CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201902422

Link to VoR: http://dx.doi.org/10.1002/chem.201902422

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10.1002/chem.201902422

Organocatalysis

~~DOI: 10.1002/anie.200((will be filled in by the editorial staff))~~

Highly Enantioselective Catalytic Kinetic Resolution of α-Branched Aldehydes via Formal Cycloaddition with Homophthalic Anhydrides

*Umar Farid, Maria Luisa Aiello and Stephen J. Connon**

Abstract: *A new catalytic methodology was developed to promote an efficient one-pot kinetic resolution of racemic aldehydes with selectivity (s*) of up to 91 (99:1* dr, *>99% ee) in a cycloaddition reaction with enolizable anhydrides to afford dihydroisocoumarin products (a core prevalent in natural products and molecules of medicinal interest) containing three contiguous stereocentres.*

The catalytic Kinetic Resolution (KR) of racemates remains an indispensable method for obtaining enantioenriched compounds.[1] While the substrate scope of this technology is generally broad, very few non-enzymatic methods for the KR of racemic *α*-substituted aldehydes – arguably the most synthetically versatile of functional groups - have emerged. Aldol type reactions involving KR of keto aldehydes have been reported, however most of these reactions are either non-catalytic or substrate-specific and result in poor enantioselectivity.[2] Among other approaches, kinetic and parallel kinetic resolution of *α*-amino aldehydes with chiral phosphonates,[3] metal-based (parallel) KR of *α* − and *β* −substituted aldehydes,[4] and the KR of *α*,*α*-disubstituted *α*-siloxy aldehydes[5] have been reported. In 1991, Oguni *et al*. disclosed the moderately selective KR of racemic aldehydes **1** *via* the enantioselective addition of diethyl zinc in the presence of a *β*-amino alcohol ligand **2** (Fig. 1A).[6] Unreacted aldehyde **3** could be recovered in high *ee* only at high conversions. Organocatalytic asymmetric fluorination of *α*-chloroaldehydes **5** involving KR remains among the few examples of the KR of *α*-branched aldehydes (Fig. 1B).[7] Enantiodiscrimination was such that low conversions were required to achieve high product *ee* – resulting in poor *ee* of the unreacted aldehyde. In 2008, a highly selective protocol for the KR of racemic specialized *N*-protected amino aldehydes **9** by oxidation with *N*-iodosuccinimide in the presence of Cu(II)/(*R*,*R*)-Ph-BOX to afford amino acid methyl esters **11** was reported (Fig. 1C).[8]

While the dynamic kinetic resolution of *α*-branched aldehydes[9] involving their *in situ* racemization and subsequent enantioselective conversion to less acidic non-aldehydic compounds has received considerable attention; the simple KR of α-branched aldehydes - potentially important building blocks (*e.g.* **13a-b**, Fig. 1D) - remains elusive, due in part to the requirement for an enantiodiscriminatory reaction at the aldehydic center while simultaneously avoiding both mid- and post-reaction racemization.

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[**] Financial support from Science Foundation Ireland (SFI – 12-IA-1645) is gratefully acknowledged. We thank Dr Brendan Twamley for X-ray crystal diffraction analysis.
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the

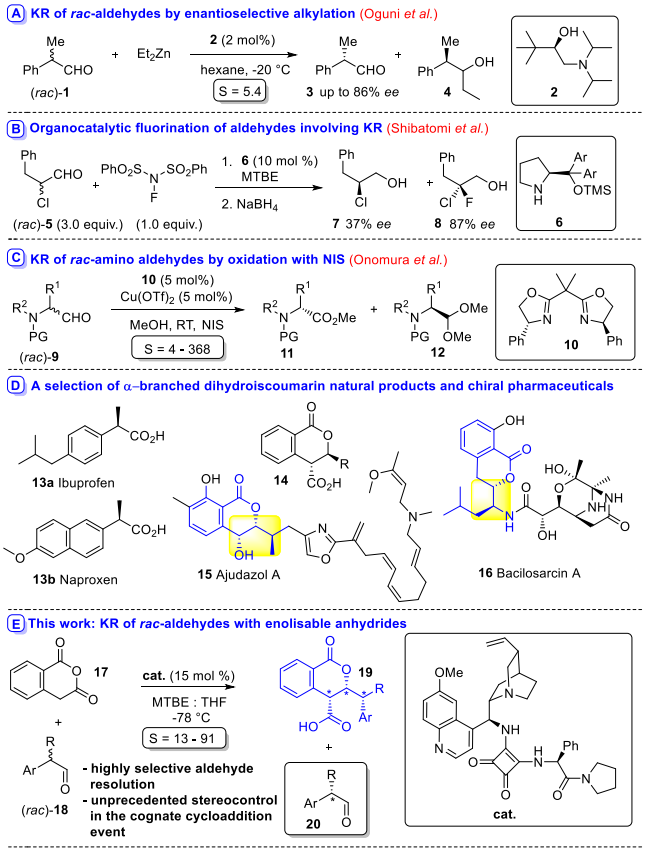


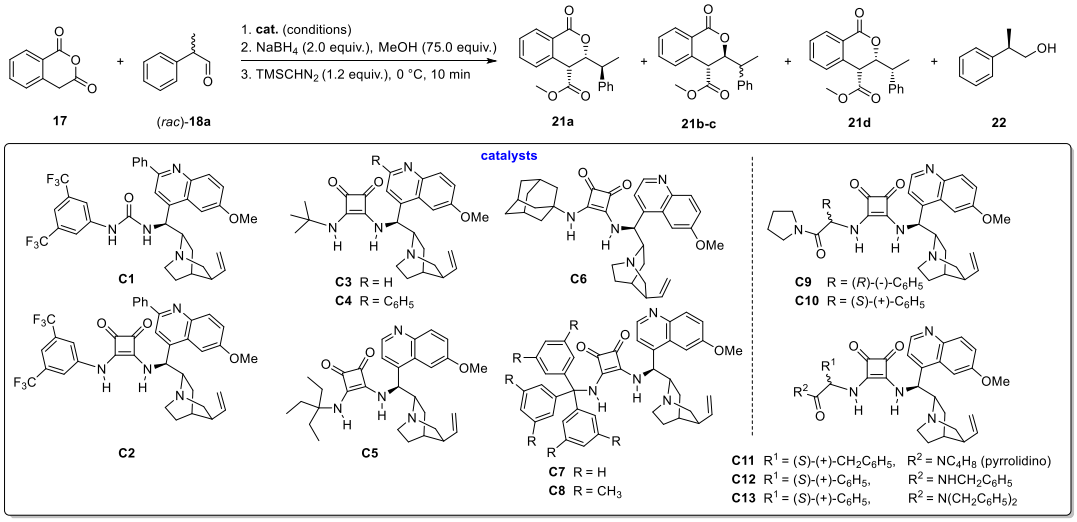
Figure 1. Literature processes involving the KR of aldehydes and relevant products of biological importance.

We (and others) have reported catalytic asymmetric cycloaddition reactions between homophthalic anhydrides **17**, behaving as nucleophiles, with different electrophiles *e.g*, aldehydes,[10] ketones,[11] alkylidene oxindoles,[12] imines[13] and nitrostyrenes.[14] The processes involving aldehydes provide one-pot access to dihydroisocoumarins such as **14** (Fig. 1D): core structural units in a range of natural products possessing a diverse array of medicinally relevant biological activities, for instance: cytotoxic/antiproliferative,[15,16,17] antimicrobial,[18,19] antifungal,[20] antiulcer,[21,22] antimalarial,[23] anti-inflammatory,[21,22] antioxidant[24] and antiallergic[25] properties. A weakness associated with these methodologies is that they provide no catalytic access to dihydroisocoumarins incorporating a stereocentre adjacent to the lactone core – a feature of a number of structurally important natural products, such as the potent respiratory chain inhibitor Ajudazol A (**15**)[26] and the recently discovered highly active herbicide Bacilosarcin (**16**, Fig 1D).[27] Herein we report the results of a study aimed at simultaneously addressing these twin synthetic challenges: a catalytic cycloaddition between anhydride **17** and racemic *α*-branched aldehydes **18** which allows the one-pot formation of stereochemically challenging *a*-branched 3,4-dihydroisocoumarins

19 with unprecedented levels of diastereo- and enantiocontrol, while bringing about the first efficient catalytic KR of simple aldehydes with good-outstanding levels of enantiodiscrimination (Fig. 1E).

Our study began with the reaction between **17** and racemic 2-phenylpropionaldehyde ((*rac*)-**18a**) in the presence of a range of *cinchona* alkaloid derived bifunctional catalysts (Table 1).

Table 1. Catalyst screening and optimization



entry	cat.	loading (mol %)	solvent (0.1 M)	temp (ºC)	t (d)	**17** (equiv.)	dr[a] **21 (a : b : c : d)**	*ee* (%)[b] **21 (a : b : c :d)**	conv.[c] **18** (%)	*ee* (%)[b] **22**	s*[d]
1	***i*-Pr$_2$NEt**	15	THF	RT	2	1.0	20 : 9 : 20 : 51	-	100 (47)[e]	-	-
2	**C1**	5	MTBE	RT	2	1.0	32 : 9 : 9 : 50	69 : - : - : 72	100 (78) [e]	-	-
3	**C2**	5	MTBE	RT	2	1.0	44 : 14 : tr[f] : 42	99 : 99 : - : 99	100 (74) [e]	-	-
4	**C3**	5	MTBE	RT	2	1.0	35 : 3 : 6 : 56	94 : 93 : - : 93	100	-	-
5	**C4**	5	MTBE	RT	2	1.0	39 : 6 : 6 : 49	94 : - : - : 93	100	-	-
6	**C2**	5	MTBE	-30	9	0.5	53 : 3 : tr : 44	99 : 99 : - : 99	50	0	-
7	**C3**	5	MTBE	-30	13	0.5	31 : tr : tr : 69	97 : - : - : 97	50	42	3.6
8	**C5**	5	MTBE	-30	9	0.5	21 : tr : 9 : 70	98 : - : - : 99	50	49	4.6
9	**C6**	10	MTBE	-30	9	0.5	24 : tr : tr : 76	98 : - : - : 99	50	51	5.0
10	**C7**	5	MTBE	-30	5	0.5	12 : tr : 15 : 73	97 : - : - : 97	50	50	4.8
11	**C7**	10	MTBE : THF[g]	-60	1	0.5	13 : tr : 10 : 77	98 : - : - : 99	50	53	5.4
12	**C8**	10	MTBE : THF	-60	4	0.5	12 : tr : 9 : 79	98 : - : - : 99	50	49	4.6
13	**C9**	5	MTBE	-30	19	0.5	39 : 4 : tr : 57	92 : 90 : - : 84	50	6	1.2
14	**C10**	5	MTBE	-30	19	0.5	18 : 2 : tr : 80	86 : - : - : 96	50	60	7.2
15	**C10**	5	MTBE	RT	1	0.5	22 : 6 : 5 : 67	n.d.[h]	50	40	3.4
16	**C11**	5	MTBE	RT	1	0.5	38 : 4 : tr : 58	n.d. [h]	50	20	1.8
17	**C12**	5	MTBE	RT	1	0.5	23 : 6 : 6 : 65	n.d. [h]	50	38	3.2
18	**C13**	5	MTBE	RT	1	0.5	33 : 11 : 5 : 51	n.d. [h]	50	24	2.0
19	**C10**	10	MTBE : THF	-60	5	1.0	4 : tr : tr : 96	90 : - : - : 99	54	80	12.6
20	**C10**	15	MTBE : THF	-78	8	1.0	3 : tr : tr : 97	- : - : - : 99	52	98	91.3

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by CSP-HPLC. [c]Conversion of **18** was determined by ^{1}H NMR spectroscopy using *p*-iodoanisole as an internal standard (note: conversion = 100 X $ee_{S.M.}$/($ee_{S.M.}$ + $ee_{Prod.}$) could not be used because of multiple chiral centres). [d]Selectivity (s*) = ln[(1-C)(1-$ee_{S.M.}$)]/ln[(1-C)(1+$ee_{S.M.}$)].[10e,28] [e]Isolated yield of product **21**. [f]Traces. [g]1:1 ratio. [h]not determined.

The use of Hünig's base (devoid of a hydrogen bond donating unit) as a catalyst in the reaction between anhydride **17** and 2-phenylpropionaldehyde (**18a**, 1:1 ratio), led to the formation of all possible dihydroisocoumarin diastereomers **21a-d** (isolated after esterification with trimethylsilyldiazomethane to facilitate CSP-HPLC analysis) in racemic fashion (entry 1). When bifunctional urea **C1** and squaramide-based catalysts (*i.e.* **C2**) were employed, the latter proved to be far superior: promoting the formation of **21** with improved (yet still impractical) diastereocontrol and outstanding enantioselectivity (entries 2-3). However, both the *t*-butyl-substituted squaramide C3 and its arylated-quinoline derivative (*i.e.* **C4** (highly efficacious in the previous studies[10]) promoted the catalysis with lower stereocontrol (entries 4-5). At this point it was clear that even without the KR element of the process, achieving the requisite control over the cycloaddition reaction is not trivial.

10.1002/chem.201902422

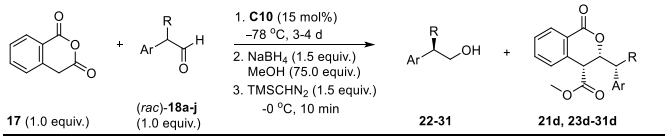
Initial results involving the KR of (*rac*)-**18a** (1.0 equiv.) with **17** (0.5 equiv.) with were far from encouraging: cycloaddition proceeded smoothly at -30 °C catalyzed by squaramide **C2** but resulted in racemic alcohol **22** (isolated after reduction of unreacted aldehyde with sodium borohydride to facilitate purification and CSP-HPLC analysis, entry 6). Employing **C3** led to improved performance and the first direct catalytic asymmetric KR of *α*-branched aldehyde, albeit with impractically low enantiodiscrimination (entry 7). Augmentation of the steric requirement of the squaramide-substituent *via* the design of triethyl- (*i.e.* **C5**, entry 8), adamantyl (*i.e.* **C6**, entry 9) and trityl (*i.e.* **C7**, entry 10) variants allowed selectivity to reach s* = 5. At -60 °C the reaction was no longer homogeneous and use of a mixture of methyl *tert*-butyl ether (MTBE) and tetrahydrofuran (THF) was required (entry 11). Evaluation of the even larger hexasubstituted trityl catalyst (*i.e.* **C8**, entry 12) did not lead to an appreciable improvement in terms of selectivity.

Faced with this 'diminishing returns' scenario stemming from simply increasing the bulk of the squaramide group, yet cognisant that this unit appears to be occupying space which influences the stereochemical outcome of the process, we sought to introduce a chiral *N*-substituent here seeking an advantageous (*i.e.* synergistic with the alkaloid-derived catalyst chiral substituents) diastereomeric interaction with the reacting partners in the transition state and bring about 'matched' and 'mismatched' catalyst diastereomers.

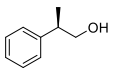
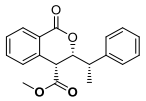
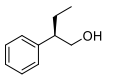
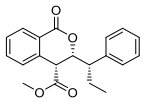
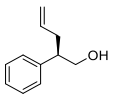
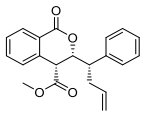
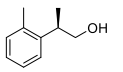
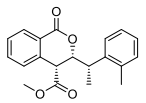
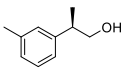
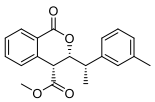
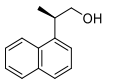
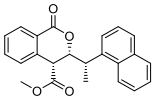
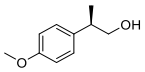
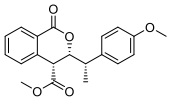
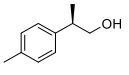
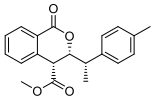
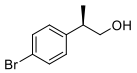
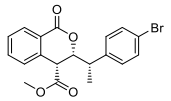
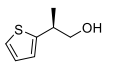
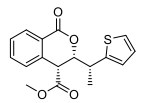
We synthesized both (*R*)- (*i.e.* **C9**) and (*S*)-phenylglycine-derived (*i.e.* **C10**) squaramide-substituted catalysts C-functionalized as pyrrolidine amides. While **C9** proved a particularly poor 'mismatched' catalyst, its epimer **C10** delivered a reasonable (and highest hitherto obtained) selectivity of 7.2, even at the higher temperature of -30 °C (entries 13-14). Use of a (*S*)-phenylalanine-derived catalyst containing either secondary- or bulky tertiary amides did not improve catalyst performance relative to **C10** (*i.e.* **C11-13** respectively, entries 15-18). Further optimization of the conditions using **C10** led to outstanding selectivity; allowing the formation of the cycloadduct **21d** (97:3 dr) in 99% *ee* and the reduced alcohol **22** in 98% *ee* at close to 50% conv. at -78 °C (s* = 91.3, entries 19-20). It is interesting to note that no post-reaction racemization was observed under these conditions even when the reaction was left for more than 10 days.

Attention now turned to the question of substrate scope (Table 2). Diverse *α*-substituted aldehydes were well tolerated by the catalyst: for instance, *α*-methyl, -ethyl and -allyl derivatives (entries 1-3) could be resolved with excellent selectivity (s* = 20-91); allowing the isolation of reduced aldehydes **22-24** with 90-98% *ee* along with novel cycloaddition products with outstanding diastereo- and enantiocontrol (up to 32:1 dr and >99% *ee*). It was found that the installation of methyl groups on the aldehyde's aromatic substituent resulted in excellent selectivity in the case of -*ortho* and -*meta* substituents (s* = 50-51, entries 4-5) but it proved to be a greater challenge when the phenyl unit was exchanged for a 1-naphthyl moiety. However, synthetically useful selectivity was still possible (s* = 12, entry 6). Variation at the *para*-position of the aldehydes produced interesting results. Aldehydes with electron-donating substituents reacted at slower rates and could be resolved with s* = 13 (entries 7 and 8). The *p*-bromo analogue reacted more rapidly, with excellent selectivity (s* = 27) and outstanding stereocontrol over the product (up to 99:1 dr and >99% *ee*, entry 9). A heteroaromatic substrate also could be resolved with good selectivity (entry 10).

Table 2. Substrate scope: aldehyde component.



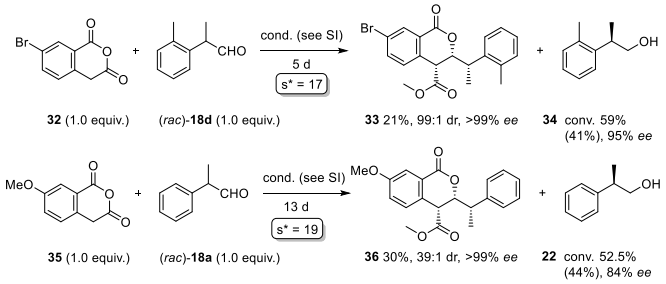
17 (1.0 equiv.) + (*rac*)-**18a-j** (1.0 equiv.) → **22-31** + **21d, 23d-31d**

entry	alcohol	lactone	t (d)	conv (%)[a]	s*[b]
1	 **22** 98% *ee*	 **21d** 35%, 24:1 dr, >99% *ee*	8	52 (45)[c]	91
2	 **23** 94% *ee*	 **23d** 39%, 32:1 dr, >99% *ee*	5	56 (31)[c]	23
3	 **24** 90% *ee*	 **24d** 38%, 10.5:1 dr, >99% *ee*	5	54.8 (45)[c]	20
4	 **25** 98% *ee*	 **25d** 27%, 9:1 dr, >99% *ee*	9	54 (43)[c]	50
5	 **26** >99.9% *ee*	 **26d** 29%, 24:1 dr, >99% *ee*	4.5	57 (43)[c]	51
6	 **27** 77% *ee*	 **27d** 24%, 10:1 dr, >99% *ee*	9	53 (47)[c]	12
7	 **28** 88% *ee*	 **28d** 39%, 48:1 dr, >99% *ee*	5	58 (42)[c]	13
8	 **29** 91% *ee*	 **29d** 26%, 49:1 dr, >99% *ee*	10	59 (27)[c]	13
9	 **30** 92% *ee*	 **30d** 27%, 99:1 dr, >99% *ee*	2	54 (46)[c]	27
10	 **31** 82% *ee*	 **31d** 24%, 32:1 dr, 96% *ee*	4	52 (48)[c]	18

[a]Determined by ^{1}H NMR spectroscopy using *p*-iodoanisole as an internal standard. [b]s* = ln[(1-C)(1-ee$_{S.M.}$)]/ln[(1-C)(1+ee$_{S.M}$)],[10e] ee determined by CSP-HPLC, dr by ^{1}H NMR spectroscopy. [c]Isolated yield of the alcohol in parenthesis.

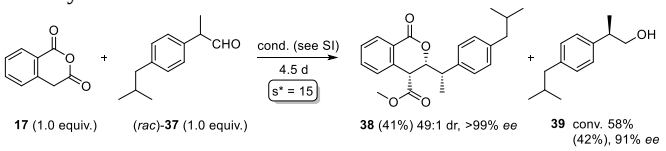
It is particularly noteworthy that in all but the latter case, the dihydroisocoumarin products – the generation of which involves the formation of two contiguous stereocentres inside the heterocycle and one (for the first time) being resolved outside it – were formed with >99% *ee* and between 9:1 and 99:1 dr. It seems clear therefore that the resolution and cycloaddition are synergistic; leading to unparalleled stereocontrol over the lactone. Even in the case of the thiophene-substituted aldehyde; the lactone *ee* is 96%.

Several medicinally relevant bicyclic dihydroisocoumarin compounds are substituted at the aromatic ring.[29] Therefore we installed electron-withdrawing and electron-donating functionality on the homophthalic anhydride (Scheme 1). The bromo-derivative **32** was reacted with aldehyde **18d** to generate lactone **33** with near perfect enantio- and diastereocontrol, with concurrent resolution characterised by good enantiodiscrimination. The enolate-destabilizing methoxy-substituted anhydride **35** underwent cycloaddition with **18a** with similar levels of stereocontrol.



Scheme 1. Resolution involving substituted homophthalic anhydrides

To demonstrate the potential utility of this methodology, we carried out the KR of the aldehyde (*rac*)-**37** with **17** to furnish the alcohol **39** with 91% *ee*; with the corresponding lactone **38** formed with excellent dr and *ee*. The reduced aldehyde can be oxidised to obtain (*R*)-Ibuprofen.[30] It is thus conceivable that this process could serve as a method for the synthesis of other *α*-2-arylpropionic acids leading to chiral pharmaceuticals. The development of new routes leading to these drugs have received considerable attention recently.[31]



Scheme 2. Ibuprofen precursor synthesis

In summary, it has been demonstrated that in the presence of a novel amino acid-derived squaramide-based bifunctional catalyst, simple *α*-aryl-substituted branched aldehydes can be kinetically resolved with excellent efficiency (s* up to 91) for the first time; with a concomitant (and synergistic from a stereocontrol standpoint) cycloaddition reaction with enolizable anhydrides occurring with unprecedented diastereo- and enantiocontrol. In addition to the resolved aldehydes being potentially serviceable as precursors to chiral pharmaceuticals, the lactone products represent a previously not directly catalytically accessible class of dihydrocoumarins with a stereocenter outside the ring system similar to the cores of several important natural products. Studies to further explore this phenomenon from are underway.

Keywords: Dynamic Kinetic resolution, cycloaddition reaction, enolizable anhydrides, lactones.

[1] For selected articles and reviews concerning kinetic resolution see: a) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974; b) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 1613.

[2] F R. W. Hoffmann, M. Julius, F. Chemla, T. Ruhland, G. Frenzen, *Tetrahedron* **1994**, *50*, 6049; b) C. Agami, N. Platzer, C. Puchot, H. Sevestre, *Tetrahedron* **1987**, *43*, 1091; c) F. B. Jimènez,. D. E. Ward, *Org. Lett.* **2012**, *14*, 1648; d) D. E. Ward, A. Kazemeini, *J. Org. Chem.* **2012**, *77*, 10789; e) D. Strand, P. -O. Norrby, T. Rein, *J. Org. Chem.* **2006**, *71*, 1879.

[3] a) T. M. Pedersen, J. F. Jensen, R. E. Humble, T. Rein, D. Tanner, K. Bodmann, O. Reiser, *Org. Lett.* **2000**, *2*, 535; b) T. Furuta, M. Iwamura, *J. Chem. Soc. Chem. Commun.* **1994**, *18*, 2167; c) T. H. Pedersen, E. L. Hansen, J. Kane, T. Rein, P. Helquist, P. -O. Norrby, D. Tanner, *J. Am. Chem. Soc.* **2001**, *123*, 9738; d) T. Rein, J. Anvelt, A. Soone, R. Kreuder, C. Wulff, O. Reiser, *Tetrahedron Lett.* **1995**, *36*, 2303; e) R. Kreuder, T. Rein, O. Reiser, *Tetrahedron Lett.* **1997**, *38*, 9035.

[4] a) B. R. James, C. G. Young, *J. Organometallic Chem.* **1985**, *285,* 321; b) M. Imai, M. Tanaka, H. Suemune, *Tetrahedron* **2001**, *57*, 1205; c) K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10296; d) K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 8078; e) K. Tanaka, Y. Hagiwara, M. Hirano, *Angew. Chem. Int. Ed.* **2006**, *45*, 2734; f) C. G. Rodríguez, S. R. Parsons, A. L. Thompson, M. C. Willis, *Chem. Eur. J.* **2010**, *16*, 10950; g) S. Y. Kang, J. Baek, Y. K. Ko, C. Im, Y. S. Park, *Synlett* **2013**, *24*, 630.

[5] T. Ooi, K. Ohmatsu, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 2410.

[6] M. Hayashi, H. Miwata, N. Oguni, *J. Chem. Soc. Perkin Trans. I* **1991**, *5*, 1167.

[7] K. Shibatomi, T. Okimi, Y. Abe, A. Narayama, N. Nakamura, S. Iwasa, *Beilstein. J. Org. Chem*. **2014**, *10*, 323.

[8] D. Minato, Y. Nagasue, Y. Demizu and O. Onomura, *Angew. Chem. Int. Ed.* **2008**, *47*, 9458.

[9] a) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074; b) J. H. Xie, Z. T. Zhou, W. L. Kong, Q. L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 1868; c) D. Giacomini, P. Galletti, A. Quintavalla, G. Gucciardo, F. Paradisi, *Chem. Commun.* **2007**, *39*, 4038.

[10] a) C. Cornaggia, F. Manoni, E. Torrente, S. Tallon, S. J. Connon, *Org. Lett*. **2012**, *14*, 1850; b) F. Manoni, C. Cornaggia, J. Murray, S. Tallon, S. J. Connon, *Chem. Commun*. **2012**, *48*, 6502; c) C. Trujillo, I. Rozas, A. Botte, S. J. Connon, *Chem. Commun*. **2017**, *53*, 8874; d) R. Claveau, B. Twamley, S. J. Connon, *Chem. Commun*. **2018**, *54*, 3231; e) R. Claveau, B. Twamley, S. J. Connon, *Org. Biomol. Chem*. **2018**, *16*, 7574; f) M. L. Aiello, U. Farid, C. Trujillo, B. Twamley, S. J. Connon, *J. Org*. Chem, DOI 10.1021/acs.joc.8b02332.

[11] a) C. Cornaggia, S. Gundala, F. Manoni, N. Gopalasetty, S. J. Connon, *Org. Biomol. Chem*. **2016**, *14*, 3040; b) J.-L. Wu, B.-X. Du, Y.-C. Zhang, Y.-Y. He, J.-Y. Wang, P. Wu, F. Shi, *Adv. Synth. Catal*. **2016**, 358, 2777.

[12] F. Manoni and S. J. Connon, *Angew. Chem. Int. Ed*. **2014**, *53*, 2628.

[13] a) S. A. Cronin, A. Gutiérrez Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley and S. J. Connon, *Org. Biomol. Chem*. **2016**, *14*, 6955; b) C. L. Jarvis, J. S. Hirschi, M. J. Vetticatt, D. Seidel, *Angew. Chem. Int. Ed*. **2017**, *56*, 2670.

[14] a) F. Manoni, U. Farid, C. Trujillo, and S. J. Connon, *Org. Biomol. Chem*. **2017**, *15*, 1463; b) U. Nath, C. Pan, *J. Org. Chem.* **2017**, *82*, 3262.

[15] S. Wan, F. Wu, J. C. Rech, M. E. Green, R. Balachandran, W. S. Horne, B. W. Day, P. E. Floreancig, *J. Am. Chem. Soc.* **2011**, *133*, 16668.

[16] R. H. Cichewicz, F. A. Valeriote, P. Crews, *Org. Lett*. **2004**, *6*, 1951.

[17] Y. F. Huang, L. –H. Li, L. Tian, L. Qiao, H. -M. Hua, Y. -H Pei, *J. Antibiot*. **2006**, *59*, 355.

[18] T. K. Tabopda, G. W. Fotso, J. Ngoupayo, A. –C. Mitaine-Offer, B. T. Ngadjui, M. –A. Lacaille-Dubois, *Planta Med*. **2009**, *75*, 1228.

[19] M. G. Bogdanov, M. I. Kandinska, D. B. Dimitrova, B. T. Gocheva, M. D. Palamareva, *Naturforsch*. **2007**, *62*, 477.

[20] H. Hussain, N. Akhtar, S. Draeger, B. Schulz, G. Pescitelli, P. Salvadori, S. Antus, T. Kurtán, K. Krohn, *Eur. J. Org. Chem*. **2009**, 749.

[21] B. V. McInerney, W. C. Taylor, M. J. Lacey, R. J Akhurst, R. P. Gregson, *J. Nat. Prod*. **1991**, *54*, 785.

[22] Y. Shimojima, T. Shirai, T. Baba, H. Hayashi, *J. Med. Chem*. **1985**, *28*, 3.

[23] P. Kongsaeree, S. Prabpai, N. Sriubolmas, C. Vongvein, S. Wiyakrutta, *J. Nat. Prod*. **2003**, *66*, 709.

[24] N. Nazir, S. Koul, M. A. Quirishi, M. A. Najar, M. I. Zargar, *Eur. J. Med. Chem*. **2011**, *46*, 2415.

[25] M. Yoshikawa, E. Uchida, i N. Chatan, H. Kobayashi, Y. Naitoh, Y. Okuno, H. Matsuda, J. Yamahara, N. Murakami, *Chem. Pharm Bull*. **1992**, *40*, 3352

[26] S. Essig, S. Bretzke, R. Müller, D. Menche, *J. Am. Chem. Soc*. **2012**, *134*, 19362.

[27] M. Enomoto, S. Kuwahara, *Angew. Chem. Int. Ed*. **2009**, *121*, 1144.

[28] H. B. Kagan, J. C. Fiaud, *Top. Stereochem*. **1988**, *18*, 249.

[29] a) R. H. Cichewicz, F. A. Valeriote, P. Crews, *Org. Lett.* **2004**, *6*, 1951; b) Y. F. Huang, L. H. Li, L. Tian, L. Qiao, H. M. Hua, Y. H. Pei, *J. Antibiot.* **2006**, *59*, 355; c) M. Enomoto, S. Kuwahara, *Angew. Chem., Int. Ed.* **2009**, *121*, 1144; d) P. Kongsaeree, S. Prabpai, N. Sriubolmas, C. Vongvein, S. Wiyakrutta, *J. Nat. Prod.* **2003**, *66*, 709; N. Nazir, S. Koul, M. A. Quirishi, M. A. Najar, M. I. Zargar, *Eur. J. Med. Chem.* **2011**, *46*, 2415.

[30] P. Galletti, M. Pori, D. Giacomini, *Synlett* **2010**, *17*, 2644.

[31] a) Y. Shimoda, H. Yamamoto, *J. Am. Chem. Soc.* **2017**, *139*, 6855; b) X. Chen, J. Z. M. Fong, J. Xu, C. Mou, Y. Lu, S. Yang, B. A. Song, Y. R. Chi, *J. Am. Chem. Soc.* **2016**, *138*, 7212.

10.1002/chem.201902422

10.1002/chem.201902422

Entry for the Table of Contents
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Organocatalysis

U. Farid, M. L. Aiello and S. J. Connon*
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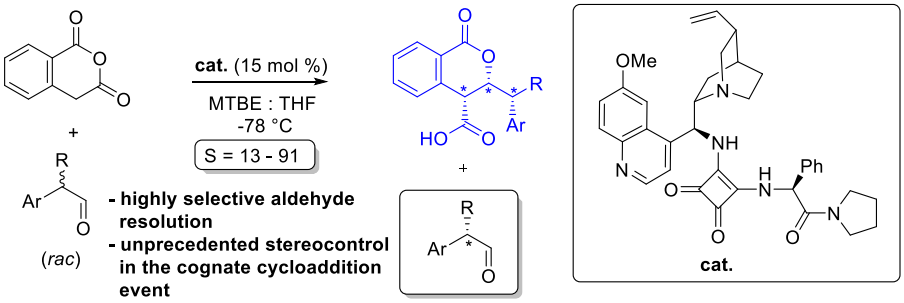
Highly Enantioselective Catalytic Kinetic Resolution of α-Branched Aldehydes via Formal Cycloaddition with Homophthalic Anhydrides **



A new bifunctional organocatalyst was developed to promote an efficient kinetic resolution of α-branched aldehydes with a selectivity (s) of up to 91 in a cycloaddition reaction with enolizable anhydrides to afford highly functionalized six-membered lactones containing three contiguous stereocenters in a one pot reaction with excellent stereocontrol (up to 99:1* dr, *>99% ee).*

10.1002/chem.201902422