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Multi-Component Catalytic Asymmetric Aziridination of Aldehydes

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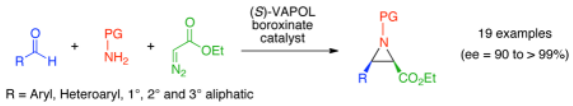
Abstract



The first multi-component catalytic asymmetric aziridination reaction is developed to give aziridine-2-carboxylic esters with very high diastereo- and enantioselectivity from aromatic and aliphatic aldehydes. This new method pushes the boundary of the aziridination reaction to substrates that failed with pre-formed imines.

In recent times, multicomponent reactions have been quite extensively studied and applied in the field of asymmetric catalysis.[1] Over the past few years, considerable advances have been made in the field of catalytic asymmetric aziridination.[2] However, to the best of our knowlegde, no example of a multi-component catalytic asymmetric aziridination has been reported.[1,3–5] A true multi-component reaction involves the reaction of three or more reagents added simultaneously.[1] Multicomponent reactions that involve reaction between two reagents and then interception of the resulting intermediate by the addition of a third reagent are sequential component reactions.[1,4] Herein, we report the first multi-component catalytic asymmetric aziridination (MCAZ) which incorporates the most simplified protocol yet developed for our catalytic asymmetric aziridination reaction (Figure 1).

We have previously developed chiral catalysts for the asymmetric synthesis of aziridines from the reaction of diazo compounds and imines (AZ reaction) (Figure 1A).[6]

With chiral Brønsted acid catalysts generated from the VANOL and VAPOL ligands (Scheme 1), it is possible to obtain aziridine-2-carboxylates of the type **3** with very high enantioselectivities and diastereo-selectivities. The highest stereoselectivities are typically delivered by imines derived from the amine **12** which bears a bis-(dimethylanisyl)methyl group (MEDAM).[6e] The catalyst for the AZ reaction has been identified as the novel boroxinate species **11** which is an ion-pair consisting of a boroxinate anion and a protonated iminium.[6d,g,i] The boroxinate catalyst is typically generated with either of two methods (Scheme 1). Heating VANOL or VAPOL with $B(OPh)_3$ and then removing volatiles under vacuum with heating generates a mixture of **9** and **10** as a pre-catalyst, both of which are converted to the boroxinate upon treatment with the imine at ambient temperature (Method B). Although $B(OPh)_3$ and VAPOL are inert to each other at room temperature, the boroxinate is formed immediately upon addition of imine (Method A).[6i]

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

Up to this point, all of the aziridination reactions we have published have involved pre-formed imines. A drawback to the use of imines of course is the requirement of an additional step. The difficulty in the purification of imines can vary from drawback to limitation. The method of choice for purification is crystallization since most imines tend to decompose on silica gel or upon distillation. For non-crystalline imines this usually necessitates the use of non-purified imines. This can be an serious problem, especially for unbranched aliphatic aldehydes where in many cases no aziridine product is observed at all.[7] We found in these cases, the imine can't be generated in a clean fashion. For example, when aldehyde **4g** is treated with amine **12**, long before complete formation of the imine **13g** can be realized, self-condensation of the imine begins to occur which gives rise to the conjugated imine **14g** (Scheme 2).[8] This mixture of species appears to kill the catalyst and this may very well be due to the amine **12** which is released in the formation of **14g**. This imposes a serious limitation on the implimentation of the AZ reaction and the molecules in Figure 2 are illustrative of the point.[9]

Given the greater basicity of an amine versus an imine, it was anticipated that the MEDAM amine **12** could also generate the boroxinate catalyst from VAPOL and $B(OPh)_3$ in much the same way as does imine **13a** (Scheme 1) and indeed this was confirmed by NMR analysis (see supporting information). What was not clear was whether the amine would be subsequently converted completely to the imine such that the more basic amine won't tie up the catalytst and stop the reaction.

Given the problems with aliphatic aldehydes described above, the multi-component aziridination was first examined with benzaldehyde (Scheme 3). The VAPOL ligand was mixed with 3 equiv of $B(OPh)_3$ and 20 equiv of amine **12** and stirred in toluene at 80 °C for 0.5 h to ensure complete formation of the boroxinate catalyst. This was followed by the addition of 4 Å MS and benzaldehyde. After subsequent addition of EDA **2**, the resulting mixture was stirred at 25 °C for 24 h to give the aziridine **19a** in 97% yield and 98% ee (Procedure B, Scheme 3). It was also found that generating the catalyst at 25 °C for 1 h gave the same results. (Procedure A, Scheme 3). Very similar results were obtained if the diazo compound **2** was added before the aldehyde **4a** and this reveals that this is a true multi-component reaction since imine formation can occur in the presence of all other components.[10] Interestingly, the reaction stops if 0.6 equiv of **4a** is added (Scheme 3) which suggests that the amine can kill the catalyst which is consistent with the failure of pre-formed imine **13g** to give any aziridine (Scheme 2).

The problem of imine self-condensation was encountered in the multi-component aziridination (MCAZ) of *n*-butanal **4b** (Table 1). The three-component aziridination of *n*-butanal with MEDAM amine **12** at room temperature with 5 mol % VANOL catalyst gave only a 25% yield of aziridine **19b** along with a 20% yield of the condensation product **14b.** However, the formation of the side-product **14b** was found to be disfavored at lower temperatures (entry 2). The yield was increased to 74% at 0 °C with 10 mol % catalyst (entry 4). With 5 mol% catalyst, increased yields up to 94% were observed with increased amounts of ethyl diazoacetate **2** (entries 8 and 9).[11] Finally, it was found that reaction with 3 mol % catalyst and 2 equiv EDA provides 2.4 g (5.5 mmol) of aziridine **19b** in 92% yield and 96% ee (entry 12).

A series of eight additional aliphatic aldehydes were screened in the multi-component aziridination reaction (Table 2). Excellent asymmetric inductions were observed for the aziridination of a number of functionalized unbranched, α-branched and α,α-branched aliphatic aldehydes. These include a number of "problem" aldehydes that have failed to give aziridines via in-situ generated imines such as dihydrocinnamyl aldehyde **4g**, phenyl acetaldehyde **4h** and ethyl-5-oxopentanoate **4e** due to the problem pertaining to the

condensation product (Scheme 2). [7,8] Even with the three-component protocol, the aziridination of the "problem" aldehyde **4g** proceeds to give only a 24% yield of the aziridine **19g** (entry 8). The yield can be increased to 96% if excess (8 equiv) of EDA is used and this is interpreted to mean that the imine undergoes aziridination before it can self condense (entry 9).[11] The MCAZ is also readily scalable as aziridine **19c** can be obtained with essentially the same induction and in slightly higher yield when the scale is increased ten-fold (Table 2, entries 1 and 2). It was observed that excellent results could obtained for 2° and 3° aliphatic aldehydes at room temperature. (Table 2).

A survey of the scope of the multi-component protocol for aromatic aldehydes is given in Scheme 4. Excellent yields and asymmetric inductions were observed for a number of substituted benzaldehydes including those with both electron-withdrawing and electron-donating groups. The reaction with benzaldehyde **4a** was complete in 1 h with 5 mol % catalyst by ^{1}H NMR.[12] Excellent inductions could also be obtained with heteroaryl aldehydes giving aziridines **19p** – **19s** in 90–97% ee.[11,13]

The synthetic utility of MCAZ reaction is illustrated by the direct transformation of aldehyde **4a** to α-amino esters **21** and **22** in a one-pot fashion. The crude aziridine **19a** obtained from MCAZ reaction is subjected to deprotection followed by water assisted ring opening and boc protection of free amine in **20** to afford β-hydroxy-α- amino ester **21** in very high optical purity in 60% overall yield from amine **12**. Alternatively, the crude aziridine **19a** can be treated under reductive deprotection and ringopening conditions to afford α-amino ester **22** in high optical purity and in 70% overall yield from amine **12**.

In summary, a highly robust multicomponent catalytic asymmetric aziridination reaction has been realized.[14] This method incorporates a very simplified protocol and it provides an effective solution to the long-standing problem with imines from unbranched aliphatic aldehydes in two-component methods. The fact that the imines are generated in-situ permits introduction of functionality in the aziridine not possible with two-step methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Minakata S, Takahashi T, Oderaotoshi Y, Komatsu M. J Org Chem. 2002; 67:2101–2110. [PubMed: 11925215]

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10. In this experiement, EDA **2** was added with the VAPOL, $B(OPh)_3$ and amine **12**.
11. No attempt was made to optimize the amount of EDA.
12. Minimum reaction times were not determined for all substrates.
13. (a) We have compared the preparation of aziridine **19r** by the MCAZ method described here with that of a two-step method involving the isolation of the imine from aldehyde **4r** and amine **12**. Substantial material loss is encountered in the two-step method as a result of purification of the imine (see supporting information). (b) pyridine-3-carboxaldehyde gave no aziridine (not shown)
14. Part of this work was presented at the 240th American Chemical Society National Meeting, Boston (2010), ORGN 636.

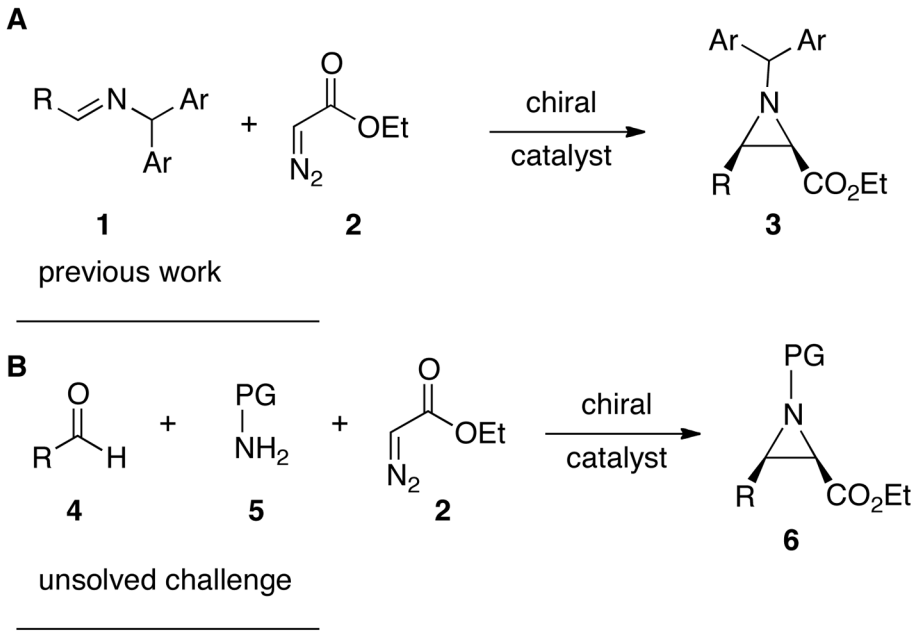


Figure 1.
A: catalytic asymmetric aziridination of imines. B: three-component catalytic asymmetric aziridination.

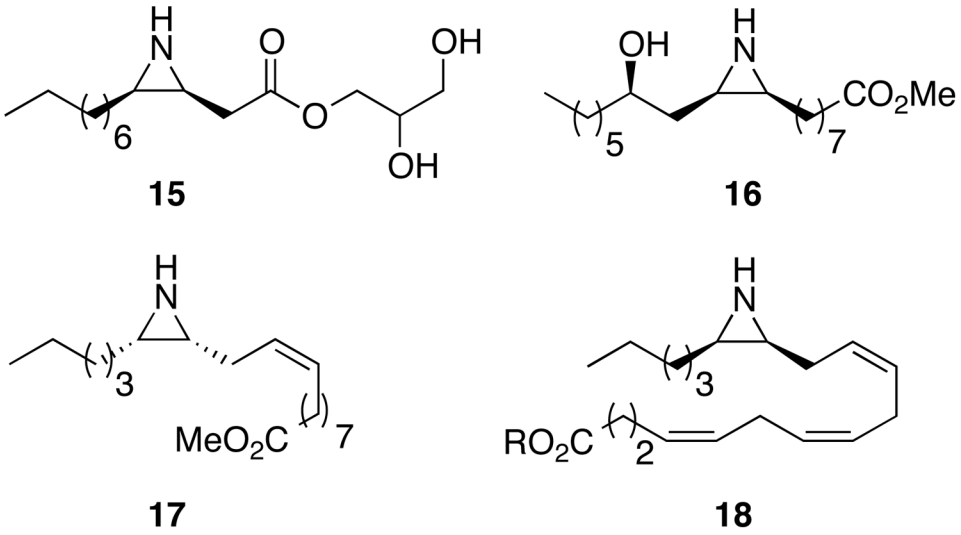
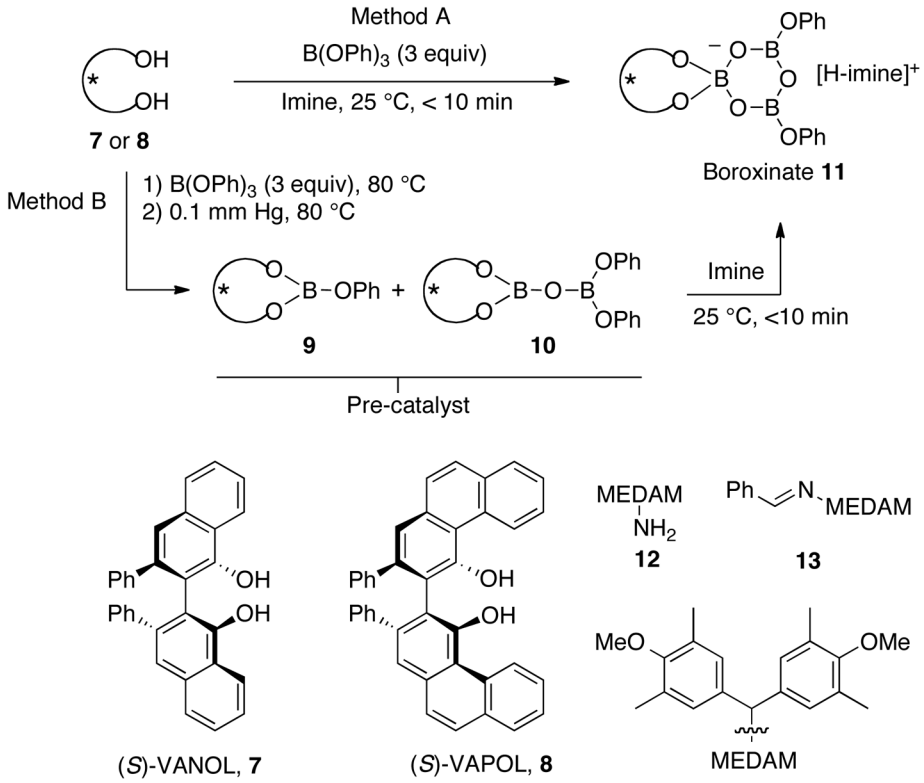
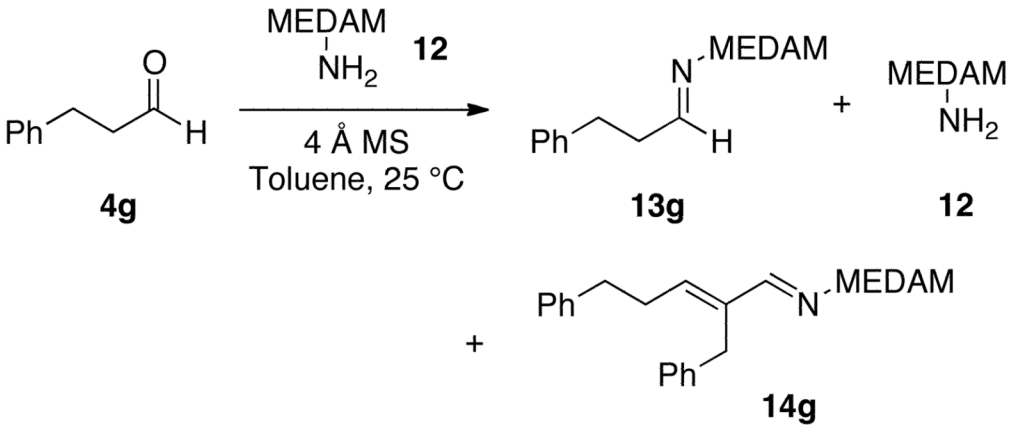


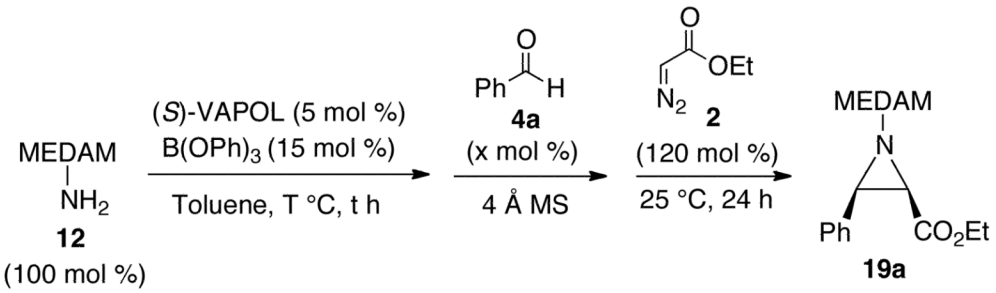
Figure 2.
Biologically Important Alkyl Aziridines. **15**: antimicrobial activity against Gram-positive bacteria.[9b] **16** and **17**: cytotoxic and antimicrobial activity.[9c] **18**: inhibitor of arachidonate epoxygenase.[9d]



Scheme 1.
Methods for Catalyst Formation.

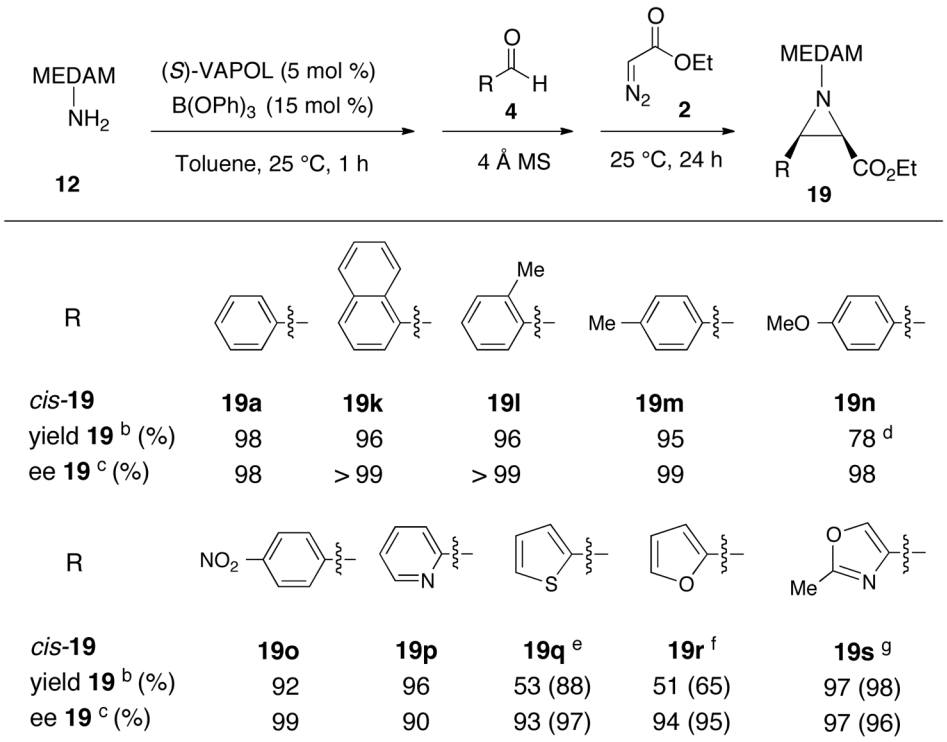


Scheme 2.
Self-condensation of Imine **13g**.



Procedure A (T = 25 °C, t = 1 h)	**4a** (105 mol %) added before **2** (yield = 98%; ee = 98%) **2** added before **4a** (105 mol %) (yield = 94%; ee = 98%) **4a** (60 mol %) added before **2** (yield = <1%)
Procedure B (T = 80 °C, t = 0.5 h)	**4a** (105 mol %) added before **2** (yield = 97%; ee = 98%)

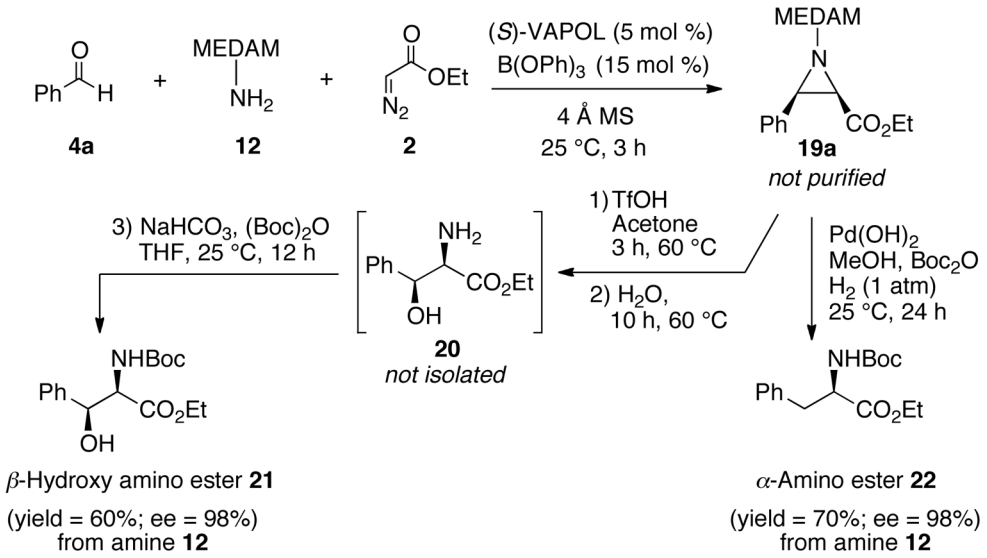
Scheme 3.
Multicomponent AZ reaction of Benzaldehyde **4a**.



Scheme 4.

Multicomponent AZ reaction of Aryl Aldehydes.[a]

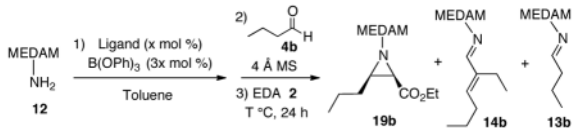
[a] Unless otherwise specified, all reactions were performed as described in Table 2 with 1.2 equiv of **2** with Procedure A and went to 100% completion and gave aziridine **19** with a *cis/trans* ratio of >50:1. Data in parentheses is with 8 equiv EDA **2**. [b] Isolated yield. [c] Determined by chiral HPLC. [d] *cis/trans* = 20:1. [e] *cis/trans* = 25:1 with 8 equiv EDA. [f] *cis/trans* = 8.3:1 with 8 equiv EDA. [g] Reaction with 2 equiv EDA **2**.



Scheme 5.
One-pot Synthesis of amino esters **21** and **22**.

Table 1

Optimization of the Multicomponent AZ reaction for *n*-butanal **4b**.[a]



entry	ligand	proc	catalyst (x mol %)	T (°C)	equiv 2	yield % 19b[b]	ee % 19b[c]	yield % 14b[d]	yield % 13b[d]
1	(*R*)-VANOL	A	5	25	1.2	25[d]	nd	20	38
2	(*R*)-VANOL	A	5	0	1.2	50[d]	nd	6	21
3	(*R*)-VANOL	B	5	0	1.2	53[d]	nd	6	17
4	(*R*)-VANOL	B	10	0	1.2	74	−95	2	< 1
5	(*R*)-VANOL	B	10	−10	1.2	80	−96	< 1	< 1
6	(*R*)-VANOL	B	10	−30	1.2	45[e]	−96	11	30
7	(*S*)-VAPOL	B	10	−10	1.2	82	98	< 1	< 1
8	(*S*)-VAPOL	B	5	−10	8	91	96	< 1	< 1
9	(*S*)-VAPOL	A	5	−10	8	94	96	< 1	< 1
10	(*S*)-VAPOL	A	5	−10	3	85[f]	96	< 1	< 1
11	(*S*)-VAPOL	A	4	−10	6	97[g]	95	< 1	< 1
12	(*S*)-VAPOL	A	3	−10	2	92	96	< 2	< 2

[a] Unless otherwise specified, all reactions were performed with 0.5 mmol amine **12** (0.5 M) and 1.05 equiv of *n*-butanal **4b** and 1.2 equiv EDA **2** with Procedure A or B (see Scheme 3) and went to 100% completion. nd = not determined.

[b] Isolated yield.

[c] Determined by chiral HPLC.

[d] Yield determined by ^{1}H NMR with Ph$_3$CH as internal standard.

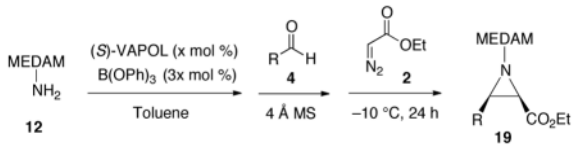
[e] Reaction went to 61% completion.

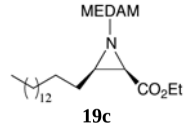
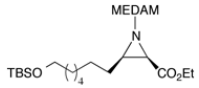
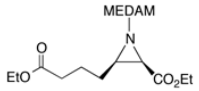
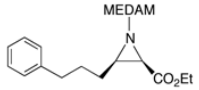
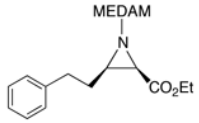
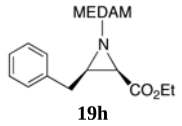
[f] Reaction on 2.5 mmol scale.

[g] Reaction on 6 mmol scale.

Table 2

Multicomponent AZ reaction of Alkyl Aldehydes. [a]



entry	proc	catalyst (x mol %)	equiv 2	yield % 19 [b]	ee % 19 [c]	aziridine 19
1	B	10	1.2	80	96	 **19c**
2	B	10	3	85	95[d]	
3	B	10	1.2	80	98	 **19d**
4	B	10	1.2	70	94	 **19e**
5	A	5	8	82	97	
6	B	10	1.2	55	93	 **19f**
7	A	5	8	50	90	
8	B	10	1.2	24[e]	nd	 **19g**
9	B	10	8	96	97	
10	A	5	8	91	96	
11	B	10	1.2	19[e]	nd	 **19h**
12	B	10	8	94	98	
13	A	5	8	86	98	

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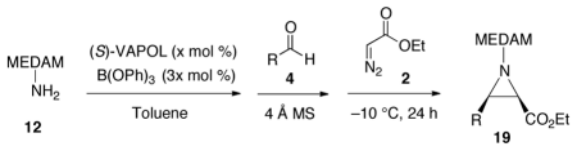
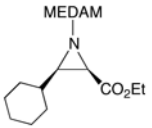
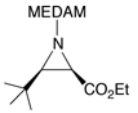


entry	proc	catalyst (x mol %)	equiv 2	yield % 19 [b]	ee % 19 [c]	aziridine 19
14[f]	A	5	1.2	95	90	 **19i**
15[f]	B	10	1.2	89	94	 **19j**
16[f]	A	10	2	95	92	
17[f]	A	10	8	97	90	

[a] Unless otherwise specified, all reactions were performed with 0.5 mmol of amine **12** (0.5 M) with 1.05 equiv aldehyde **4** and 1.2 equiv EDA **2** with Procedure A or B (see Scheme 3) and went to 100% completion with a *cis/trans* ratio of >50:1.

[b] Isolated yield.

[c] Determined by chiral HPLC.

[d] Reaction on 5.0 mmol scale.

[e] Yield determined by ^{1}H NMR with Ph3CH as standard; nd = not determined.

[f] Reaction at 25 °C.