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# Catalytic Asymmetric Synthesis of Trisubstituted Aziridines

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Supporting Information

**ABSTRACT:** A method is described which provides for the direct asymmetric catalytic synthesis of trisubstituted aziridines from imines and diazo compounds. While unactivated imines were not reactive to α-diazo carbonyl compounds in which the diazo carbon was disubstituted, *N*-Boc imines react with both α-diazo esters and α-diazo-*N*-acyloxazolidinones to give trisubstituted aziridines with excellent diastereo- and enantioselectivities.

Significant advances in the catalytic asymmetric synthesis of aziridines have occurred in recent years; yet, limitations and challenges for continued improvement still exist.[1] We have had success with the reaction of diazo compounds with imines and chiral polyborate Brønsted acid catalysts derived from either the VANOL 6 or VAPOL 7 ligands (Scheme 1).[1c,2−4] The analogous catalysts employing the BINOL ligands **8**−**10** have been less effective.[1c,2c,2e] The VANOL and VAPOL catalysts can provide *cis*-aziridines **3** with diazo acetate esters[2,5] and diazomethyl ketones[3] and *trans*-aziridines **5**[4,6] with *sec*-diazoacetamides. Despite these advances, however, a general method for the direct catalytic asymmetric synthesis of trisubstituted aziridines is still lacking.[7,8] We report here the first highly asymmetric catalytic method for the synthesis of trisubstituted aziridines.

The MEDAM imine **11** (Scheme 2) became a focus for the search for a trisubstituted aziridine synthesis since it was among the best imine substituents we have identified.[2c] The aziridination of the **11** is ten times faster than the corresponding diphenylmethyl imine and gives a much higher yield and asymmetric induction. For example, the reaction with ethyl diazoacetate gives aziridine **13a** in 94% yield and 97% ee and is complete within 1 h at rt with 5 mol % catalyst (Scheme 2). We were thus surprised to find that the high reactivity of **11** with this catalyst did not translate to α-diazopropionate **14a**. Heating **11** and a 5-fold excess of diazo compound **14a** with 20 mol % catalyst at 80 °C did not give any detectable amount of the aziridine **13b** but, rather, lead only to a 98% recovery of the imine after 64 h (only 16% of **14a** survived).

The introduction of a *tert*-butyloxycarbonyl group (Boc) on the imine nitrogen was sufficient to induce reactivity even at −78 °C as indicated in Table 1. It was quickly found that the catalyst prepared from the VAPOL ligand gave very low induction (entry 2) whereas the catalyst prepared from the VANOL ligand under the same conditions gave the trisubstituted aziridine **17** in 83% ee (entry 3).[9] This stark difference between these two ligands was unexpected, since the two are comparable in aziridinations giving *cis*-aziridines **3**[2c] and *trans*-aziridines **5**[4] (Scheme 1). The yields are modest and the reactions are quite fast, but the yields for **17a** do not increase or decrease with increased reaction times (entries 3−5). The yields also do not depend on whether an excess of imine **15** or diazo compound **14a** is employed (entry 3 vs 6). The asymmetric induction does not increase significantly when the temperature is lowered to −100 °C (entry 7), but it does when the catalyst solution is precooled to −78 °C before addition to the solution of reactants (entry 8). Trisubstituted aziridines could also be obtained for the diazo compounds **14b** and **14c**, but the more hindered **14d** with an *iso*-propyl group on the diazo carbon failed to give any detectable amount of aziridine (entry 14).

While reaction with the α-diazo esters **14** did give good to excellent asymmetric inductions, the yields of the trisubstituted aziridines were moderate at best (Table 1). In the search for a more suitable diazo partner for the *N*-Boc imines, we were pleased to find that the α-diazo-*N*-propanoyloxazolidinone **18a** reacted with imine **15** with the VANOL catalyst to give the aziridine **19a** in 80% yield and 94% ee with >100:1 selectivity for the *trans*-diastereomer (Table 2, entry 1).[10] As with the diazo ester **14a**, the VAPOL catalyst gave low and reversed asymmetric induction (entry 1 vs 2). BINOL ligands **8**−**10** did not give useful selectivities (entries 3−6). The catalyst loading could be lowered to 10 mol % and the degree of asymmetric induction retained if the catalyst solution was precooled to −78 °C before addition to the reaction mixture (entry 1 vs 11). The optimized protocol was identified as that in entry 12 of Table 2.

The results of an examination of the scope of aziridination of various N-Boc imines with the α-diazo-*N*-acyloxazolidinone **18a** and **18b** are presented in Table 3. Uniformly excellent asymmetric inductions were observed for nearly all substrates. The reactions with electron-withdrawing groups are generally faster and those with *para*-substituents give high inductions, but this falls off with the *meta*-bromo substituent (entry 8). The *para*-methyl substituted aryl imine is slower, but the induction is high (entry 10) as it also is for the *meta*-methyl substituent (entry 12). The *ortho*-methyl substituent is not tolerated, and there is essentially no reaction for this substrate (entry 13) nor for the imine from cyclohexane carboxaldehyde (entry 19). The *para*-methoxy substituent slows the reaction considerably and provides the aziridine **43** in only 15% yield in 11 h with 20 mol % catalyst (entry 14). However, the reactivity can largely be recovered for a *para*-oxygenated substituent in the guise of the pivaloyl substituted imine **30** which gives aziridine **44** in 69% yield and 98% ee with 10 mol % catalyst (entry 15). The reactions of the 3,4-dioxygenated phenyl imines **31** and **32** also gave aziridines in good yields and high asymmetric inductions. Finally, the α-diazo-*N*-butanyloxazolidinone **18b** also gives trisubstituted aziridines with good yields and excellent asymmetric inductions.

The method for the asymmetric catalytic synthesis of trisubstituted *trans*-aziridines described here and our previously

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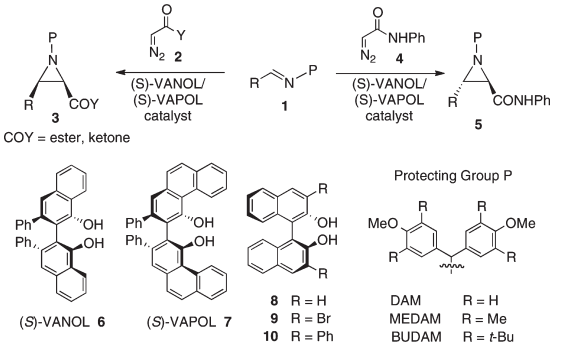
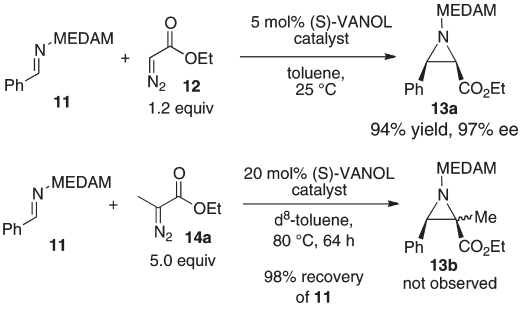
**Scheme 1**



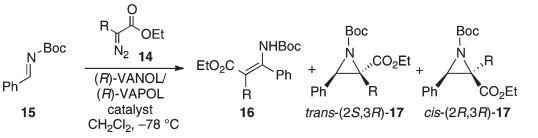

**Scheme 2**




published[2b] work on the alkylation of disubstituted *cis*-aziridines together provide stereocomplementary avenues to *cis*- and *trans*-trisubstituted aziridines. Specifically, the VANOL catalyst can be utilized to obtain either the *cis*- or *trans*-isomers of trisubstituted aziridines-2-carboxylate esters in either a two- or one-step process, respectively. (Scheme 3). This is illustrated in the enantio- and diastereoselective synthesis of the *cis*- and *trans*-isomers of the *N*-Boc aziridines **17a** shown in Scheme 4. The reaction of the BUDAM imine **48** (Scheme 1) and ethyl diazoacetate **12** with the VANOL catalyst gives the *cis*-aziridine **49** in 97% yield and 98% ee (Scheme 4).[2c] It is known that aziridines of this type can be alkylated with retention,[2b] and thus, in the present case, methylation, removal of the BUDAM group, and reaction with Boc anhydride give *cis*-**17a** (Scheme 4), the diastereomer of the product obtained from the aziridination of *N*-Boc imine **15** with the diazo ester **14a** (Table 1) and also a diastereomer with the aziridine obtained from the reaction of **15** with the diazo oxazolidinone **18a** and subsequent ethanolysis (Scheme 4). Note that the (*S*)-VANOL catalyst gives different face selectivities with **48** and **15**. The same chemistry can be used to prepare the *cis*-aziridines **17b** and **17c** which were used as standards to check the diastereoselection of the aziridinations of diazo esters **14b** and **14c** shown in Table 1. Thus, with the proper choice of the catalytic asymmetric method and the proper choice of the chirality of the ligand, all four stereoisomers of the trisubstituted aziridines **17** can be obtained in good yield and with very high diastereoselectivity and optical purity.

The possibility for direct access to *cis*-trisubstituted aziridines is suggested by the observation that, while diazo acetamides of the type **4** containing a secondary amide give *trans*-aziridines of the type **5**[4,6e,6f] (Scheme 1), tertiary diazo acetamides lacking the N−H bond will react with a switch in the diastereoselectivity to give *cis*-aziridines.[2c,4] The pertinent question thus becomes, will a

**Table 1. Catalytic Asymmetric Aziridination of α-Diazo Esters 14**[a]




| entry | diazo | R | ligand | mol % cat | time (min) | % yield 16 [b] | *trans*/*cis* [b] | % yield *trans* [b,c] | % ee *trans* [d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 [e] | **14a** | Me | TfOH | 20 | 15 | 25 | 3:1 | 42 | — |
| 2 [f] | **14a** | Me | (*R*)-VAPOL | 20 | 60 | 14 | 12:1 | 49 | −5 |
| 3 | **14a** | Me | (*R*)-VANOL | 20 | 15 | 13 | 20:1 | 48 | 83 |
| 4 | **14a** | Me | (*R*)-VANOL | 20 | 60 | 13 | 20:1 | 48 | 83 |
| 5 | **14a** | Me | (*R*)-VANOL | 20 | 240 | 13 | 20:1 | 48 | 84 |
| 6 [g] | **14a** | Me | (*R*)-VANOL | 20 | 15 | 12 | nd | 45 | nd |
| 7 [h] | **14a** | Me | (*R*)-VANOL | 20 | 15 | 9 | 10:1 | 32 | 86 |
| 8 [e,f] | **14a** | Me | (*S*)-VANOL | 20 | 15 | 12 | 20:1 | (46) | −93 |
| 9 [f] | **14a** | Me | (*R*)-VANOL | 10 | 30 | 9 | 25:1 | 36 | 84 |
| 10 [f] | **14a** | Me | (*R*)-VANOL | 5 | 30 | 11 | 25:1 | 34 | 83 |
| 11 [e,f,i] | **14a** | Me | (*R*)-VANOL | 20 | 15 | 23 | 14:1 | 27 | 88 |
| 12 [f] | **14b** | Et | (*S*)-VANOL | 20 | 60 | nd | 16:1 | (32) | −82 |
| 13 [f] | **14c** | *n*-Pr | (*S*)-VANOL | 20 | 60 | nd | 5:1 | (25) | −70 |
| 14 [f] | **14d** | *i*-Pr | (*S*)-VANOL | 20 | 60 | — | — | ≤1 | — |

[a] Unless otherwise specified, all reactions were performed with a solution of 0.10 mmol of diazo compound with 2.0 equiv of imine **15** in 0.6 mL of $CH_2Cl_2$ at −78 °C. A solution of the catalyst in 0.4 mL of $CH_2Cl_2$ was then added dropwise over a few minutes, and then the solution stirred for the indicated time after which the reaction was quenched by the addition of 0.5 mL of $Et_3N$. The catalyst was prepared by heating 1 equiv of the ligand, 3 equiv of $BH_3 \cdot SMe_2$, 2 equiv of PhOH, and 3 equiv of $H_2O$ in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mmHg. The residue was then taken up in the proper amount of $CH_2Cl_2$ to have the desired amount of catalyst in 0.4 mL. [b] Determined from the $^1H$ NMR spectrum of the crude reaction mixture with $Ph_3CH$ as internal standard, nd = not determined. [c] The yields in parentheses are isolated yields after silica gel chromatography. [d] Determined by HPLC on purified *trans*-**17**. When *trans*-**17** is not purified, % ee was determined on reaction mixture that was passed through silica gel. A minus sign indicates that the (2*R*,3*S*)-enantiomer of *trans*-**17** is formed. [e] 3.0 equiv of imine used. [f] The catalyst was added as a solution precooled to −78 °C. [g] Reaction performed with 0.10 mmol of imine and 4.0 equiv of diazo ester **14a**. [h] Solvent is a 3:2 $Et_2O/CH_2Cl_2$ mixture (1.0 mL total), and the temperature was −100 °C. [i] Catalyst prepared as in footnote a except that the ratio of VANOLPhOH/$BH_3$/$SMe_2$ was 1:1:1 and no $H_2O$ was used.

secondary α-diazo amide of the type **51** (Scheme 5), which has two substituents on the diazo carbon, also reverse the diastereoselectivity to give the *cis*-trisubstituted aziridines? The answer is that while there is a large change in the level of diastereoselectivity from >100:1 for the diazo compound **18a** to 1.5:1 for diazo compound **51**, the *trans*-compound is still the major product. The low yields observed at complete conversion and the low asymmetric inductions found for both *cis*- and *trans*-**52** serve to stem any further consideration for continued investigation of this approach to *cis*-trisubstituted aziridines.

The synthetic utility of the oxazolidinone function of the trisubstituted aziridines is illustrated in the facile conversion of **19a** to the ester **53** and the acid **54** (Scheme 5). The absolute configuration of **53** has been reported,[7j] and thus conversion of **19a** to **53** establishes the absolute configuration of **19a**. The conversion of **54** to the amide **52** serves to identify the absolute configuration of the *trans*-aziridine **52** obtained from the reaction of the N−H diazo amide **51**. Note that the difference in the diastereoselectivity between *cis*- and *trans*-**52** is the result of the change in the facial selectivity to the imine and not to the diazo compound. This same phenomenon was observed in the catalytic asymmetric synthesis of *cis*- and *trans*-disubstituted aziridines (Scheme 1).[4]


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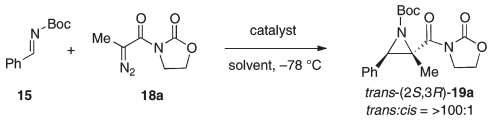
**Table 2. Optimization of the Aziridination of α-Diazo-*N*-Acyloxazolidinone 18a[a]**




**15** **18a** *trans*-(2*S*,3*R*)-**19a** *trans*:*cis* = >100:1

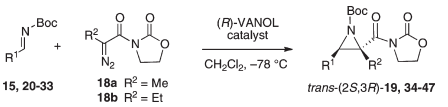
| entry | ligand | mol % cat | solvent | time (h) | conv %[b] | % yield[c] *trans*-**19a** | % ee[d] *trans*-**19a** |
|---|---|---|---|---|---|---|---|
| 1 | (*R*)-**6** | 20 | $CH_2Cl_2$ | 4 | 100 | 80 | 94 |
| 2 | (*R*)-**7** | 20 | $CH_2Cl_2$ | 4 | 66 | 21 | –8 |
| 3 | (*R*)-**8** | 20 | $CH_2Cl_2$ | 4 | 92 | 56 | 40 |
| 4[e] | (*R*)-**8** | 60 | $CH_2Cl_2$ | 4 | 100 | 65 | –16 |
| 5 | (*R*)-**9** | 20 | $CH_2Cl_2$ | 4 | 100 | 79 | 53 |
| 6 | (*R*)-**10** | 20 | $CH_2Cl_2$ | 4 | 65 | 14 | 0 |
| 7 | (*R*)-**6** | 10 | $CH_2Cl_2$ | 4 | 100 | 78 | 90 |
| 8 | (*S*)-**6** | 10 | toluene | 6 | 96 | 74 | –84 |
| 9 | (*S*)-**6** | 10 | THF | 8 | 93 | 67 | –77 |
| 10 | (*S*)-**6** | 10 | $Et_2O$ | 8 | 100 | 83 | –79 |
| 11[f] | (*S*)-**6** | 10 | $CH_2Cl_2$ | 4 | 100 | 78 | –94 |
| 12[f,g] | (*S*)-**6** | 10 | $CH_2Cl_2$ | 6 | 98 | 72 | –94 |
| 13[f,h] | (*S*)-**6** | 10 | $CH_2Cl_2$ | 6 | 85 | 58 | –94 |
| 14[f,i] | (*S*)-**6** | 20 | $CH_2Cl_2$ | 4 | 100 | 80 | –95 |

[a] Unless otherwise specified, all reactions were performed with a solution of 0.10 mmol of diazo compound with 3.0 equiv of imine **15** in $CH_2CI_2$ at −78 °C at 0.2 M in **18a** with 10 mol % catalyst and 0.1 M with 20 mol % catalytst. A solution of the catalyst in the proper amount of $CH_2CI_2$ to give the desired concentration was then added dropwise over a few minutes, and then the solution stirred for 4−8 h at −78 °C after which the reaction was quenched with 0.5 mL of $Et_3N$. The catalyst was prepared as described in Table 1. *cis*-**19a** could not be detected by $^1$H NMR in the crude reaction mixtures. The trans/cis selectivity was determined to be >100:1 for the reaction in entry 11 (see Supporting Information). [b] Determined from the $^1$H NMR spectrum of the crude reaction mixture. [c] Isolated yields after silica gel chromatography. [d] Determined by HPLC on purified *trans*-**19a**. A minus sign means that *trans*-(2*R*,3*S*) **19a** was formed. [e] The catalyst was prepared by heating 2 equiv of (*R*)-BINOL **8** and 1 equiv of $BH_3$/$SMe_2$ in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mmHg. The catalyst loading of 60 mol % is based on amount of ligand used. [f] The catalyst was added as a solution precooled to the reaction temperature. [g] 2.0 equiv of **15** used. [h] 1.5 equiv of **15** used. [i] Catalyst prepared as indicated in footnote i of Table 1.

There has been a large body of work devoted to the synthesis of α,α-disubstituted amino acids, but only a few involve aziridines as intermediates.[11] An example of how biological activity is a function of α-substitution is L-dopa **58** and L-methyldopa **59**. L-dopa is used clinically in the treatment of Parkinson's disease, whereas L-methyldopa is an antihypertensive agent used in the treatment of high blood pressure, especially gestational hypertension. We have previously reported that the disubstituted aziridine *cis*-(2*S*,3*S*)-**57** can be used to access L-dopa.[2a] Here, we show that the trisubstituted aziridine *trans*-(2*S*,3*R*)-**46** can provide access to L-methyldopa. Treatment of **46** with bromomagnesium methoxide allows for cleavage of the oxazolidinone and generates the methyl ester **55** in 86% yield. The aziridine ring can be opened by simple hydrogenation to give the α,α-disubstituted amino ester **56** in 92% yield as a protected form of L-methyldopa (Scheme 6).

With the development of the catalytic asymmetric synthesis of trisubstituted aziridines presented here, it will be of interest to investigate the mechanistic differences in the reactions of electron-rich *N*-alkyl imines giving disubstituted aziridines[2b,4b] and electron-poor *N*-Boc imines giving trisubstituted aziridines, both from VANOL derived borate catalysts. The catalyst for these reactions is prepared[9] in the manner used to generate the catalyst for the aziridination with *N*-alkyl imines where the imine causes the assembly of the boroxinate catalyst.[2d,e] Given the lower

**Table 3. Catalytic Asymmetric Aziridination with α-Diazo-*N*-Acyloxazolidinone 18[a]**

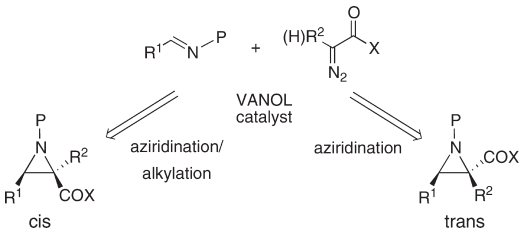



**15, 20-33** **18a** $R^2$ = Me **18b** $R^2$ = Et *trans*-(2*S*,3*R*)-**19, 34-47**

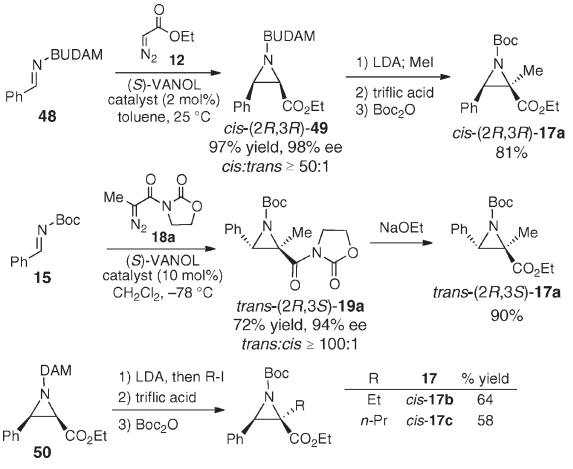
| entry | imine | $R^1$ | $R^2$ | mol % cat | time (h) | conv %[b] | aziridine | % yield[c] | % ee[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **15** | $C_6H_5$ | Me | 10 | 6 | 98 | **19a** | 72 | –94 |
| 2 | **20** | 4-$NO_2C_6H_4$ | Me | 10 | 6 | 100 | **34** | 62 | 90 |
| 3 | **21** | 4-$CF_3C_6H_4$ | Me | 10 | 1 | 100 | **35** | 58 | 95 |
| 4 | **22** | 4-$BrC_6H_4$ | Me | 10 | 8 | 100 | **36a** | 70 | 96 |
| 5 | **23** | 4-$ClC_6H_4$ | Me | 10 | 6 | 92 | **37** | 74 | –93 |
| 6 | **24** | 4-$FC_6H_4$ | Me | 20 | 6 | 100 | **38** | 64 | –96 |
| 7 | **24** | 4-$FC_6H_4$ | Me | 10 | 8 | 80 | **38** | 55 | –96 |
| 8 | **25** | 3-$BrC_6H_4$ | Me | 10 | 4 | 100 | **39** | 56 | 85 |
| 9 | **26** | 4-$MeC_6H_4$ | Me | 10 | 9 | 60 | **40** | 42 (70) | 95 |
| 10 | **26** | 4-$MeC_6H_4$ | Me | 10 | 27 | 100 | **40** | 83 | –97 |
| 11 | **27** | 3-$MeC_6H_4$ | Me | 20 | 6 | 100 | **41** | 83 | 92 |
| 12 | **27** | 3-$MeC_6H_4$ | Me | 10 | 8 | 84 | **41** | 71 | 92 |
| 13 | **28** | 2-$MeC_6H_4$ | Me | 20 | 9 | — | **42** | trace | — |
| 14 | **29** | 4-$MeOC_6H_4$ | Me | 20 | 11 | 40 | **43** | 15 | — |
| 15 | **30** | 4-$PivOC_6H_4$ | Me | 10 | 11 | 87 | **44** | 69 | 98 |
| 16 | **31** | 3,4-$(OAc)_2C_6H_3$ | Me | 10 | 11 | 100 | **45** | 65 | 88 |
| 17 | **32** | 3,4-$(OPiv)_2C_6H_3$ | Me | 20 | 10 | 100 | **46** | 63 | 88 |
| 18 | **32** | 3,4-$(OPiv)_2C_6H_3$ | Me | 10 | 10 | 85 | **46** | 46 | 88 |
| 19 | **33** | cyclohexyl | Me | 20 | 8 | — | **47** | nd | — |
| 20 | **15** | $C_6H_5$ | Et | 10 | 9 | 35 | **19b** | 30 (86) | 83 |
| 21 | **15** | $C_6H_5$ | Et | 10 | 30 | 68 | **19b** | 55 (81) | –85 |
| 22 | **22** | 4-$BrC_6H_4$ | Et | 20 | 6 | 100 | **36b** | 85 | –98 |
| 23 | **22** | 4-$BrC_6H_4$ | Et | 10 | 8 | 100 | **36b** | 62 | 94 |

[a] Unless otherwise specified, all reactions were performed as indicated in entry 12 in Table 2. The reaction with 20 mol % catalyst performed at 0.1 M in **18**, and those with 10 mol % catalyst performed at 0.2 M. *cis*-Aziridines could not be detected in the $^1$H NMR spectrum of the crude reaction mixture. The data from all reactions with 10 mol % catalyst are the average of 2 runs except entry 10. [b] Determined from the $^1$H NMR spectrum of the crude reaction mixture. [c] Isolated yields after silica gel chromatography. Yields in parentheses are based on recovered diazo compound **18**. nd = not detected. [d] Determined by HPLC on purified aziridine.

**Scheme 3**




**Scheme 4**





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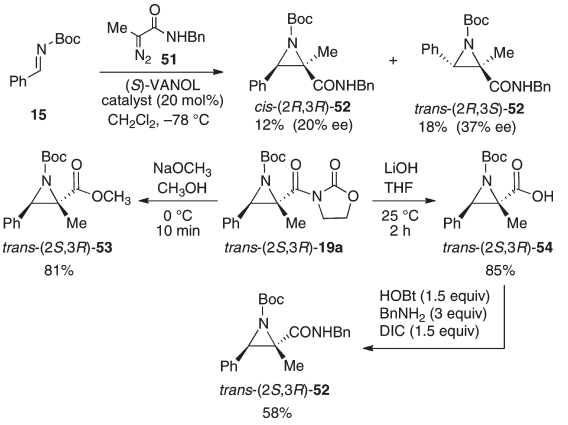
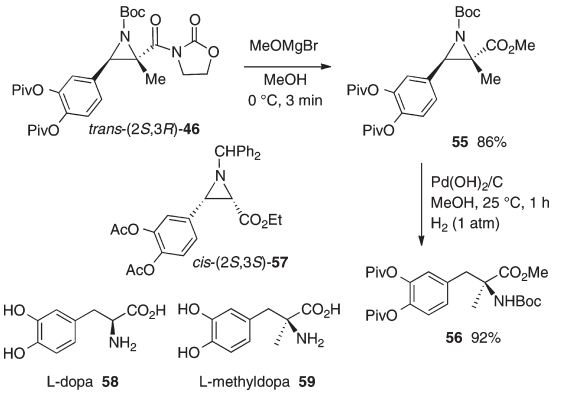
**Scheme 5**




**Scheme 6**




basicity of the *N*-Boc imines, it is not clear that the assembly of a boroxinate is induced. Further studies on the structure of the catalyst for these reactions are needed.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Synthetic procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Following a previously developed protocol (ref 4a), the catalyst was prepared by heating 1 equiv of the ligand, 3 equiv of $BH_3$•$SMe_2$, 2 equiv of PhOH, and 3 equiv of $H_2O$ in toluene at 100 °C for 1 h followed by removal of volatiles at 100 °C for 0.5 h at 0.1 mmHg.

(10) Maruoka and co-workers reported (refs 7i and 7j) that diazo compound **18a** reacts with imine **15** in the presence of 20 mol% $BF_3$•$OEt_2$ to give aziridine **19a** in 52% yield and with a >20:1 trans/cis ratio.

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