One-Pot Catalytic Enantioselective Synthesis of 2-Pyrazolines

Connor J. Thomson[a], David M. Barber[b] and Darren J. Dixon[*][a]

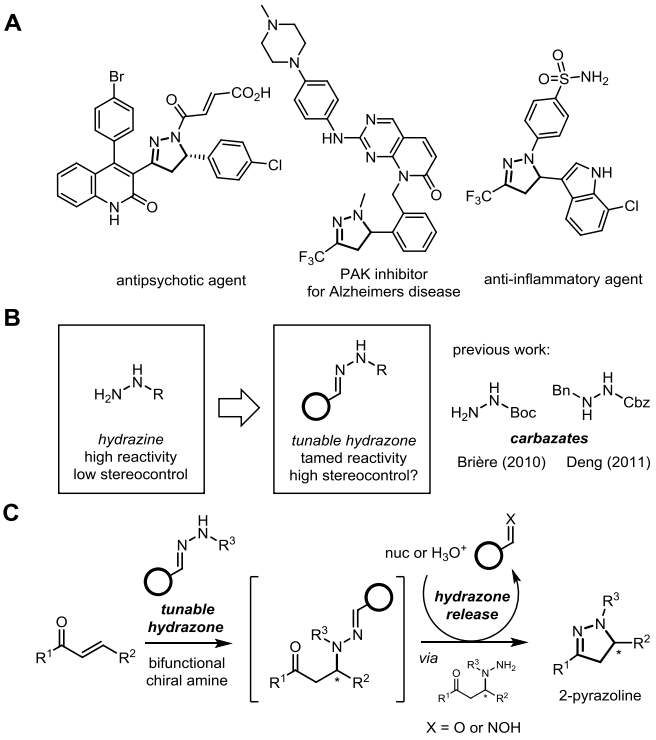
Abstract: *A scalable, one-pot, enantioselective catalytic synthesis of 2-pyrazolines from beta-substituted enones and hydrazines is described. Pivoting on a two stage catalytic Michael addition / condensation strategy, the use of an aldehyde to generate a suitable hydrazone derivative of the hydrazine was found to be key for curtailing background reactivity and tuning the catalyst-controlled enantioselectivity. The new synthetic protocol is easy to perform, uses a new and readily prepared cinchona-derived bifunctional catalyst, is broad in scope, and tolerates a range of functionalities with high enantioselectivity (up to >99:1 er). The significant scalability of this methodology has been demonstrated with the synthesis of >80 grams of a pyrazoline product with 89% catalyst recovery.*

Heterocycles containing an N-N bond are abundant in natural products, synthetic therapeutics, and agrochemicals.[1] In particular, optically active pyrazolines and their derivatives are in high demand for their intrinsic biological properties.[2] 2-Pyrazolines specifically find widespread use in small-molecule drugs, agrochemicals, and have been noted for their valuable properties in material science (Scheme 1).[3] Furthermore, the use of 2-pyrazolines as valuable intermediates in the synthesis of cyclopropanes and pyrazoles is well-documented.[4]

Although there are many examples describing the synthesis of 2-pyrazolines as racemates, methods for the efficient preparation of enantiomerically enriched 2-pyrazolines remain limited.[5] In 2000, Kanai reported the first enantioselective synthesis of 2-pyrazolines, using a Lewis acid catalyzed 1,3-dipolar cycloaddition.[6] This was subsequently followed by the acid catalyzed electrocyclization methodology of List, and independent reports from Cordova and Carillo on the synthesis of 2-pyrazolines via pyrazolidines.[7] Brière also disclosed the elegant phase-transfer catalyzed addition of carbazates to chalcones.[8] Deng later reported the use of benzyl-protected carbazates in the enantioselective synthesis of 2-pyrazolines (Scheme 1B).[9]

Despite these elegant examples, we were attracted to the challenge of developing a broadly applicable platform for the metal-free, expeditious synthesis of enantioenriched 2-pyrazolines. Whilst the use of hydrazine nucleophiles in the synthesis of racemic pyrazolines is well-established, the high reactivity of these reagents has, to date, restricted the development of a corresponding enantioselective method.[10] As a strategy to circumvent their high inherent nucleophilicity, we envisaged the use of an aldehyde to generate a suitable hydrazone derivative to impart tunability and dampen reactivity of the hydrazine moiety (Scheme 1B).[11] Such an approach could grant stereoselective access to enantioenriched 2-pyrazolines after *in-situ* cleavage of the hydrazone and subsequent intramolecular condensation (Scheme 1C). Herein we wish to report our findings.

The reaction of methylhydrazine-derived hydrazone **1a**



Scheme 1. (A) Bioactive pyrazolines and their uses; (B) Rationale for use of protected hydrazines and previous work with carbazates; (C) Platform for aza-Michael addition of the hydrazine sython enabled by a cleavable hydrazone.

with chalcone **2a** was chosen as a model system and we hypothesized that bifunctional Brønsted base/H-bond donor catalysts could affect the desired enantioselective aza-Michael addition. [12] A screen of potential catalysts revealed the cinchona family to be effective, with quinidine (Figure 1, catalyst **A**) offering promising selectivity; aza-Michael adduct **3a** was obtained in 71:29 er. Encouraged by the early success with quinidine as catalyst, other cinchona-derived systems were investigated (Table 1A, entries 1-6). Use of the *O*-benzyl catalyst **B** resulted in a selectivity decrease, while bifunctional urea **C** showed an enhancement to 80:20 er. Interestingly, the formation of Michael adduct **4** was observed as a competitive side-product in some cases.[13] Despite this, selectivity for **3a** was improved with the use of catalyst **D**. Enantioselectivity was further improved with amide **E**, suggesting the need for a single H-bond donor for appropriate organization of the hydrazone-chalcone transition state. A screen of various amide groups revealed 3,5-dichlorobenzoylamide catalyst **F** to be optimal (see ESI).

Our attention then turned to the structure of the hydrazone and its influence on the stereochemical outcome of the reaction. The presence of a methyl group at the 2, 3, or 4 positions of the arene ring of **1** all improved enantioselectivity (see Table 1A and ESI for details). Pleasingly, 4-*tert*-butyl benzaldehyde was found to give the most substantial enantioselectivity when compared with benzaldehyde (entry 9, 90:10 er). Lowering the reaction temperature to -15 °C and extending the reaction time to 48 hours further improved the er and conversion, to 95:5 er and 93%, respectively. Furthermore, quantitative *in situ* cleavage of the chiral hydrazone intermediate (thereby releasing oxime **6b**)

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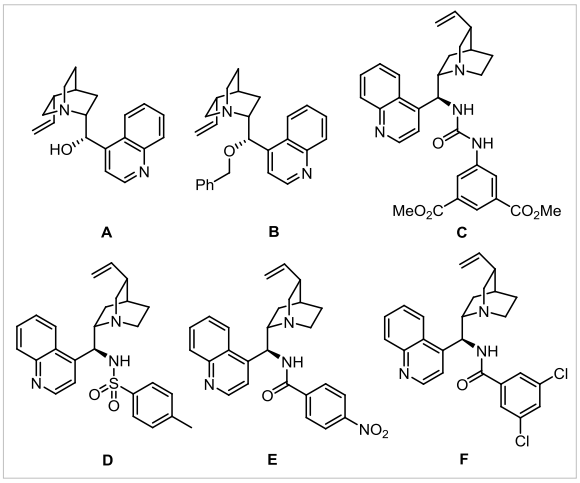


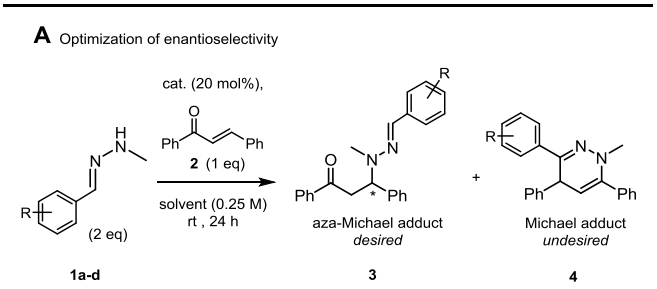
Figure 1. Selected catalysts investigated for the aza-Michael addition of **1a-d** to chalcone **2**.

could be achieved using hydroxylamine, without compromising the enantioselectivity (see Entry 4, Table 1B).

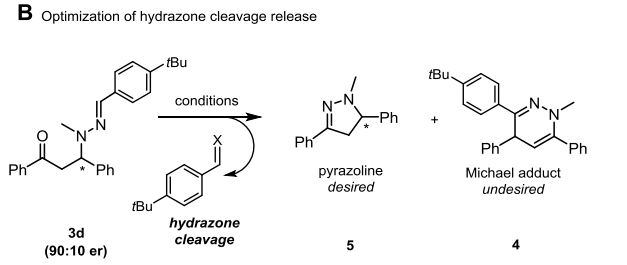
Combining these optimized transformations delivered a streamlined one-pot route to 2-pyrazolines from methylhydrazine, which was then ready for assessment of its scope. When substituents on both aromatic rings of the chalcone were varied, minimal fluctuation in enantioselectivity was observed across a range of electron-rich and electron-poor substrates (Scheme 2A). Potentially incompatible functionalities such as cyano, vinyl and ester groups were all well-tolerated. Difluorocyclopropane **5l** and benzodioxole **5q** are particularly appealing, with potential applications in medicinal chemistry programs.[14] Substrates derived from alkyl aldehydes were compatible with this chemistry, giving excellent er's of up to >99:1 for hexyl pyrazoline **5w** (82% yield). Ynenone **5z**, enynone **5x** and alkenyl enone **5y** were successfully employed to afford the corresponding alkynyl and alkenyl scaffolds in moderate to excellent er. Notably, heterocycles were competent substrates; furnishing the pyrazine, pyridine and thiophene structures **5r**-**5t**. Furthermore, variation of the hydrazine moiety afforded the *N*-ethyl (**5ab**), *N*-cyanoethyl (**5ac**) and *N*-benzyl (**5ad**) 2-pyrazolines in good yield and er at reaction rates similar to the methyl hydrazine system, thus demonstrating wider applicability of this chemistry.[15]

In order to explore the scalability of this methodology, we performed a model reaction with enone **2b** on 100 gram scale. To ensure affordability and practicality upon scale-up, the reaction was performed at room temperature, rather than -15 °C, and benzaldehyde was employed as the hydrazone precursor instead of *tert*-butyl benzaldehyde. Smooth reactivity and a clean reaction profile allowed the isolation of 84.9 grams of pyrazoline **5b** in 77% yield and >99.9:0.1 er after a single recrystallization. The mild protocol allowed **5b** to be cleanly isolated without the need for silica gel chromatography. Importantly, 89% of catalyst **F** was recovered in addition to 97% isolation of the benzaldehyde oxime by-product.[16] The recovered catalyst was reused (on 0.5 mmol scale) with no loss of reactivity or selectivity (see ESI).

With the aim of demonstrating the broader utility of our platform, pyrazoline **5b** was explored as a scaffold for late stage



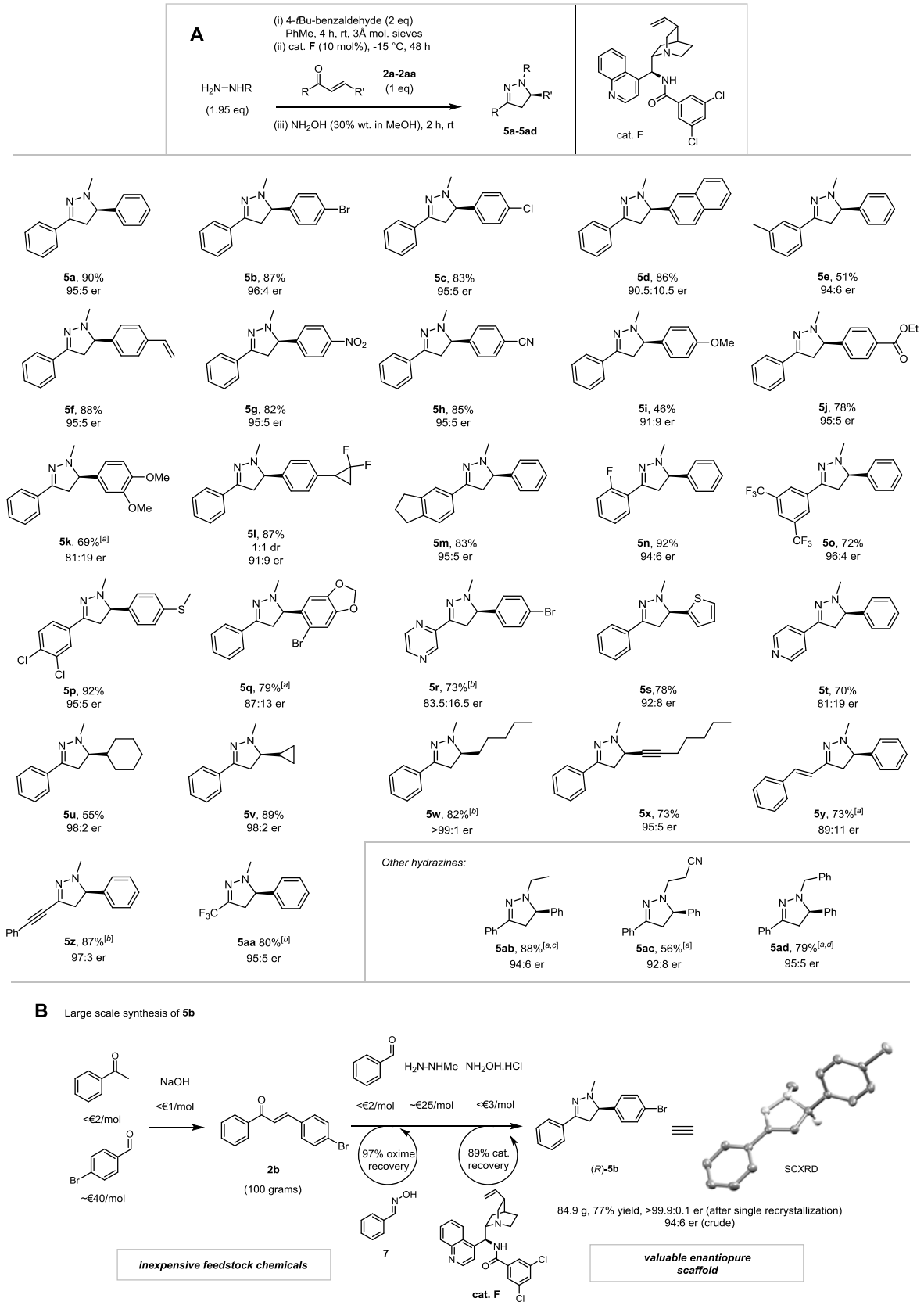
Entry	cat.	R (1)	3 (%)[a]	4 (%)[a]	3 er[b]
1	**A**	H (**1a**)	86 (**3a**)	0	71:29
2	**B**	H (**1a**)	74 (**3a**)	0	36:64
3	**C**	H (**1a**)	69 (**3a**)	9	80:20
4	**D**	H (**1a**)	50 (**3a**)	29	82:18
5	**E**	H (**1a**)	58 (**3a**)	7	86:14
6	**F**	H (**1a**)	56 (**3a**)	17	87:13
7	**F**	4-CH_3 (**1b**)	87 (**3b**)	2	89:11
8	**F**	2-CH_3 (**1c**)	65 (**3c**)	11	88:12
9	**F**	4-*t*Bu (**1d**)	90 (**3d**)	0	90:10
10[c]	**F**	4-*t*Bu (**1d**)	68 (**3d**)	0	88:12
11[d]	**F**	**4-*t*Bu** (**1d**)	**93** (**3d**)	**0**	**95:5**
12[e]	-	H (**1a**)	trace	-	-



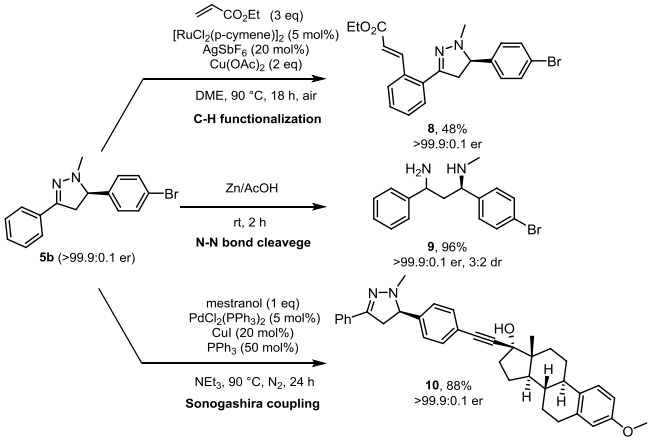
Entry	Reagent	5 (%)[a] (er)	4 (%)[a,b]
1	Amberlyst-15R®	0 (N.D.)	0
2	aq. HCl (1.5 eq)	0 (N.D.)	0
3	aq. H_2SO_4 (0.5 eq)	76 (N.D.)	24
4	30% NH_2OH in MeOH	100 (90:10)	0

Table 1. (A) Optimization of the organocatalyzed aza-Michael addition; (B) Optimization of conditions for hydrazone cleavage. [a]determined by ^{1}H NMR. [b]**4** was always obtained as a racemic mixture. [c]10 mol% of catalyst **F** was used.[d]performed at -15 °C for 48 hours with 10 mol% catalyst **F**. [e]performed for 7 days. N.D: not determined.

functionalization (Scheme 3). Accordingly, **5b** was treated with ethyl acrylate under ruthenium catalysis to obtain the *ortho*-alkenylated product **8** in 48% yield. [17] To the best of our knowledge, this is the first example of pyrazoline-directed C-H functionalization; this method could find use in library synthesis for lead-optimization in medical chemistry/agrochemical programs. Furthermore, treatment of **5b** with zinc in acetic acid



Scheme 2. (A) Scope of aza-Michael addition of *in-situ* generated **1d** to enones **2a-2aa**; (B) Large scale synthesis of **5b** (see ESI for details). [a]performed in CH_2Cl_2. [b]performed at -40 °C. [c]with EtNHNH$_2$.oxalate and 1.95 eq DIPEA. [d]with BnNHNH$_2$.2HCl and 3.8 eq DIPEA. Stereochemical configuration was assigned by analogy with (*R*)-**5b** (determined by single crystal X-ray diffraction studies).



Scheme 3. Derivatization of pyrazoline **5b**.

furnished a 3:2 diastereomeric mixture of the enantioenriched diamine **9** in 96% yield. Methods to access diamine structures are limited and this example represents the first protocol to obtain optically active 1,3-diamines from pyrazolines. Lastly, Sonogashira coupling with the hormone drug mestranol readily furnished enantiopure alkyne **10** in 88% yield.

In summary, an efficient platform for the synthesis of enantioenriched 2-pyrazoline scaffolds from beta-substituted enones and monoalkyl-substituted hydrazine-derived hydrazones has been designed and developed. Deployment of a novel cinchonidine-derived bifunctional catalyst in conjunction with an optimized hydrazone derivative allowed good control of reactivity and enantioselectivity in the initial Michael addition step. A staged addition of hydroxylamine then facilitated 2-pyrazoline formation after cleavage of the chiral hydrazone intermediate. The new synthetic protocol was found to be compatible with a range of functionalities including esters, nitriles, heterocycles, alkenes and alkynes, and was amenable to decagram scale synthesis. The scalability of this method, coupled with a range of novel late-stage derivatizations has highlighted the synthetic versatility of the reaction products, with potential applications in biomedical and agrochemical contexts.

Acknowledgements

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Keywords: hydrazone, enantioselective catalysis, pyrazolines, aza-Michael addition, bifunctional catalysis

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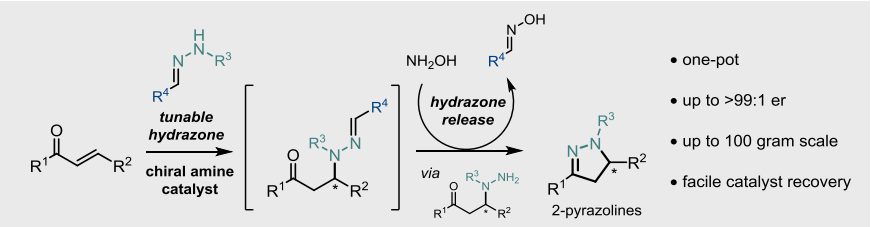

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