

# A Journal of the Gesellschaft Deutscher Chemiker A Deutscher Chemiker GDCh International Edition www.angewandte.org

# **Accepted Article**

Title: One-Pot Catalytic Enantioselective Synthesis of 2-Pyrazolines

Authors: Connor Jack Thomson, David M Barber, and Darren James Dixon

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Angew. Chem. Int. Ed. 10.1002/anie.201811471 Angew. Chem. 10.1002/ange.201811471

Link to VoR: http://dx.doi.org/10.1002/anie.201811471 http://dx.doi.org/10.1002/ange.201811471

# WILEY-VCH

#### WILEY-VCH

# **One-Pot Catalytic Enantioselective Synthesis of 2-Pyrazolines**

Connor J. Thomson<sup>[a]</sup>, David M. Barber<sup>[b]</sup> and Darren J. Dixon<sup>[\*][a]</sup>

**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.<sup>[1]</sup> In particular, optically active pyrazolines and their derivatives are in high demand for their intrinsic biological properties.<sup>[2]</sup> 2-Pyrazolines specifically find widespread use in small-molecule drugs, agrochemicals, and have been noted for their valuable properties in material science (Scheme 1).<sup>[3]</sup> Furthermore, the use of 2-pyrazolines as valuable intermediates in the synthesis of cyclopropanes and pyrazoles is well-documented.<sup>[4]</sup>

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.<sup>[6]</sup> In 2000, Kanai reported the first enantioselective synthesis of 2-pyrazolines, using a Lewis acid catalyzed 1,3-dipolar cycloaddition.<sup>[6]</sup> 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.<sup>[7]</sup> Brière also disclosed the elegant phase-transfer catalyzed addition of carbazates to chalcones.<sup>[8]</sup> Deng later reported the use of benzyl-protected carbazates in the enantioselective synthesis of 2-pyrazolines (Scheme 1B).<sup>[9]</sup>

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.<sup>[10]</sup> 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).<sup>[11]</sup> 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.<sup>[13]</sup> 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 3,5dichlorobenzoylamide 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**)

<sup>[</sup>a] C. J. Thomson, Prof. Dr. D. J. Dixon, Department of Chemistry, Chemistry Research Laboratory, University of Oxford, United Kingdom, Mansfield Road, Oxford OX1 3TA

<sup>[</sup>b] Dr. D. M. Barber, Research & Development, Weed Control Chemistry Bayer AG, Crop Science Division, Industriepark Höchst, Frankfurt am Main, 65926, Germany

<sup>[\*]</sup> darren.dixon@chem.ox.ac.uk

#### WILEY-VCH



Figure 1. Selected catalysts investigated for the aza-Michael addition of  $\ensuremath{\text{1a-d}}$  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 51 and benzodioxole 5q are particularly appealing, with potential applications in medicinal chemistry programs.<sup>[14]</sup> 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 Nethyl (5ab), N-cyanoethyl (5ac) and N-benzyl (5ad) 2pyrazolines 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.<sup>[16]</sup> 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

A Optimization of enantioselectivity								
	cat.	(20 mol%), 0 2 (1 eq) ent (0.25 M) rt , 24 h aza	N N + Ph -Michael adduc desired	R R t	Ph Ph Michael adduct undesired			
1a-d			3		4			
Entry	cat.	R (1)	3 (%) <sup>a</sup>	4 (%) <sup>a</sup>	3 er <sup>b</sup>			
1	Α	H ( <b>1a</b> )	86 ( <b>3a</b> )	0	71:29			
2	в	H ( <b>1a</b> )	74 ( <b>3a</b> )	0	36:64			
3	С	H ( <b>1a</b> )	69 ( <b>3a</b> )	9	80:20			
4	D	H ( <b>1a</b> )	50 ( <b>3a</b> )	29	82:18			
5	Е	H ( <b>1a</b> )	58 ( <b>3a</b> )	7	86:14			
6	F	H ( <b>1a</b> )	56 ( <b>3a</b> )	17	87:13			
7	F	4-CH <sub>3</sub> ( <b>1b</b> )	87 ( <b>3b</b> )	2	89:11			
8	F	2-CH <sub>3</sub> ( <b>1c</b> )	65 ( <b>3c</b> )	11	88:12			
9	F	4- <i>t</i> Bu ( <b>1d</b> )	90 ( <b>3d</b> )	0	90:10			
10 <sup>c</sup>	F	4- <i>t</i> Bu ( <b>1d</b> )	68 ( <b>3d</b> )	0	88:12			
11 <sup>d</sup>	F	4- <i>t</i> Bu (1d)	93 (3d)	0	95:5			
12 <sup>e</sup>	-	H ( <b>1a</b> )	trace	-	-			

B Optimization of hydrazone cleavage release



Entry	Reagent	5 (%) <sup>a</sup> (er)	4 (%) <sup>a,b</sup>
1	Amberlyst-15R <sup>®</sup>	0 (N.D.)	0
2	aq. HCl (1.5 eq)	0 (N.D.)	0
3	aq. H <sub>2</sub> SO <sub>4</sub> (0.5 eq)	76 (N.D.)	24
4	30% NH2OH in MeOH	100 (90:10)	0

**Table 1.** (A) Optimization of the organocatalyzed aza-Michael addition; (B) Optimization of conditions for hydrazone cleavage. <sup>*a*</sup>determined by <sup>1</sup>H NMR. <sup>*b*</sup>4 was always obtained as a racemic mixture. <sup>*c*</sup>10 mol% of catalyst **F** was used. <sup>*d*</sup>performed at -15 <sup>o</sup>C for 48 hours with 10 mol% catalyst **F**. <sup>*e*</sup>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. <sup>[17]</sup> 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

#### WILEY-VCH



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). <sup>a</sup>performed in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup>performed at -40 °C. <sup>c</sup> with EtNHNH<sub>2</sub>.oxalate and 1.95 eq DIPEA. <sup>d</sup> with BnNHNH<sub>2</sub>.2HCl and 3.8 eq DIPEA. Stereochemical configuration was assigned by analogy with (*R*)-5b (determined by single crystal X-ray diffraction studies).

### WILEY-VCH



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 monoalkyl-substituted hydrazine-derived enones and 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 2pyrazoline 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

DJD and CJT wish to thank Bayer AG for generous financial support and Dr. Uwe Döller for helpful discussions. We are grateful to Dr. Jamie Leitch for help in the preparation of this manuscript. Heyao Shi is also thanked for X-ray structure determination of compound 5b, and Dr Amber L. Thompson and Dr Kirsten E. Christensen (Oxford Chemical Crystallography) for X-ray mentoring.

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

- (a) L. C. Behr, R. Fusco, C. H. Jarboe, Pyrazoles, Pyrazolines, [1] Pyrazolidines, Indazoles and Condensed Rings, The Chemistry of Heterocyclic Compounds 22, Interscience Publishers, New York, 1967; b) L. M. Blair, J. Sperry, J. Nat. Prod. 2013, 76, 794; c) V. Kumar, K. Kaur, G. K. Gupta, A. K. Sharma, Eur. J. Chem. 2013, 69, 735; d) G. Le Goff, J. Ouazzani, J. Bioorg. Med. Chem. 2014, 22, 6529; e) Y.-L. Du, H.-Y. He, M. A. Higgins, K. S. Ryan, Nat. Chem. Bio. 2017, 13, 836.
- (a) J. H. Lange, H. K. Coolen, H. H. van Stuiven-berg, J. A. Dijksman,
  A. Herremans, E. Ronken, H. G. Keizer, K. Tipker, A. C. McCreary,
  W. Veerman, H. C. Wals, B. Stork, P. C. Verveer, A. P. den Hartog, N. [2] M. de Jong, T. J. Adolfs, J. Hoogendoorn, C. G. Kruse, J. Med. Chem. 2004, 47, 627; b) J. R. Goodell, F. Puig-Basagoiti, B. M. Forshey, P.-Y. Shi, D. M. Ferguson, J. Med. Chem. 2006, 49, 2127; c) P. K. Mykhailiuk, Angew. Chem. Int. Ed. 2015, 54, 6558.

- (a) X. C. Gao, H. Cao, L. Q. Zhang, B.W. Zhang, Y. Cao, C. H. Huang, J. Mater. Chem. 1999, 9, 1077; b) A. Gurspy, S. Demirayak, G. Capan, [3] K. Erol, K. Vural, Eur. J. Med. Chem. 2000, 35, 359; c) H. B. Fu, J. N.Yao, J. Am. Chem. Soc. 2001, 123, 1434; d) M. E. Camacho, J. Leon, A. Entrena, G. Velasco, M. D. Carrion, G. Escames, A. Vivo, D. Acuna-Castroviejo, M. A. Gallo, A, Espinosa, J. Med. Chem. 2004, 47, 5641; e) X. Zhang, X. Li, G. F. Allan, T. Sbriscia, O. Linton, S. G. Lundeen, Z. Sui, J. Med. Chem. 2007, 50, 3857; f) A. S. Girgis, A. H. Basta, H. El-Saied, M. A. Mohamed, A. H. Bedair, A. S. Salim, R. Soc. Open Sci. 2018, 5, 171964.
- [4] (a) D. E. Applequist, R. D. Gdanski, J. Org. Chem. 1981, 46, 2502; b) R. S. Padmavathi, R. Venugopal, B. R. Padmaja, *Heteroat. Chem.* 2003, 14, 155; c) D.-H. Lee, B. S. Jung, S. Jung, J. Song, W. K. Sueng, Tettrahedron Lett., 2005, 46, 7721; d) B. Dipanwita, K.Utpal, K. Rajiv, M. Gourhari, Tetrahedron Lett. 2014, 55, 5333; e) D. Havrylyuk, O. Roman, R. Lesyk, *Eur. J. Med. Chem.* **2016**, *113*, 145. For key publications see: (a) M. P. Sibi, L. M. Stanley, C. P. Jasperse, *J.*
- [5] Am. Chem. Soc. 2005, 127, 8276; b) T. Kano, T. Hashimoto, Maruoka, J. Am. Chem. Soc. 2006, 128, 2174; c) M. P. Sibi, L. M. Stanley, T. Soeta, Adv. Synth. Catal. 2006, 348, 2371; d) M. P. Sibi, L. M. Stanley, T. Soeta, *Adv. Synth. Catal.* **2006**, *348*, 2371; e) M. P. Sibi, L. M. Stanley, T. Soeta, *Org. Lett.* **2007**, *9*, 1553; f) L. Gao, G.-S. Hwang, M. Y. Lee, D. H. Ryu, Chem. Commun. 2009, 5460; g) E. Frank, Z. Mucsi, I. Zupko, B. Rethy, G. Falkay, G. Schneider, J. Wolfing, J. Am. Chem. Soc. 2009, 131, 3894; h) J.-R. Chen, W.-R. Dong, M. Candy, F.-F. Pan, M. Jörres, C. Bolm, J. Am. Chem. Soc. 2012, 134, 6924; i) O. Mahé, I. Dez, V. Levachera, J.-F. Brière, Org. Biomol. Chem. 2012, 10, 3946; j) X. Kou, Q. Shao, C. Ye, G. Yang, W. Zhang, J. Am. Chem. Soc. 2018. 140. 7587
  - S. Kanemasa, T. Kanai, *J. Am. Chem. Soc.* **2000**, *122*, 10710. (a) S. Müller, B. List, *Angew. Chem. Int. Ed.* **2009**, *48*, 9975; b) S.
- [6] [7] Müller, B. List, Synthesis 2010, 13, 2171; c) M. Rueping, M. S. Maji, H. B. Kucuk, I. Atodiresei, Angew. Chem. Int. Ed. 2012, 51, 12864; d) L. Deiana, G.-L. Zhao, H. Leijonmarck, J. Sun, C. W. Lehmann, A. Cordova, ChemistryOpen, 2012, 1, 134; e) M. Fernandez, E. Reyes,
- J.L. Vicario, D. Badia, L. Carrillo, Adv. Synth. Catal. 2012, 354, 371. O. Mahe, I. Dez, V. Levacher, J.-F. Brière, Angew. Chem. Int. Ed. 2010, [8] 49.7072
- N. R. Campbell, B. Sun, R. P. Singh, L. Deng, Adv. Synth. Catal. 2011, [9] 353. 3123
- [10] In our initial studies, a wide screen of organocatalysts failed to produce enantioselectivities >65:35 er in the aza-Michael addition of methylhydrazine to 2a (due to a significant background reaction). For G.Wu, R. Liang, Y. Chen, L. Wu, *Syn. Comm.* **2010**, *40*, 129; b) Z.-P. Lin, J.-T. Li, *E-Journal of Chemistry*, **2012**, *9*, 267. For more on the nucleophillicity of hydrazines see: (a) J. M. Garver, S. Gronert, V. M. Bierbaum, J. Am. Chem. Soc. 2011, 133, 13894; b) T. A. Nigst, A. Antipova, H. Mayr, J. Org. Chem. 2012, 77, 8142.
- [11] For publications on the diverse reactivity of hydrazones in organic synthesis see: (a) M. Sugiura, S. Kobayashi, Angew. Chem. Int. Ed. 2005, 44, 5176; D. Perdicchia, K. A. Jørgensen, J. Org. Chem. 2007, 72, 3565; b) E. Li, P. Xie, L. Yang, L. Liang, Y. Huang, Chem. Asian J.
   2013, 8, 603; c) M. d. G. Retamosa, E. Matador, D. Monge, J. M. Lassaletta, R. Fernandez, Chem. Eur. J. 2016, 22, 13430; d) Y. Wang, Q. Wang, J. Zhu, Angew. Chem. Int. Ed. 2017, 56, 5612
- [12] For publications on bifunctional organocatalysis: (a) T. Okino, Y. Hoashi, . Takemoto, J. Am. Chem. Soc. 2003, 125, 12672; b) H. Li, Y. Wang, L. Tang, L. Deng, J. Am. Chem. Soc. 2004, 126, 9906; c) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.*, **2005**, 127, 119; d) B. Vakulya, S.Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, 7, 1967; e) J. Ye, D. J Dixon, P. Hynes, *Chem. Commun.* **2005**, *0*, 4481; f) J. Song, Y. Wang, L. Deng, J. Am. Chem. Soc. 2006, 128, 6048; g) S. H. McCooey, S. J. Connon, Angew. Chem. Int. Ed. 2005, 44, 6367; h) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, Synlett, **2005**, 4, 603; i) M. G. Nunez, A. F. M. Farley, D. J. Dixon, J. Am. Chem. Soc. 2013, 135, 16348. For reviews, see: (a) Y. Takemoto, Org. Biomol. Chem. 2005, 3, 4299; b) S. Connon, Chem. Commun. 2008. 2499.
- [13] See ESI for possible mechanism of formation. For the enantioselective synthesis of such structures, see: W. Wu, X. Yuan, J. Hu, X. Wu, Y. Wei, Z. Liu, J. Lu, J. Ye, Org. Lett. 2013, 15, 4524.
- (a) F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angew. Chem. Int. Ed.* **2011**, *50*, [14] 7153; b) C. J. Thomson, Q. Zhang, N. Al-Maharik, M. Buehl, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Comm.* **2018**, *54*, 8415. PhNHNH<sub>2</sub> afforded only trace amounts of the desired 2-pyrazoline. [15]
- 7 could be recycled to benzaldehyde via hydrolysis with HCI (see ESI). [16]
- [17] (a) J. Li, C. Kornhaass, L. Ackermann, Chem. Commun. 2012, 48, (11343; b) J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y Bhonoah, I. H. Williams, C. G. Frost, *ACS Catal.* **2016**, *6*, 5520.

### WILEY-VCH

#### Entry for the Table of Contents (Please choose one layout)

Layout 1:

### COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here))

Layout 2:

### COMMUNICATION



Connor J. Thomson, David M. Barber and Darren J. Dixon\*

#### 1 – 5

One-Pot Catalytic Enantioselective Synthesis of 2-Pyrazolines