Asymmetric Catalysis

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Chiral Brønsted Acid-Catalyzed Asymmetric Synthesis of *N*-Aryl-*cis*-aziridine Carboxylate Esters

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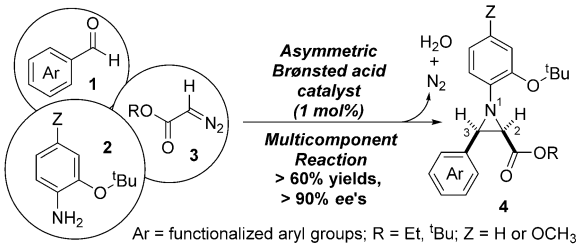
Abstract: *We report a multi-component asymmetric Brønsted acid-catalyzed aza-Darzens reaction which is not limited to specific aromatic or heterocyclic aldehydes. Incorporating alkyl diazoacetates and, important for high ee's, ortho-tert-butoxyaniline our optimized reaction (i.e. solvent, temperature and catalyst study) affords excellent yields (61–98 %) and mostly >90 % optically active cis-aziridines. (+)-Chloramphenicol was generated in 4 steps from commercial starting materials. A tentative mechanism is outlined.*

Such is the versatility of organocatalysis and its ability to mediate a plethora of diverse reaction types[1] it is, now, an indispensable "tool" in the synthetic chemists "toolbox".[2] Indeed, improving atom- and reaction-efficiency is a key driver to developing new reactions and protocols; in this context organocatalysis has demonstrated its importance by efficiently mediating many different convergent reactions or multi-component syntheses. The work here supports these aspects by generating structure and function-diverse motifs via fewer synthetic, isolation and purification steps.

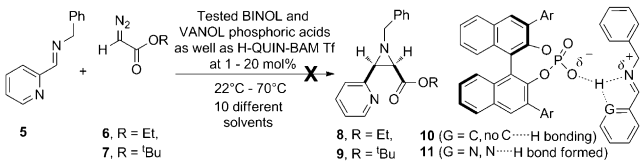
Optically active aziridines have many diverse uses, especially as key intermediates[3] "on route" to important "secondary" products for example, α-/β-amino acids, polymers, azasugars, auxilaries, oxazolidinones, imidazolidines, β-lactams and pyrrolidines. Further applications include synthesis of non-aziridine containing bioactive compounds for example, kainoids, (−)-mesembrine, (−)-platynesine, actinomycin and feldamycin, in addition to synthetic bioactive aziridines for example, NSC676892 as well as natural products for example, azinomycin and maduropeptide.[4]

Using a BINOL *N*-triflylphosphoramide Brønsted acid a 61–98 % yielding asymmetric aza-Darzens reaction affords *N*-aryl-*cis*-aziridines in, mostly, 90–99 % *ee*. The reaction is straightforward to set up and has minimal requirements for strictly anhydrous or anaerobic conditions, furthermore it does not require organocatalyst pre-generation or activation, or an "activated" arylglyoxal starting material. Exploiting the protocol synthesis of aziridines based on **4** uses readily generated or commercially available aldehydes (**1**), amines (**2**) and alkyl diazoacetates (**3**, Scheme 1).



Scheme 1. Multicomponent asymmetric synthesis of *N*-aryl-*cis*-aziridines **4**.

Activating the C=N bond of an imine with a BINOL phosphoric acid[5] lowers its LUMO energy and generates an imminium ion pair that can, but not always will, react with a nucleophile. Seminal work by Akiyama et al. established chiral BINOL phosphoric acids [$pK_a \approx 13$ (CH_3CN)[6]] activate aldimines (derived from, specifically, arylglyoxals and *p*-anisidine) and react with ethyl diazoacetate (EDA) affording *cis*-aziridines in 92–97 % *ee*.[7] Similarly, other Brønsted acids[8] and pyridinium triflate activate a diverse array of imines, including for example, 2-pyridyl derived **5**, enabling the presumed imminium ion-pair (not shown) to react with EDA and afford *cis-rac*-aziridine (**8**, 83 % yield) (Scheme 2).[9] With these racemic studies complete our focus shifted to developing a substrate enhanced and diverse, multi-component asymmetric aza-Darzens reaction. Inspired by the work of Akiyama et al.[7] and the Mannich reaction reported by Yamanaka et al. we considered the inclusion of **5** may generate a constrained hydrogen-bonded and activated complex similar to **11**; we were drawn to the use of **5** to generate **11** due to similarities in the chiral non-racemic rigid environment proposed by Yamanaka (using a *N*-(2-hydroxy-



Scheme 2. Failed attempts at synthesising *cis*-**8** and *cis*-**9**.

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phenyl)imine starting material).[10] Screening chiral non-racemic BINOL and VANOL phosphoric acids, as well as a H-QUIN-BAM triflate salt[11] we were disappointed no reactions were observed. We attribute the failure using **5**, as well as other alternative imines, to the low pK_a's of the Brønsted acids and their inability to generate a sufficiently "activated" form of **10** or **11**.

Switching to the more acidic BINOL *N*-triflylphosphoramides for example, pK_a **14** ≈6 (CH_3CN)[6] (Figure 1) the

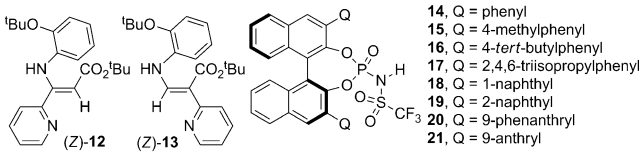


Figure 1. Enamides and 3,3′-*bis*(aryl) (*S*)-BINOL *N*-triflylphosphoramides.

synthesis of (*S*)-3,3′-*bis*(phenyl)-**14**, (*S*)-3,3′-*bis*(4-methylphenyl)-**15** and sterically encumbered (*S*)-3,3′-*bis*(4-*tert*-butylphenyl)-**16** was straightforward.[12] By using 10 mol% all three catalysts, independently, at room temperature mediated the synthesis of *cis*-aziridine **8** in 73%, 85% and 87% yields, respectively. ^{1}H-NMR of the unpurified reactions confirmed no enamide[5] i.e. *Z*-**12** or Z-**13** (Figure 1) or *trans*-**8** ($J_{2,3}$ ≈2 Hz, not shown) had formed. Disappointingly, chiral column HPLC analysis established *cis*-**8** was racemic when generated using **14** or **15**; in contrast, **16** afforded non-racemic *cis*-**8** but in a poor 16% *ee* (Table 1, Entries 1–3 respectively).

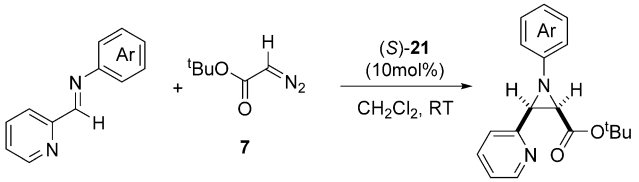
Table 1: Probing the asymmetric synthesis of *cis*-**8** and *cis*-**9** using **14**–**21**.

Entry	Catalyst	**8** (R = Et, *ee*)	Entry	Catalyst	**9** (R = ^{t}Bu, *ee*)
1	**14**	racemic	9	**14**	racemic
2	**15**	racemic	10	**15**	18%
3	**16**	16%	11	**16**	13%
4	**17**	23%	12	**17**	racemic
5	**18**	28%	13	**18**	20%
6	**19**	26%	14	**19**	20%
7	**20**	35%	15	**20**	22%
8	**21**	47%	16	**21**	31%

Clearly, the bulky 4-*tert*-butyl group had a positive stereochemical advantage over **14** and **15**. Increasing 3,3′-steric congestion at the 2- and 6- positions using (*S*)-3,3′-*bis*(2,4,6-triisopropyl)phenyl-**17** returned *cis*-**8** in excellent yield and increased 23% *ee* (entry 4).

The 69% increase in *ee* when 2- and 6-isopropyl groups were incorporated (**17**) suggests these "lateral" positions have key roles in reaction stereoselectivity. Probing this, multicyclic 1-naphthyl (**18**), 2-naphthyl (**19**), 9-phenanthryl (**20**) and 9-anthryl (**21**) were incorporated (10 mol%) into our "test" reaction (Scheme 2). All afforded excellent yields of *cis*-**8**. A gradual *increase* in *ee* was observed as the "lateral" groups were added. Thus catalyst **14** afforded *rac*-**8**, whereas 1-naphthyl-**18** offered *cis*-**8** with a 28% *ee*. An almost identical 26% *ee* was provided by 2-naphthyl-**19** and 9-phenanthryl-**20** gave an improved 35% *ee*, finally, 9-anthryl-**21** generated *cis*-**8** in a respectable 47% *ee*.

Encouraged by the results with **6**, sterically encumbered *tert*-butyl ester **7** was investigated. A gradual increase in *ee* was observed but, overall, the levels of stereoinduction were, generally, inferior. So, *N*-benzyl **5** was substituted for a rotationally *less* flexible *N*-4-(methoxyphenyl) or *N*-PMP group. Reacting the corresponding imine (not shown) with **7** mediated by **21** afforded the *cis*-aziridine in an 81% yield ($J_{2,3}$ 6.8 Hz). Further verifying the importance of including the, presumed, rotationally less flexible *N*-PMP the product was afforded with a significantly improved 67% *ee*. Exchanging the *N*-PMP for the regioisomeric *N*-2-methoxyphenyl imine **22** (Scheme 3) its activation (**21**) and reaction with *tert*-



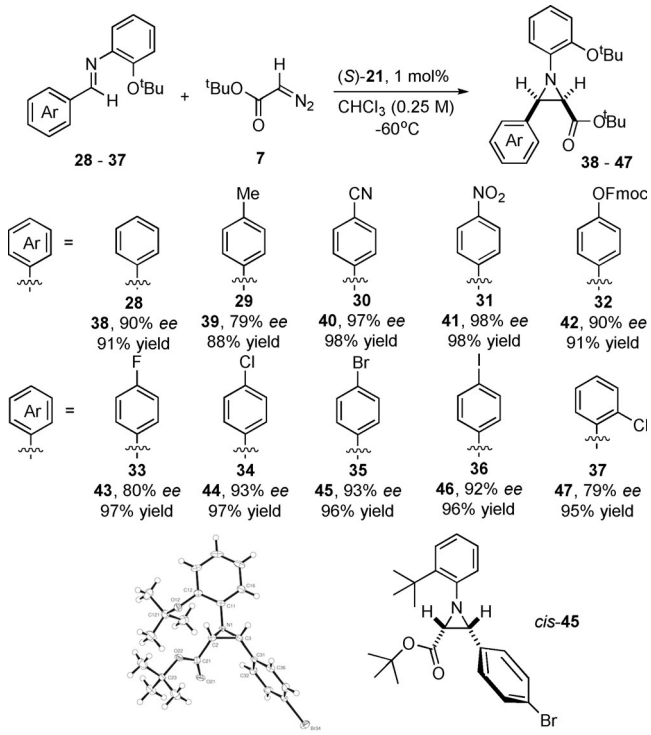
Scheme 3. Asymmetric synthesis of *N*-(alkoxyphenyl)-*cis*-aziridines **25**–**27**.

butyl ester-**7** afforded *cis*-**25** with a 72% *ee*. Evidently, the 2-methoxyphenyl had a positive influence on the stereochemical outcome of the aza-Darzens reaction. The steric effect was probed using 2-isopropoxyphenyl-**23**, 2-n-butoxyphenyl (not shown) and 2-*tert*-butoxyphenyl-**24** (Scheme 3) each reacted, independently, with **7** and **21**. In this series and at ambient temperature the *tert*-butoxy group on **24** afforded *cis*-**27** with a 74% *ee*.

A solvent and temperature study using 1 mol% of **21** established chloroform at −60 °C was the optimum combination for transforming 2-(*tert*-butoxyphenyl)-**24** into *cis*-**27** with an excellent 98% *ee* and 95% yield. Probing the catalytic activity of **21** at 0.5 and 0.25 mol% loadings the reaction times increased to 48 and 62 hours. In both examples *cis*-**27** was afforded in very similar 87%/86% *ee* and 98%/95% yield, respectively.

The synthesis of **38**–**47** (Scheme 4) was examined using **21** (1 mol%) in $CHCl_3$ at −60 °C. Incorporating (*E*)-2-(*tert*-butoxyphenyl)-**28** *cis*-**38** was afforded in an excellent 91% *ee* and 90% yield. Confirming reaction versatility electron-withdrawing 4-cyano imine-**30** and 4-nitrophenyl imine-**31** were transformed into *cis*-**40** and *cis*-**41** with excellent optical purities both 98% and yields that is, 98% and 97% respectively (Scheme 4). Similarly, electron-rich 4-hydroxybenzaldehyde (*O*-Fmoc protected) afforded *cis*-**42** in a 90% *ee* and 91% yield. *Cis*-**43** to *cis*-**47** were synthesized in excellent yields and *ee*'s; 4-bromophenyl-*cis*-**45** (93% *ee*) and 4-iodophenyl-*cis*-**46** (92% *ee*) appear readily amenable to further elaboration via transition-metal mediated transformations.

The magnitude of an aziridine coupling constant ($J_{2,3}$) indicates the relative stereochemical assignment of the $C_{2,3}$-

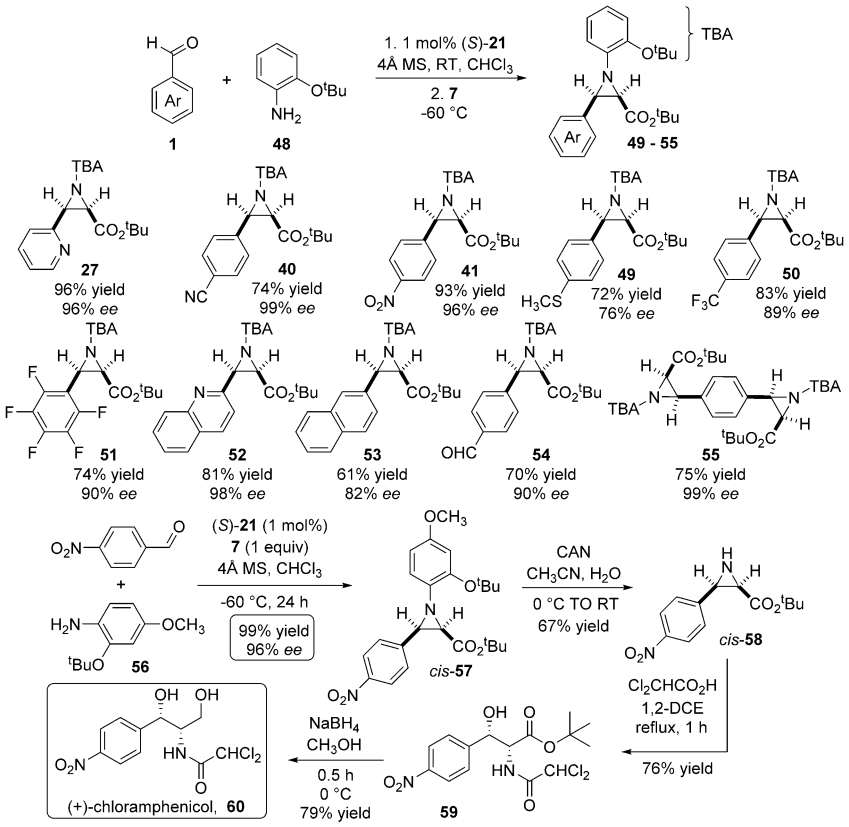


Scheme 4. Asymmetric synthesis of structure and function diverse *N*-(2-*tert*-butoxyphenyl)-*cis*-aziridines **38**–**47** and the X-ray structure of *cis*-**45**.

substituents that is, $J_{2,3}$ 5–9 Hz = *cis* and 2–6 Hz = *trans*. For **38**–**47** we tentatively assigned a *cis*-stereochemical relationship; confirming this was essential. Recrystallising **45** [$J_{2,3}$ 6.7(4) Hz] afforded colorless orthorhombic plates. X-ray diffraction established the *cis*-stereochemical relationship between the 4-bromophenyl and the *tert*-butyl carboxylate ester (Scheme 4).[13]

Generating aziridines via multicomponent asymmetric syntheses is advantageous, they are however, still, rare.[14] It was crucial to verify **21** mediated the multicomponent synthesis of *cis*-aziridines. A three-component, two-step, one-pot protocol generated 2-pyridyl-**27**, 4-cyanophenyl-**40** and 4-nitrophenyl-**41** in excellent yields that is, 74–96% and *ee*'s that is, **27** (96%) **40**, (99%) and **41** (96%, Scheme 5). These *ee*'*s* are, within experimental error, identical to those generated via the *pre-synthesis* imine route (Scheme 4). Incorporating 4-thiomethyl-, 4-trifluoromethyl- and pentafluorobenzaldehyde afforded *cis*-**49** to *cis*-**51**. The efficient synthesis of thioether *cis*-**49** is worthy of note; Davis et al. exploited similar (*S*)-*N*-(4-toluenesulfinyl)-derived aziridines transforming them into thiamphenicol and florfenicol.[15]

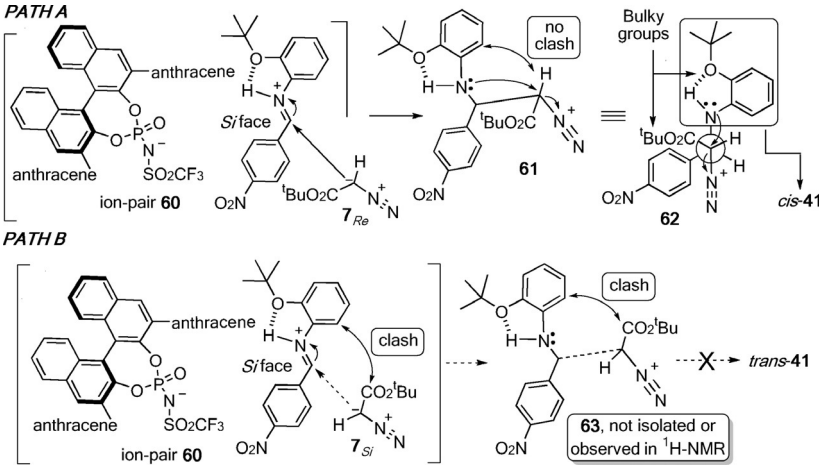
4-Trifluoromethylbenzaldehyde and pentafluorobenzaldehyde afforded *cis*-**50** and *cis*-**51** in excellent 89% and 90% *ee*'s, respectively. Integrating bicyclic quinoline-2-carboxyaldehyde was also straightforward; optically active *cis*-**52** was afforded in a 98% *ee*. Interestingly, the formation of *cis*-**27** and *cis*-**52** was faster than for example **40**, **41**, **49**–**50**; the rapid evolution of, presumably, N_2 was attributed to formation of a more reactive *intramolecular* chelated hydrogen bond (cf. **11**). Combining benzene-1,4-dicarboxyaldehyde and **48** (1 equiv) a one-pot, single asymmetric aziridination afforded mono-aziridine *cis*-**54**. Alternatively, 2 equiv of **48** generated bis-aziridine *cis*-**55**. Both reactions worked very well, *cis*-**54** was afforded in a 70% yield and 90% *ee* and bis-aziridine *cis*-**55** with a 99% *ee*. Seemingly, the installation of the second aziridine on optically active *cis*-**54** to generate *cis*-**55** was not negatively influenced by the first optically active *cis*-aziridine. (−)-Chloramphenicol is an important natural product with antibiotic properties. A one-pot multicomponent aziridination using 4-nitrobenzaldehyde, amine **56** and *tert*-butyl diazoester **7** afforded *cis*-**57** in near quantitative yield and an excellent 96% *ee*. By using cerium(IV) ammonium nitrate in aqueous acetonitrile an important objective was to establish the cleavage "potential" of the 2-*tert*-butoxy-4-methoxyphenyl on *cis*-**57**; NH-*cis*-**58** was afforded in an unoptimized 67% yield, this was ring-opened to amide **59** with dichloroacetic acid, finally reducing the *tert*-butyl ester generated primary alcohol **60** (79% yield). Physicochemical analysis and comparison with the literature



Scheme 5. Asymmetric synthesis of *cis*-aziridines and (+)-chloramphenicol.

confirmed (+)-chloramphenicol **60** had been synthesized using (*S*)-**21** in 4 steps and an overall 40% yield.[16]

Scheme 6 outlines a tentative mechanism for *cis*-aziridine diastereoselectivity. Initial *N*-protonation of **31** via Brønsted acid (*S*)-**21** [p$K_a \approx 6$ (CH_3CN)],[6] affords imminium-phosphoramide anion **60** (Path A, Scheme 6) whilst the weaker triflate salts and phosphoric acids (see Supporting Information, page 3) do not form sufficiently reactive imminium-triflate/phosphate anions.



Scheme 6. Mechanistic rational for the synthesis of *cis*-**41** and not *trans*-**41**.

Supporting protonation, not hydrogen-bond activation,[17] Houk et al. described a mechanism and origins of catalysis DFT and experimental study in which a similarly *N*-protonated, to **60**, reactive hydrazonium-phosphoramide[18] anion (not shown) was formed from a BINOL *N*-triflylphosphoramide and a hydrazone. Activation of **31** is crucial; the widely accepted aza-Darzens mechanism[19] invokes attack of a diazo nucleophile (i.e. **7**) on an imminium cation (i.e. **60**) generating an α-diazonium β-amino ester (i.e. **61**, see Path A). The importance of the latter, from a reaction kinetics and enantioselectivity point of view has been established by the reluctance of these intermediates to undergo a retro-Mannich reaction.[20] Generating, presumed, kinetic product **61** with excellent enantioselectivity is possible only if **7**, with its heterotopic faces that is, $\mathbf{7}_{Re}$ and $\mathbf{7}_{Si}$, efficiently discriminates between the *Si* and *Re* faces of optically active **60**. Path A outlines how *anti*-diazonium intermediate **62** (Scheme 6) forms when the sterically encumbered heterotopic $\mathbf{7}_{Re}$ face approaches the *Si* face of imine **60** minimising the steric interactions between the intramolecularly hydrogen bonded bulky *ortho*-(*tert*-butoxy)phenyl imminium and the *tert*-butyl ester on $\mathbf{7}_{Re}$. Although we have no direct evidence (^{1}H-NMR) for the backbone rigidifying hydrogen bond in **60** similar intramolecular hydrogen bonds in *ortho*-substituted Schiff base's are known.[21] Newman projection **62** affords a detailed depiction of the minimized steric interactions between the *tert*-butyl ester and *ortho*-*tert*-butylphenyl ether. An intramolecular S_N2 cyclization (release of N_2) between the *anti*-periplanar amine and diazonium groups affords *cis*-**41**. Path B proceeds via ion-pair **60**, however approach of $\mathbf{7}_{Si}$ onto the imine *Si* face is, now, inhibited by the two sterically bulky groups. Thus, formation of α-diazonium β-amino ester **63** and *trans*-**41** is disfavoured. The crude ^{1}H-NMRs of our reactions afforded no evidence of *trans*-**41** or α-diazonium β-amino ester **63**.

Experimental Section

A flame dried Radleys tube and stirrer bar was charged with 4-cyanobenzaldehyde (34 mg, 0.26 mmol) and 2-*tert*-butoxy-phenylamine (43 mg, 0.26 mmol). Anhydrous chloroform (1 mL) and (*S*)-**21** (2 mg, 0.0025 mmol, 1 mol%) were added followed by 40 mg of freshly powdered 4 Å molecular sieves. The reaction was stirred for 6 hours. Cooling the tube to −60 °C, **7** (40 μL, 0.29 mmol) was added via syringe. The reaction was stirred at −60 °C and monitored via TLC (hexane/ether:80/20) until the starting materials had been consumed. In vacuo removal of solvent allowed flash purification on silica gel (hexane/ether:80/20). Physicochemical analysis confirmed the identity of the solid as *cis*-**40**. Chiral column analytical HPLC established *cis*-**40** had an *ee* of 99%.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · aziridine · Brønsted acids · multicomponent reactions

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