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The diastereoselective synthesis of 2,3-diaryl-3-cyano-substituted pyrrolidines *via* the MgI_2 mediated ring expansion of aryl cyclopropyl nitriles

Darren Stead

Oncology R&D, AstraZeneca, Cambridge CB4 0WG, United Kingdom

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ABSTRACT

The MgI_2 mediated reaction of aryl substituted cyclopropyl nitriles with tosyl aldimines to give 2,3-diaryl-3-cyano-substituted pyrrolidines has been demonstrated. In all cases, the *trans*-diastereoisomer was determined to be the major product. The overall yield and diastereoselectivity of the reaction showed some sensitivity to the electronic and steric demands of the aryl cyclopropyl nitriles and the tosyl aldimines. Substitution with electron withdrawing substituents on both reacting partners proved beneficial in terms of the yield and diastereoselectivity.

The pyrrolidine motif is ubiquitous in Nature, making up the core of over 80 complex alkaloids [1]. Many of these alkaloids have profound biological effects, such as the addictive component of tobacco, (−)-nicotine **1**, the structurally more elaborate stimulant cocaine **2** [2], as well as the venom of the *Monomorium indicum* ant **3** (Fig. 1) [3]. Drug discovery programs have also sought to exploit the pyrrolidine motif, using its basic nitrogen to improve physiochemical properties or taking advantage of its 9 potential points of substitution to achieve desirable vectors. Recent examples include cholinesterase inhibitors [4], selective SphK2 inhibitors [5] and PROTACs targeting EGFR in an oncology setting [6].

As a consequence, research into the synthesis of pyrrolidines has been extensive, with every bond within the ring being subject to disconnection and a host of methodologies being used to introduce functionality at each position, with cycloaddition and annulation strategies proving popular [7]. Multicomponent, or multistep, reactions offer an attractive avenue for pyrrolidine ring synthesis because of the potential to quickly assemble pyrrolidines with complex substitution patterns [8]. At AstraZeneca, we became interested in 2,3-diaryl-3-cyano-substituted pyrrolidines. Literature syntheses of such motifs was limited [9–19], especially without further decoration [20]. However, we were intrigued by the MgI_2 mediated synthesis of 2-aryl-3-keto-substituted pyrrolidines *via* the multicomponent reaction of a cyclopropyl ketone and an

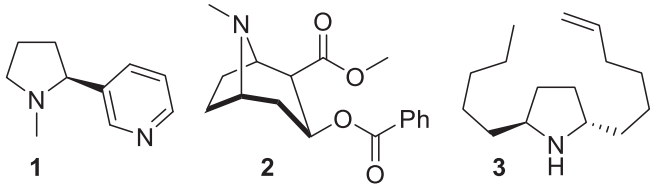

Fig. 1. Selected examples of natural products containing the pyrrolidine motif.

in situ generated aldimine, reported by Olsson and co-workers [21]. This work was itself inspired by Carreria's research into the synthesis of spiro[pyrrolidine-3-3′-oxindole] natural products [22]. Building from these contributions, we hypothesized that an electron withdrawing nitrile group could be used to activate an aryl-cyclopropyl ring [23], towards ring opening by MgI_2. Subsequent addition to an aldimine would lead to a 2,3-diaryl-3-cyano-substituted pyrrolidine (Scheme 1). This would provide a complementary approach to the elegant 1,3-dipolar cycloaddition methodology recently described by Lan and Zhang to access similar molecules [19].

From a drug discovery perspective, this approach would be particularly attractive because a number of 1-aryl-1-cyano substituted cyclopropanes were commercially available, allowing rapid exploration of SAR. Thus, we began our exploration with the commercially available cyclopropane **4**, the bromide of which could also

E-mail address: darren.stead@astrazeneca.com

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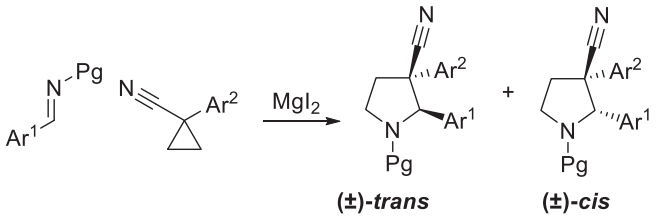
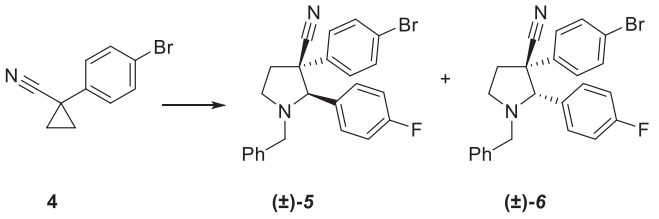


Scheme 1. Proposed reaction for this work. Pg = protecting group.



Scheme 2. Initial exploration: Reagents and conditions: Benzylamine (1 equiv.), 4-fluorobenzaldehyde (1 equiv.), MgI_2 (1.5 equiv.), THF, reflux, 16 h. Only minor signs of conversion to the desired products observed by UPLC (approx. 5% conversion to each diastereoisomer).

provide a handle for further elaboration. Subjecting cyclopropane **4** to similar conditions to those described by Olsson and co-workers [21], generating an imine *in situ* between benzylamine and 4-fluorobenzaldehyde, showed only minor signs of the desired products, *trans* and *cis* pyrrolidines **5** and **6**, by UPLC after 16 h at reflux (Scheme 2).

Despite only low conversion, this result did demonstrate that the nitrile could activate the cyclopropane ring to attack by MgI_2 and lead to the pyrrolidine products. Considering this reaction to proceed *via* an analogous mechanism to that proposed by Olsson and co-workers, it was not clear if the addition of the MgI_2 to the cyclopropyl ring was limiting the conversion, or if the reaction of the resulting anion with the formed aldimine was the issue. Pragmatically, it was simplest to investigate the latter, and so the corresponding tosyl-aldimine was prepared, reasoning that aldimine **7** would be more activated towards nucleophilic attack.

When tosyl aldimine **7** was reacted with cyclopropane **4** (Scheme 3), good conversion was apparent and gratifyingly the *trans* and *cis* diastereoisomers, **8** and **9** respectively, were readily separated by flash column chromatography (FCC) to give the *trans*-diastereoisomer **8** in 51% yield and the *cis*-diastereoisomer in 23% yield. The approximately 2:1 ratio of diastereoisomers **8** and **9** corresponded well with the expected ratio, as judged by the ^{1}H NMR spectrum of the crude product. The relative stereochemistry was determined by 2D NMR spectroscopy [24].

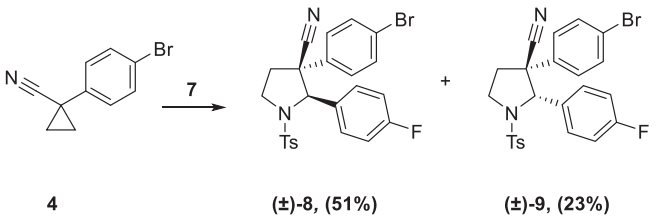
We attempted to optimize the diastereomeric ratio of products further (see ESI), however, no significant improvements were discovered, with THF being the best solvent and the reaction being seemingly insensitive to the equivalents of MgI_2. With this information in hand, we set about preparing several other aryl-cyclopropanes, using the conditions illustrated for benzonitrile **10a** (Scheme 4) and subjecting them to the pyrrolidine forming conditions (Scheme 5 and Table 1).

Table 1 shows that in all cases the *trans*-diastereoisomer was the major product of the reaction. It is clear that both electronic and steric factors are affecting the yield and diastereoselectivity. Although the overall isolated yield between entries 1 and 2 are similar, the addition of the electron withdrawing nitrile in the *para*-position (**10a**, entry 2) resulted in an improved diastereoselectivity, favoring the *trans*-diastereoisomer **11a**.

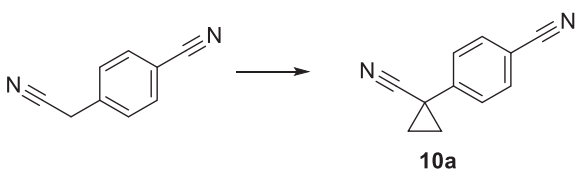
Introduction of an *ortho*-fluorine (**10c**, entry 4) resulted in an increase in the proportion of the *cis*-diastereoisomer **12c**. This effect was also observed with the *ortho*-chlorine and *ortho*-bromine examples (entries 7 and 8), albeit with greater reduction in overall yield, indicating that *ortho*-substitution is deleterious to the reaction (*vide infra*). In contrast, *meta*-substitution does not hinder the reaction (entry 5) and the reaction appears to tolerate electron rich aromatics (entry 6, the yield before diastereoisomer separation was 59% as 1.5:1 mix of *trans* to *cis* diastereoisomers), although with reduced diastereoselectivity. These results indicate that *meta* and *para* substitution is preferred for conversion to the pyrrolidine ring and that electron poor aromatics give the highest yields and *trans*-diastereoselectivities.

Intrigued by the observation that substitution on the cyclopropane with electron deficient aromatics gave the highest yields and *trans*-diastereoselectivities, we next explored reacting benzonitrile **10a** with aldimines of varying steric and electronic demands, to determine the scope of this reaction (Scheme 6 and Table 2) [25].

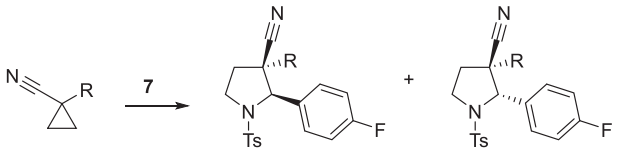
Gratifyingly, we found that a range of aldimines successfully underwent this reaction. The combination of the electron deficient cyclopropane **10a** and *para*-electron withdrawing groups on aldimine **13** gave excellent overall yields and good diastereoselectivities (Table 2, entries 1 and 2). The *trans*-diastereoisomers were produced in > 5:1 ratio over the *cis*-diastereoisomers, in each case. Introduction of an electron donating *para*-methoxy group (entry 3) saw a reduction in the diastereoselectivity, but a *para*-bromo substituent still resulted in good diastereoselectivity, with the *trans*-diastereoisomer being isolated in > 70% yield (entry 4). Interestingly, methyl substituted **13e**, resulted in a significantly lower *trans*-diastereoselectivity (3.84:1, entry 5), although these isomers could not be separated by FCC or prep-HPLC. *meta*-Substitution was tolerated with generally good yields and *trans*-diastereoselectivities (entries 6–9), again with more electron deficient examples, such as entry 8, giving the highest *trans*-diastereoselectivities. *ortho*-Substituents gave slightly reduced overall yield (entries 10 and 11), however, the *ortho*-chlorine present in **13j** (entry 10) had a large impact on the *trans*-diastereoselectivity, although the *trans*-diastereoisomer **14j** was still the predominant product in a ratio of 1.7:1. This effect on diastereoselectivity was not as marked for the *ortho*-methoxy substituent (entry 11), with the result being similar to the presence of a *para*-or *meta*-methoxy group (entries 3 and 9).



Scheme 3. Reaction of tosyl aldimine 7 with cyclopropane 4: Reagents and conditions: 4 (1 equiv.), 7 (1 equiv.), MgI_2 (1.5 equiv.), THF, reflux 16 h.

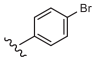
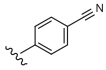
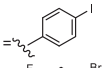
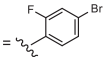
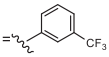
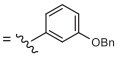
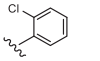
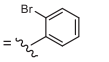


Scheme 4. Preparation of aryl-cyclopropanes: Reagents and conditions for example benzonitrile 10a: 4-(cyanomethyl)benzonitrile (1 equiv.), 1-bromo-2-chloroethane (1.5 equiv.), 50% (w/w) NaOH $_{(aq)}$ (6 equiv.), *N*-benzyl-*N*,*N*-diethylethanaminium bromide (8 mol%), 0 °C-rt, 4 days, (61%).

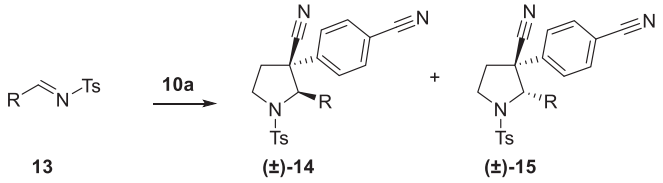


Scheme 5. Reaction of tosyl aldimine 7 with aryl cyclopropanes in Table 1: Reagents and conditions: Aryl cyclopropane (1 equiv.), 7 (1 equiv.), MgI_2 (1.5 equiv.), THF, reflux 16 h.

Table 1
Aryl cyclopropane scope from Scheme 5.

Entry	Aryl cyclopropane	*Trans*- (±)-**11** (% yield) [a]	*Cis*-(±)-**12** (% yield) [a]
1	**4**, R = 	**8** (51)	**9** (23)
2	**10a**, R = 	**11a** (68)	**12a** (7)
3	**10b**, R = 	**11b** (61)	**12b** (20)
4	**10c**, R = 	**11c** (40)	**12c** (32)
5	**10d**, R = 	**11d** (61)	**12d** (20)
6	**10e**, R = 	**11e** (20)[b]	**12e** (13)[b]
7	**10f**, R = 	**11f** (15)	**12f** (9)
8	**10g**, R = 	**11g** (22)	**12g** (12)

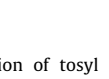
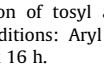
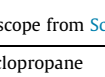
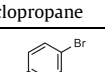
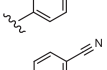
[a] Yields of separated diastereoisomers.
[b] Chiral SFC used to separate diastereoisomers. 59% yield after FCC as a 1.5:1 ratio of *trans* to *cis* diastereoisomers.



Scheme 6. Reaction of benzonitrile cyclopropane 10a with tosyl aldimines 13 in Table 2: Reagents and conditions: Aryl cyclopropane 10a (1 equiv.), aldimine (1 equiv.), MgI_2 (1.5 equiv.), THF, reflux 16 h.

Although no mechanistic studies have been conducted, a reasonable mechanism can be proposed (Fig. 2), which shares characteristics with that proposed by Olsson and co-workers for cyclopropyl ketones [21]. However, rationalization of a transition state that explains the diastereoselectivity is more challenging. The results in Tables 1 and 2 indicate that there are both steric and electronic components of the selectivity. Increasing the steric bulk of the aromatics results in an increase in steric clashes, disrupting the transition state leading to lower diastereoselectivity. The subtlety of the electronics of the system on the diastereoselectivity may be indicative of the stereo-determining step being reversible. Electron withdrawing groups on the aromatic ring could potentially stabilize the magnesium alkanide, allowing formation of the thermodynamically more stable Mannich product, resulting in higher diastereoselectivities. The erosion of this selectivity by electron donating groups on the aldimine, may be a result of increasing the reactivity of the resulting magnesium amide,

Table 2
Aldimine scope from Scheme 6.

Entry	Tosyl aldimine **13**	*Trans*- (±)-**14** (% yield) [a]	*Cis*- (±)-**15** (% yield) [a]
1	**13a**, R =	**14a** (83)	**15a** (16)
2	**13b**, R = 	**14b** (79)	**15b** (14)
3	**13c**, R = 	**14c** (48)	**15c** (14)
4	**13d**, R =	**14d** (72)	**15d** (15)
5	**13e**, R = 	**14e** (75)[b]	–
6	**13f**, R = 	**14f** (73)	**15f** (15)
7	**13g**, R = 	**14g** (62)	**15g** (14)
8	**13h**, R =	**14h** (70)	**15h** (12)
9	**13i**, R =	**14i** (60)	**15i** (15)
10	**13j**, R =	**14j** (43)	**15j** (25)
11	**13k**, R =	**14k** (54)	**15k** (17)

[a] Yields of separated diastereoisomers unless otherwise noted.
[b] 3.84:1 mixture of *trans:cis*-diastereoisomers as no separation of diastereoisomers was achieved by FCC or prep-HPLC.

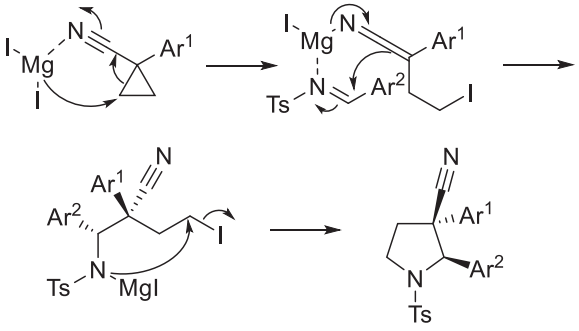


Fig. 2. Proposed mechanism.

increasing the rate of pyrrolidine formation. When the pyrrolidine is formed, the stereochemistry is then fixed.

In summary, the MgI_2 mediated reaction between a variety of aryl-substituted cyclopropyl nitriles and a number of aldimines to give 2,3-diaryl-3-cyano-substituted pyrrolidines has been developed. It was found that electron deficient aromatics on both reacting partners was beneficial for the overall yield and obtaining good *trans*-diastereoselectivity of the resulting pyrrolidine products. The reaction requires no special reaction conditions, using either reactants that are commercially available, or synthesized in one step each from such reagents. All but one set of diastereoisomeric products were readily separated by FCC and/or HPLC, often giving the *trans*-diastereoisomer of the pyrrolidine product in very good yield.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152325.

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[23] Vinylcyclcopropanes have been activated with geminal dicyano-substitutuents, to undergo palladium catalysed [3+2] cycloadditions with imines to afford pyrrolidine products. See (a) Dieskau, A. P.; Holzwarth, M. S.; Plietker, B., J. Am. Chem. Soc. 2012, 134 (11), 5048-5051. (b) Pursley, D.; Plietker, B., Synlett 2014, 25 (16), 2316-2318. (c) Ling, J.; Laugeois, M.; Ratovelomanana-Vidal, V.; Vitale, M. R., Synlett 2018, 29 (17), 2288-2292.
[24] After verification of several examples it became clear that the chemical shifts of the NTsCHAr proton in the 1H NMR spectrum were indicative of the relative stereochemistry, with the trans-diastereoisomer observed at lower ppm (typically at around 4.85 ppm) than the cis-diastereoisomer (typically at around 5.10 ppm).
[25] Representative procedure for 14a and 15a: To a stirred solution of 4-(1-cyanocyclopropyl)benzonitrile 13a (200 mg, 1.19 mmol) and N-(4-cyanobenzylidene)-4-methylbenzenesulfonamide 10a (338 mg, 1.19 mmol) in THF (4 mL) was added magnesium iodide (496 mg, 1.78 mmol). The resulting mixture was heated to reflux and stirred for 16 hours. The mixture was allowed to cool to room temperature and water (10 mL) and EtOAc (20 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organics were dried (phase separation cartridge) and concentrated under reduced pressure to give the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% EtOAc in heptane and by preparative HPLC (Waters CSH C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents to give rac-4,4'-((2R,3S)-3-cyano-1-tosylpyrrolidine-2,3-diyl) dibenzonitrile 14a (0.447 g, 83%) and rac-4,4'-((2R,3R)-3-cyano-1-tosylpyrrolidine-2,3-diyl)dibenzonitrile 14b (0.088 g, 16%) as white foamy solids.