** was isolated in 97% yield and 83% *ee* with 4 mol% of the VAPOL boroxinate catalyst (entry 6). A similar significant increase was noted for the analogous trimethysilyl imine **15b** (entry 8).

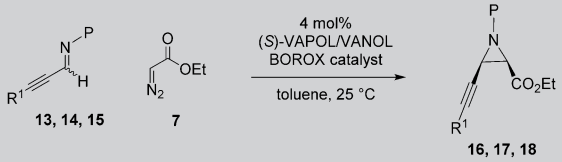
Another interesting and important finding is that the asymmetric inductions are independent of the geometry of the imines. The BUDAM imine **15b** is produced as a 1.6:1 mixture of *Z*:*E* isomers when generated from the reaction of BUDAM amine and trimethylsilyl propargyl aldehyde. Imine **15b** is crystalline and upon crystallization the ratio of diastereomers can be enhanced to 19:1 in favor of *Z*. The *Z*-isomer of **15b** slowly isomerizes to the *E*-isomer in solution at room temperature. It also appears that imine **15b** can isomerize in the presence of the catalyst since both the 1.6:1 and 19:1 mixtures give essentially the same asymmetric induction (entries 8 and 9). These reactions occur with a high degree of diastereoselection for the *cis*-isomers of the alkynyl aziridines as the *trans*-isomers were not detected in any of the reactions in Table 1 and 2.

Further studies on the BUDAM imine **15b** found that the asymmetric induction was sensitive to both the solvent and the temperature. The aziridine **18b** could be obtained in 95% *ee* and 86% yield if the reaction were performed in ether at $-20\,^{\circ}C$ (Table 1, entry 14). The reaction with the MEDAM imine **14b** also improved under these conditions (Table 1, entry 15). The asymmetric induction in **18b** was measured by HPLC after the BUDAM group had been removed. This deprotection could be achieved in 83% yield to give the N-H aziridine **20** following a protocol that had been developed for dianisylmethyl protected aziridines.[22e] Orthogonal deprotection of the alkynyl aziridine **18b** could be achieved with tetrabutylammonium fluoride to give the ethynyl aziridine **19** in 89% yield.

An examination of the scope of the aziridination of BUDAM-protected alkynyl aziridines of the type **15** is presented in Table 2. There is a significant difference in the effectiveness of the two ligands, with VAPOL giving uniformly superior performance in terms of both yield and asymmetric induction. The alkynyl aziridines **18** are generally formed in very high asymmetric inductions and moderate to good yields with aryl- and trimethylsilyl-substituted alkynyl imines.

The pyrrazole side-product **21** was observed for the aryl-substituted imines, but is not seen with the trimethylsilyl imine **15b** which is isolated in 86% yield (entry 1). The regiochemistry of this [3+2] cycloaddition to the alkyne function was not rigorously established but rather assumed to be the same as that observed for the [3+2] cycloaddition of ethyl diazoacetate

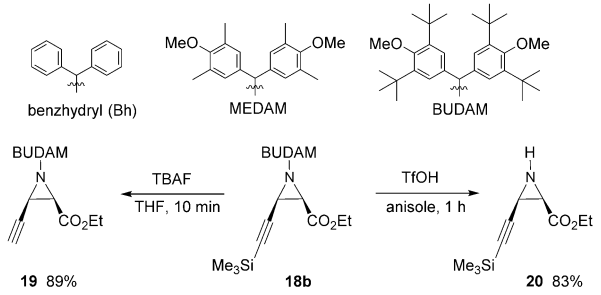
Table 1. Catalytic asymmetric aziridination of alkynyl imines.[a]



13, 14, 15 — 7 — 16, 17, 18

Entry	R^1	P	imine	*cis*/*trans* imine	Ligand	Aziridine	Yield azir [%][b]	*ee* azir [%][c]
1	iPr$_3$Si	Bh	**13a**	1.3:1	(*S*)-VAPOL	**16a**	91	32
2	iPr$_3$Si	Bh	**13a**	nd	(*R*)-VANOL	**16a**	87	−21
3	Me$_3$Si	Bh	**13b**	nd	(*S*)-VAPOL	**16b**	78	32
4	iPr$_3$Si	MEDAM	**14a**	1.5:1	(*S*)-VAPOL	**17a**	87	44
5	iPr$_3$Si	MEDAM	**14a**	nd	(*R*)-VANOL	**17a**	89	−40
6	iPr$_3$Si	BUDAM	**15a**	nd	(*S*)-VAPOL	**18a**	97[d]	83
7	iPr$_3$Si	BUDAM	**15a**	nd	(*S*)-VANOL	**18a**	97[d]	78
8	Me$_3$Si	BUDAM	**15b**	19:1[e]	(*S*)-VAPOL	**18b**	93	85
9	Me$_3$Si	BUDAM	**15b**	1.6:1	(*S*)-VAPOL	**18b**	86[f]	84
10	Me$_3$Si	BUDAM	**15b**	19:1[e]	(*R*)-VANOL	**18b**	91	−74
11	Me$_3$Si	BUDAM	**15b**	19:1[e]	(*S*)-VAPOL	**18b**	87[d,f]	80
12	Me$_3$Si	BUDAM	**15b**	nd	(*S*)-VAPOL	**18b**	90[g]	87
13	Me$_3$Si	BUDAM	**15b**	nd	(*S*)-VAPOL	**18b**	90[g]	90[h]
14	Me$_3$Si	BUDAM	**15b**	nd	(*S*)-VAPOL	**18b**	86[g]	95[h,i]
15	Me$_3$Si	MEDAM	**14b**	nd	(*S*)-VANOL	**17b**	89[g]	82[h,i]

[a] Unless otherwise specified, all reactions were performed with 0.5 M imine in toluene at 25 °C or 24 h with 1.1 equiv of EDA **7** and with 4 mol% catalyst. The catalyst was prepared from 1 equiv VAPOL or VANOL, 4 equiv $B(OPh)_3$ and 1 equiv H_2O at 80 °C in toluene for 1 h, followed by removal of volatiles under vacuum (0.5 mm Hg) at 80 °C for 0.5 h. No *trans*-aziridine was detected in any reaction. [b] Yield of isolated aziridine after silica gel chromatography. [c] Determined by HPLC on a Chiralcel OD-H column. The induction in entries 8–14 were determined after conversion of **18b** to the N-H aziridine **20**. [d] 2 mol% catalyst. [e] The isomer ratio was enhanced by crystallization from EtOAc/hexane. [f] Overall yield of **20** from **15b**. [g] Reaction at −20 °C. [h] 10 mol% catalyst. [i] Reaction in Et_2O.



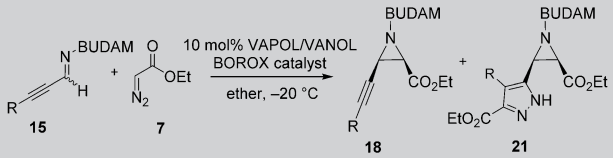
to α,β-unsaturated alkynyl esters, ketones, and aldehydes.[26] It is considered likely that the [3+2] cycloaddition occurs first giving a pyrrazole-substituted imine. A control experiment reveals alkynyl aziridine **18** will not react with **7** in the presence of the catalyst to give **21** (see Supporting Information). The alkynyl imines **15k** and **15l** with aliphatic groups on the alkyne gave very complex reaction mixtures which were not characterized (entries 12 and 13). Aziridine **18** and pyrrazole **21** could be tentatively identified as being present in an approximately 1:1 ratio in the ^{1}H NMR spectrum of the crude reaction mixtures from imines **15k** and **15l**, but were not the major species.

Extension of these studies on the reactions of alkynyl imines to diazoacetamides produced two surprises. First, the application of the optimal conditions for the aziridination with ethyl diazoacetate resulted in abject failure giving only a 4% yield of aziridine after starting materials were consumed (Table 3, entry 5). In contrast to the reactions with ethyl diazoacetate where the BUDAM imine was vastly superior to MEDAM and benzhydryl imines (Table 1), in the reactions with diazoacetamides, the BUDAM imine was vastly inferior to both the MEDAM and benzhydryl imines (see Supporting Information). After considerable effort, optimal conditions were found for the aziridination of the alkynyl imines with the diazo acetamide which involved the use of MEDAM imines with the VANOL catalyst in toluene and could be successfully extended to all thirteen substrates shown in Table 3 with very high enantioselectivities. Clearly the biggest difference in the two protocols can be traced to the BUDAM versus MEDAM group and not the VANOL versus VAPOL ligands. Under the same conditions, the VANOL and VAPOL catalysts give essentially the same yield with VANOL giving the slightly higher induction (Table 3, entries 3 vs. 4). All of the aryl-substituted alkynyl imines **14** could be taken to completion with 5 mol% catalyst at −40 °C in 4 h to give excellent yields of the aziridine **24** with inductions in the range of 96–99% *ee* with a minimum *cis*/*trans* selectivity of 23:1. The imines **14k** and **14l** with *n*-butyl and cyclohexyl substituents were a little slower and required −20 °C to go to completion in 4 h but still gave high yields and very high enantioselectivities with no significant amounts of side-products observed. The *tert*-butyl substituted imine **14m** was even slower and required 24 h to go to completion at −20 °C but still gave excellent asymmetric induction. None of the [3+2] cycloaddition products of the type **21** were observed in any of the reactions in Table 3. It is important to note that the *N*-butyl diazoacetamide **23** is nearly as effective as the *N*-phenyl derivative **22** which would be of importance where solubility is an issue since **23** is more soluble than **22** (Table 3, entries 5 vs. 6).

The second and biggest surprise in the reactions with diazoacetamides is that the aziridines are *cis* and not *trans*, and furthermore, that they are of the opposite enantiomers from the *cis*-aziridines obtained with ethyl diazoacetate with the same enantiomer of the catalyst. This was demonstated by chemical correlation of **24c** with **17c** (Scheme 2). After activation and exposure to sodium ethoxide, the amide group in **24c** was avulsed to reveal that the resulting aziridine **17c** had a configuration opposite to the **17c** obtained from the reaction of the same imine with ethyl diazoacetate with the same enantiomer of the catalyst (see Supporting Information). The absolute configuration of **17c** obtained from **24c** was determined by hydrogenation of **17c** with Pearlman's catalyst to give the known *cis*-aziridine **27**.[22a]

Theoretical Investigation: The facial selectivities of the asymmetric catalytic aziridinations with the VANOL- and VAPOL-BOROX catalysts from the point of view of the imine are summarized in Scheme 1. With the (*S*)-catalysts, *Si*-face addition to

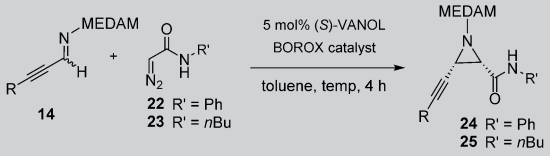
Table 2. Aziridination of alkynyl imines with ethyl diazo acetate.[a]



Entry	R	Imine	Ligand	Aziridine	Yield azir **18** [%][b]	*ee* azir **18** [%][c]	Yield **21** [%][d]
1	Me_3Si	**15b**	(*S*)-VAPOL	**18b**	86	95	–
2	C_6H_5	**15c**	(*S*)-VAPOL	**18c**	66	97	18
3	C_6H_5	**15c**	(*R*)-VANOL	**18c**	49	−85[e]	17
4	*p*-$MeOC_6H_4$	**15d**	(*S*)-VAPOL	**18d**	45	96	27
5	*p*-$MeOC_6H_4$	**15d**	(*R*)-VANOL	**18d**	24	−83[e]	11
6	*p*-BrC_6H_4	**15e**	(*S*)-VAPOL	**18e**	54	97	24
7	*p*-BrC_6H_4	**15e**	(*R*)-VANOL	**18e**	25	−53[e]	5
8	*p*-$(CO_2Me)C_6H_4$	**15f**	(*S*)-VAPOL	**18f**	57	94	19
9	*p*-$(CO_2Me)C_6H_4$	**15f**	(*R*)-VANOL	**18f**	30	−54[e]	5
10	*p*-$NO_2C_6H_4$	**15g**	(*S*)-VAPOL	**18g**	35	88	22
11	*p*-$NO_2C_6H_4$	**15g**	(*R*)-VANOL	**18g**	28	−41[e]	3
12[f]	*n*-butyl	**15k**	(*S*)-VAPOL	**18j**	nd	nd	nd
13[f]	cyclohexyl	**15**	(*S*)-VAPOL	**18k**	nd	nd	nd

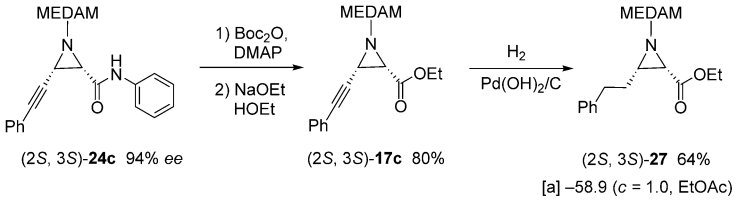
[a] Unless otherwise specified, all reactions were performed with 0.5 M **15** in ether with 1.2 equiv EDA **7** at −20 °C for 24 h with 10 mol% catalyst. The catalyst was prepared as described in Table 1. nd = not determined. No trans aziridine was detected in any reaction. [b] Isolated yield after chromatography on silica gel. [c] Determined on purified *cis*-**18** by HPLC. [d] Determined from ^{1}H NMR spectra of the crude reaction mixture and based on isolated yield of **18**. [e] Enantiomer of **18** is formed. [f] Complex mixture of products was formed. The ratio of **18**:**21** was ~1:1 but neither was the major species.

Table 3. Aziridination of alkynyl imines with diazo acetamides.[a]



Entry	R	Imine	Temp	*cis/trans*[b]	Aziridine	Yield azir [%][c]	*ee* azir [%][d]
1	iPr_3Si	**14a**	−20	50:1	**24a**	87	98
2	Me_3Si	**14b**	−20	5:1	**24b**	80	85
3[e]	C_6H_5	**14c**	0	12:1	**24c**	78	94
4[e,f]	C_6H_5	**14c**	0	20:1	**24c**	77	−90
5	C_6H_5	**14c**	−40	50:1	**24c**	91	97
6[g]	C_6H_5	**14c**	−40	40:1	**25c**	84	94
7[h]	C_6H_5	**15c**	−20	4:1	**26c**	4[i]	nd
8	4-$MeOC_6H_4$	**14d**	−40	>50:1	**24d**	90	99
9[j]	4-BrC_6H_4	**14e**	−40	>50:1	**24e**	93	−99
10	4-$MeO_2CC_6H_4$	**14f**	−40	23:1	**24f**	90	96
11	4-$NO_2C_6H_4$	**14g**	−40	25:1	**24g**	90	96
12	3-MeC_6H_4	**14h**	−40	33:1	**24h**	90	96
13	2-MeC_6H_4	**14i**	−40	33:1	**24i**	93	96
14	1-naphthyl	**14j**	−40	25:1	**24j**	95	97
15	*n*-butyl	**14k**	−20	25:1	**24k**	82	98
16	cyclohexyl	**14l**	−20	25:1	**24l**	84	97
17[k]	cyclohexyl	**14l**	−40	>50:1	**24l**	78	99
18[l]	*tert*-butyl	**14m**	−20	4:1	**24m**	78	91

[a] Unless otherwise specified, all reactions were performed on 0.2 mmol in toluene at 0.2 M imine with 1.4 equiv of diazoacetamide **22** for 4 h and went to 100% completion. Each entry is the average of 2 runs except 13 and 14. The catalyst was prepared by heating a mixture of the ligand, 3 equiv $BH_3{\cdot}SMe_2$, 2 equiv phenol, 3 equiv H_2O in toluene at 100 °C for 1 h. The volatiles were then removed under vacuum (0.1 mm Hg) at 100 °C for 1 h. nd = not determined. [b] Determined from ^{1}H NMR spectrum of the crude reaction mixture. [c] Average yield of isolated pure *cis*-aziridine after silica gel chromatography. [d] Determined by HPLC on pure *cis*-aziridine and average of two runs. [e] Reaction with 10 mol% catalyst for 24 h. [f] Reaction with (*R*)-VAPOL. [g] Reaction with diazo acetamide **23**. [h] Reaction with 10 mol% catalyst from (*R*)-VAPOL in Et_2O with BUDAM imine **15c** which went to 100% completion in 24 h. [i] Determined from the ^{1}H NMR spectrum of the crude reaction mixture with Ph_3CH as internal standard. The same reaction with (*S*)-VANOL gave a 16% yield with a *cis*/*trans* of 1.2:1. [j] (*R*)-VANOL was used in catalyst preparation. [k] Reaction went to 81% completion. [l] Reaction time was 24 h.



Scheme 2.

the imine is observed with ethyl diazoacetate and *Re*-face addition is observed with diazo acetamides. For alkyl and aryl imines, this switch in facial selectivity is accompanied by a switch in diastereoselectivity—with ethyl diazoacetates giving *cis*- and diazoacetamides giving *trans*-aziridines. The origin of this switch in diastereoselectivity has previously been rationalized.[28b] In this section, we present a computational investigation of the origin of enantiodivergence observed in the (*S*)-VANOL-BOROX-catalyzed reactions of alkynyl imines with ethyl diazoacetate (**7**) and diazoacetamide (**22**).

All transition structures for the (*S*)-VANOL-BOROX-catalyzed reaction of **14b** and **7**/**22** were located in ONIOM(M062x/6-31+G**:AM1) calculations[29] as implemented in Gaussian 09.[30] The division of layers for the ONIOM calculations is shown in Figure 1. All reported distances are in angstroms. Rel-

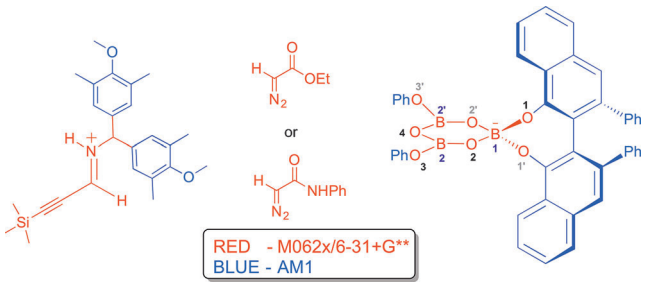


Figure 1. Division of layers for ONIOM calculations and the key descriptors of the (*S*)-VANOL-BOROX anion.

ative energies of the transition structures reported in this work are the *E*+zpe energies from the ONIOM calculations. Figure 1 also shows the key descriptors of the (*S*)-VANOL-BOROX anion. The oxygen atoms O1, O2, and O3 are the H-bond acceptors in one of the chiral pockets while O1′, O2′, and O3′ are their counterparts in the complementary chiral pocket. The boroxinate core has one tetracoordinate boron atom B1 and two identical tricoordinate boron atoms B2 and B2′.

Based on our previous computational studies,[28b,c,31] we designed a systematic approach (Figure 2) to explore the carbon–carbon bond forming transition state for the reaction of **14b** and **7**/**22**. The goal of this theoretical investigation is to identify the origin of enantiodivergence observed in these reactions of alkynyl imines. The fundamental difference between aryl imines and alkynyl imines is that while aryl imines with a benzhydryl (or MEDAM/BUDAM) protecting group prefer to adopt an *E* geometry, alkynyl imines can adopt both the *E* and *Z* geometry, about the imine double bond. As a result, there is a two-fold increase in the geometries to be considered while exploring the addition of diazo nucleophiles to the catalyst-bound protonated alkynyl imine. Figure 2 effectively illustrates this point. For R = aryl, **1E**–**4E** are the four main geometries of the catalyst-imine complexes to be considered. For R = alkynyl, there are four additional geometries **1Z**–**4Z** that need to be considered. Out of these eight geometries, four have the *Re*-face exposed, while the other four have their *Si*-face exposed, for approach of the catalyst-bound diazo nucleophile (indicated in green). Consideration of the resulting eight transition structures leading to the diazonium ion intermediates (which are pre-cursors to the formation of both enantiomers of the *cis*-aziridines) will enable prediction of enantioselectivity. This systematic approach can be applied to each of the diazo nucleophiles.

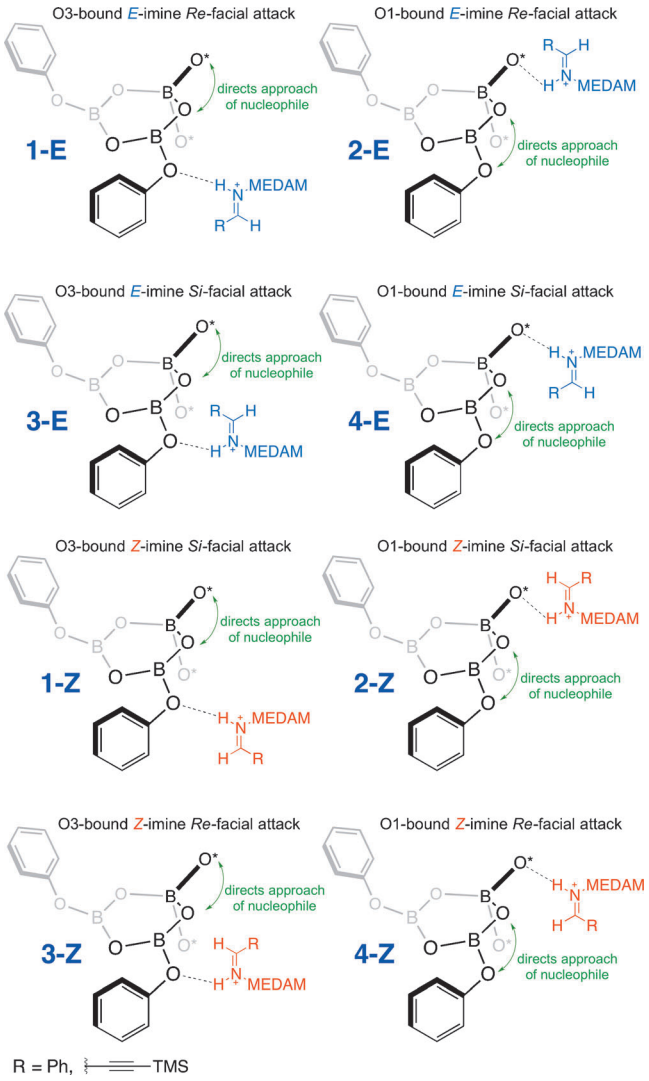


Figure 2. Imine binding modes and systematic approach to predict origin of enantioselectivity in the aziridination reaction of imines and diazo nucleophiles.

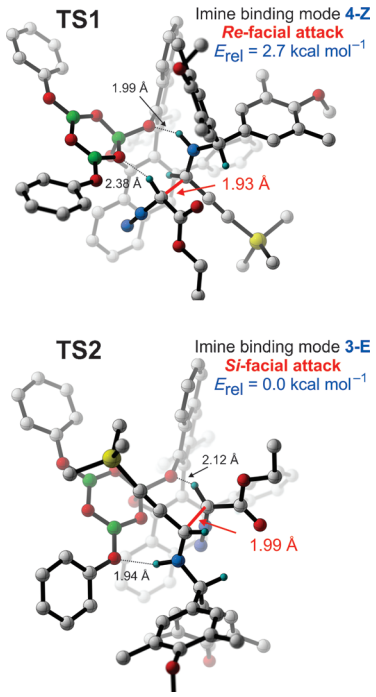


Figure 3. Lowest energy carbon–carbon bond-forming transition structures leading to either enantiomer of the diazonium ion intermediate (enantioselectivity-determining step) in the reaction of **14b** and **7** catalyzed by the (*S*)-VANOL-BOROX catalyst

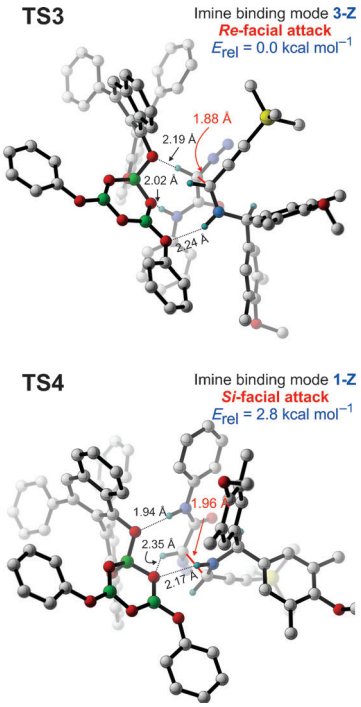


Figure 4. Lowest energy carbon–carbon bond-forming transition structures leading to either enantiomer of the diazonium ion intermediate (enantioselectivity-determining step) in the reaction of **14b** and **22**.

The lowest energy carbon–carbon bond-forming transition structures from *Re*- and *Si*-facial approach of ethyl diazoacetate are shown in Figure 3. Consistent with the observed enantioselectivity, **TS1**—the lowest energy transition structure for the *Re*-facial approach of ethyldiazoacetate—is 2.7 kcal mol^{-1} higher in energy (E+zpe) than the lowest energy transition structure for the preferred *Si*-facial approach (**TS2**). Of the four possible imine binding modes allowing the *Re*-facial attack of **7** (see Figure 2), binding mode **4-Z** was found to be the most favored (**TS1**). In contrast, the *E* geometry of the imine (binding mode **3-E**) was found to be preferred in the most favored transition structure for the *Si*-facial attack of **7**—namely **TS2**. In both **TS1** and **TS2**, the α-CH of **7** is H-bonded to one of the oxygen atoms of the boroxinate core. The *E*-geometry of the imine and the shorter α-CH···O bond (2.12 Å in TS2 versus 2.38 Å in **TS1**) likely contributes to the energetic favorability of **TS2**.

Figure 4 shows the corresponding transition structures when *N*-phenyldiazoacetamide (**22**) replaces ethyldiazoacetate (**7**) as the nucleophile. Consistent with the reversal in enantioselectivity, **TS3**—the lowest energy transition structure for the *Re*-facial approach of *N*-phenyldiazoacetamide—is now favored by 2.8 kcal mol^{-1} (E+zpe) over the lowest energy transition structure for the *Si*-facial approach (**TS4**). Unlike **TS1** and **TS2**, transition structures **TS3** and **TS4** have the same *Z* orientation about the imine double bond with the only difference being the mode of binding of the imine to the catalyst (**3-Z** versus **1-Z**). In both **TS3** and **TS4**, the nucleophile **22** forms two H-bonding interactions with oxygen atoms in the boroxinate core—a α-CH···O interaction and an NH···O interaction. The energetic preference for **TS3** over **TS4** likely arises from two factors —i) the shorter α-CH···O interaction in **TS3** versus **TS4** (2.19 Å versus 2.35 Å) and (ii) the NH···O interaction being between the more electron-rich oxygen atom O2 in **TS3** versus O1 in **TS4**.

In our previous computational analysis of the AZ reaction of phenyl MEDAM imine with **7** and **22**, we accounted for the observed diastereo- and enantiodivergence based on a competition between binding modes **3E** and **1E**.[28b,c] The most intriguing observation in the current study is that upon changing the imine to an alkynyl imine, the observed enantiodivergence (upon switching from **7** to **22**) is now a result of competition between binding modes **3E** and **3Z**. Therefore, enantioselection in reactions catalyzed by chiral BOROX catalysts is attributable to a dynamic process that is dependent on 1) the geometry of the protonated imine and 2) the transition state geometry that accommodates the most favorable network of H-bonding interactions between the reactants and the chiral catalyst. Additional experimental mechanistic investigations to validate the proposed computational model are currently underway.

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Keywords: Asymmetric catalysis · aziridine · BOROX catalyst · imine isomerization · VANOL · VAPOL

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