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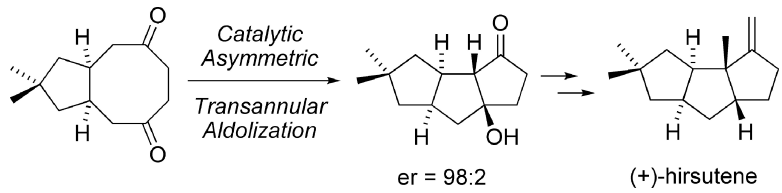

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Catalytic, Asymmetric Transannular Aldolizations: Total Synthesis of (+)-Hirsutene

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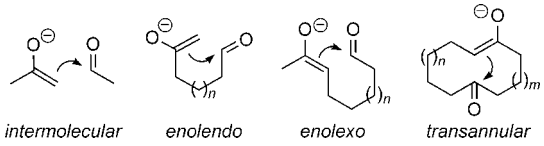
Few transformations have stimulated more research on the development of asymmetric processes than the aldol reaction. Indeed, a great variety of effective chiral auxiliaries, reagents, and catalysts have been introduced that efficiently control its relative and absolute stereochemistry.[1] Interestingly, although enzymes,[2] transition metal complexes,[3] and organocatalysts have all been used to catalyze direct asymmetric intermolecular aldol reactions, only proline and its derivatives have found general utility in intramolecular variants.[4] Of these, there are three types: (a) enolendo aldolizations,[5] in which the nucleophilic double bond is part of the ring that is being formed; (b) enolexo aldolizations,[6] in which this double bond is exocyclic; and (c) transannular aldolizations, which may be considered enolendo and enolexo simultaneously.

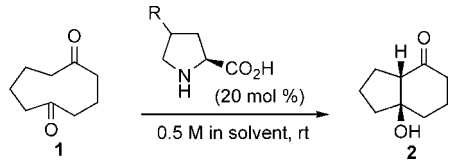


While proline-catalyzed enolendo and enolexo aldolizations have been developed with high enantioselectivities,[1] catalytic, asymmetric transannular aldolizations, which create two new rings and at least two new stereogenic centers, have previously been unknown with any type of catalysis.[7] Here we describe highly enantioselective transannular aldolizations of cyclic diketones that are catalyzed by *trans*-4-fluoro proline and provide polycyclic products of utility for natural product synthesis as illustrated in a short synthesis of (+)-hirsutene.

At the outset of the investigation, we focused our attention on proline derivatives to catalyze the transannular aldol reaction of 1,5-cyclononanedione (**1**, Table 1). (*S*)-proline itself catalyzed the reaction with promising enantioselectivity (77:23 er) and conversion in DMF at room temperature to give β-hydroxy ketone **2** as a single diastereomer (entry 1). During initial catalyst screenings we noticed a pronounced effect on the reaction outcome for proline catalysts bearing a substituent at the 4-position. For example, *trans*-4-hydroxy proline gave slightly elevated levels of enantiocontrol (82:18 er), whereas the corresponding *tert*-butyldimethyl silyl ether produced an adverse effect on the enantioselectivity (entries 2 and 3). Substitution with a *tert*-butyl ether linkage at this position dramatically enhanced the reaction rate giving high conversion but modest selectivity (entry 4). The *trans*-4-fluoro derivative was identified as the most promising catalyst, providing the highest levels of enantioselectivity with good conversion (entry 5). Changing the solvent to DMSO in combination with *trans*-4-fluoro proline (entry 8) produced the highest enantioselectivity (91:9 er) for aldol adduct **2** and good conversion from **1**.

Using *trans*-4-fluoro proline, we set out to investigate the effect of ring-size on the outcome of the reaction (Table 2). A variety of 8- to 10-membered ring diones were prepared following known literature methods[8] and subjected to the newly identified aldolization conditions. Dodecanediones **3** and **5** proved to be much less reactive than substrate **1**, and conversions were low (Table 2, entries 2 and 3). Notably, aldol **4**, the major diastereomer observed for the reaction of 1,6-cyclodecanedione (**3**), was obtained with reasonable enantioselectivity (82:18 er, entry 2). Diketone **5** did not provide the aldol addition product but upon heating furnished only the corresponding condensation adduct **6** (entry 3). Similarly, 1,4-cyclononanedione **7** failed to deliver the desired β-hydroxy ketone when subjected to the reaction conditions, but only gave condensation product **8** (entry 4). Remarkably, ene-diones **9** and **11**, the unsaturated analogues of diketones **5** and **7**, gave high yields of aldol adducts **10** and **12**, respectively, albeit with low enantioselectivities (entries 5 and 6). Finally, commercially available 1,4-cyclooctanedione (**13**) provided the desired bicyclo[3.3.0]octane derivative **14** with excellent enantioselectivity (97:3 er, entry 6). Encouraged by these studies, we prepared several 1,4-cyclooctanedione derivatives[8] and investigated their catalytic, asymmetric transannular aldol reactions (Table 3).

Table 1. Catalyst Identification for the Aldolization of Dione **1**



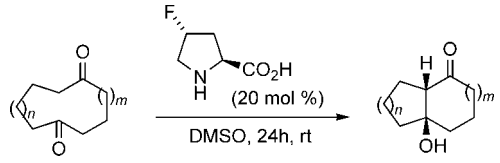
1 **2**

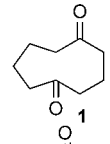
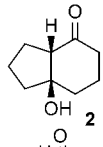
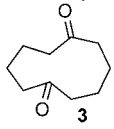
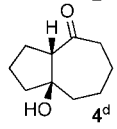
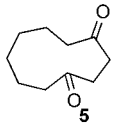
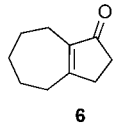
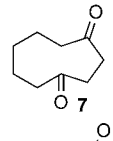
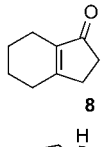
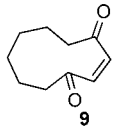
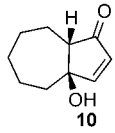
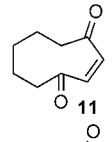
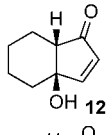
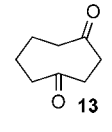
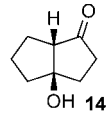
entry	R	solvent	time [h]	conversion [%][a]	er[b]
1	H	DMF	16	60	77:23
2	*trans*-OH	DMF	24	50	82:18
3	*trans*-OTBS	DMF	15	60	39:61
4	*trans*-O*t*-Bu	DMF	2	95	80:20
5	*trans*-F	DMF	24	75	90:10
6	*cis*-F	DMF	24	50	79:21
7	*trans*-F	CH_3CN	24	50	56:44
8	*trans*-F	DMSO	24	75	91:9

[a] Determined by GC. [b] Determined by chiral-phase GC.

In addition to diketone **13**, benzocyclooctanediones **15** and **17** gave the corresponding aldols **16** and **18** with excellent enantioselectivites and in good yields (entries 2 and 3). Cis-fused cyclohexyl 3,6-cyclooctanedione (**19**) underwent reaction to give cis/anti/cis[9] tricyclic compound **20** as a single diastereomer, in good yield and with high enantioselectivity (97:3 er, entry 4). Interestingly, racemic cis-fused cyclohexyl 2,5-cyclooctanedione (*rac*-**21**) underwent a kinetic resolution to provide tricyclic β-hydroxy ketone **22** in 42% yield and with 95:5 er (entry 5).[10] Finally, cyclopentane annulated diketone **23** furnished the desired hydroxyl triquinane **24** in high yield and with excellent diastero- and enantioselectivity (entry 6). The aldolization of diketone **23** has been implemented as the key step in a synthesis of the natural product (+)-hirustene (**34**) (Scheme 1). Hirsutene is a fungal metabolite isolated from Basidomycete *Coriolus consors*[11] which, with its cis:anti:cis tricyclo [6.3.0.0^{2,6}]-undecane core, is a logical target for the application of our transannular aldolization. As a biogenetic precursor to several antibiotic and/or antitumor compounds, including hirsutic acid C and coriolin,[12,13] hirsutene has drawn considerable interest from the synthetic community including several reports of enantioselective total and formal syntheses.[14–16]

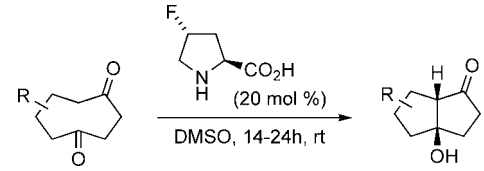
Table 2. Substrates Studied in Transannular Aldolizations[a]

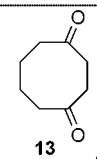
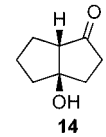
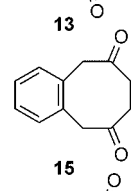
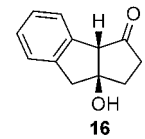
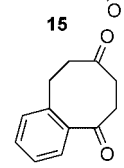
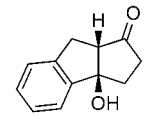
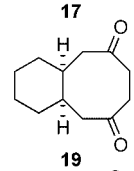
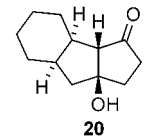
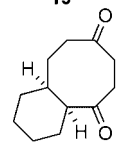
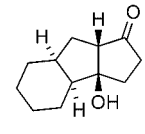
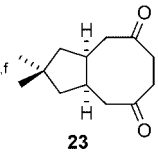
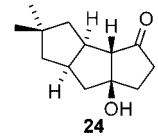


entry	substrate	product	yield [%][b]	er[c]
(1)	 **1**	 **2**	57(84)	91:9
(2)	 **3**	 **4**[d]	22(91)	82:18
(3)[e]	 **5**	 **6**	32(93)	-
(4)	 **7**	 **8**	97	-
(5)	 **9**	 **10**	67(92)	50:50
(6)	 **11**	 **12**	82	71:39
(7)	 **13**	 **14**	53(95)	97:3

[a] Reactions were run with 20 mol% of catalyst at a substrate concentration of 0.5 M in DMSO at room temp for 24 h. [b] Isolated yield. Yields in parentheses are based on recovered starting material. [c] Determined by chiral-phase GC. [d] dr = 7:1. [e] Reaction run at 50 °C.

Table 3. 1,4-Cyclooctanediones in Transannular Aldolizations[a]



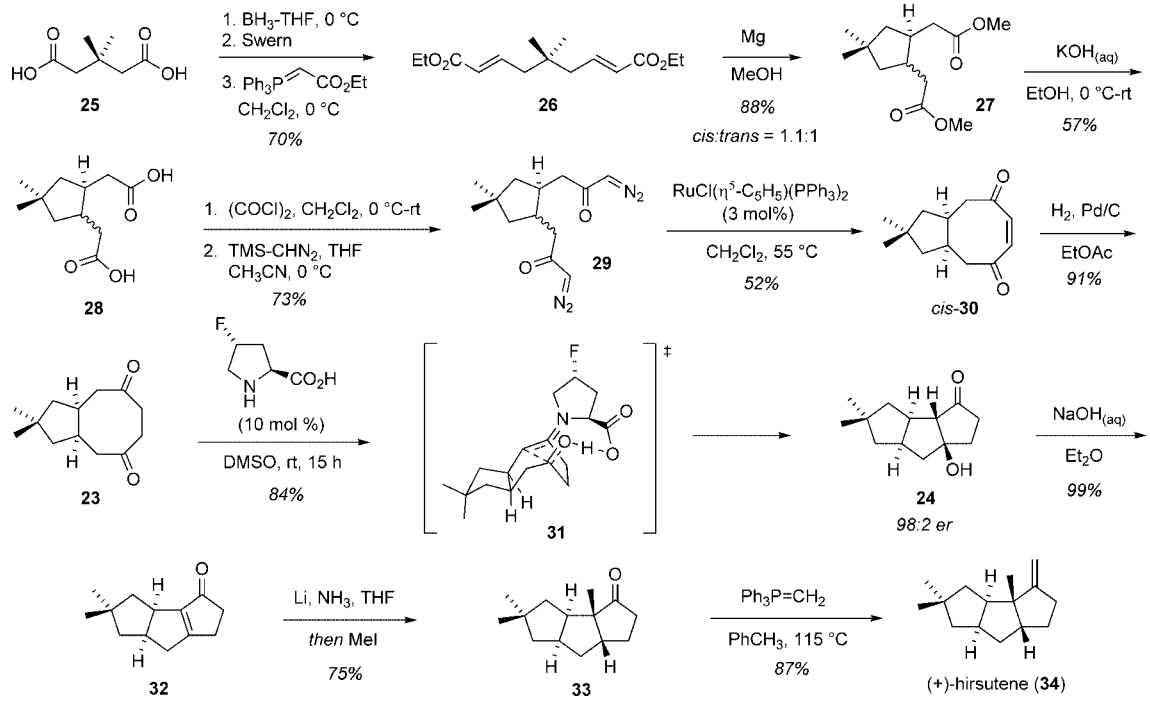
entry	substrate	product	yield [%][b]	er[c]	dr[c]
(1)	 **13**	 **14**	53(95)	97:3	-
(2)[d]	 **15**	 **16**	67(93)	97:3	-
(3)[e]	 **17**	 **18**	80	97:3	-
(4)	 **19**	 **20**	68(95)	97:3	>20:1
(5)[f]	 *rac*-**21**	 **22**	42(98)	95:5	>20:1
(6)[e,f]	 **23**	 **24**	84	98:2	>20:1

[a] Reactions were run with 20 mol% of catalyst at a substrate concentration of 0.5 M in DMSO at room temperature for 24 h. [b] Isolated yield. Yields in parentheses are based on recovered starting material. [c] Determined by chiral-phase GC. [d] One equivalent of water was added to the reaction. [e] Reaction run for 15 h. [f] Only 10 mol % of catalyst was used.

Our synthesis commences with a straightforward chain-elongation of commercially available 3,3-dimethylpentane-1,5-diacid (**25**)[17] to α,β-unsaturated diester **26**. Bis-enoate **26** was identified as a viable substrate for a reductive cyclization via intramolecular trapping of the intermediate radical anion. Indeed, desired cyclopentane **27** was formed in 88% yield as a 1.1:1 mixture of cis:trans isomers upon treating **26** with magnesium metal in methanol.[18] Cyclic diester **27** was converted to corresponding α-diazo ketone **29** via hydrolysis to diacid **28** followed by acid chloride formation and in situ reaction with trimethylsilyl diazomethane.[19]

The strategy for the preparation of requisite cyclooctanedione **23** is based on a powerful and yet relatively undeveloped method reported by Del Zotto et al.[20] for the intramolecular coupling of diazo compounds exploiting a commercially available ruthenium(II) catalyst. Gratifyingly, when **29** was subjected to $CpRuCl(PPh_3)_2$ in refluxing CH_2Cl_2, a 52% yield of cis-fused ene-dione **30** was obtained after separation from the corresponding trans-isomer. Following hydrogenation, 1,4-cyclooctanedione **23** was obtained in 91% yield. Upon treating diketone **23** with *trans*-4-fluoro proline (10 mol %) in DMSO at room temperature, the aldol reaction was complete in 15 h and furnished cis/anti/cis[21] β-hydroxy ketone **24** in 84% yield and with 98:2 er. The absolute and relative stereochemical outcome of the reaction was rationalized by transition state **31** on the basis of our transition state model.[22] After stirring **24** overnight in the presence of aqueous 2 N sodium hydroxide, elimination occurred to give enone **32** in near quantitative yield without a decrease in the enantiomeric ratio (i.e., retro-aldol/aldol pathway is not occurring). We then completed the total synthesis of hirsutene based on the protocol Iyoda and co-workers implemented in their synthesis of *rac*-**34**.[23] Treatment of enone **32** with lithium in ammonia followed by methylation of the intermediate enolate gave ketone **33** with $\alpha^{20}_D = +41.0$ (*c* 0.1 M, hexane), confirming the predicted absolute configuration of the transannular aldol products. Finally, olefination of ketone **33** with methylene triphenylphosphorane gave (+)-hirsutene (**34**) with $\alpha^{20}_D = +13.0$

Scheme 1. Application of an Organocatalytic, Asymmetric Transannular Aldol Reaction in the Total Synthesis of (+)-Hirsutene



(*c* 0.1 M, hexane) in 87% yield.[24] The synthetic material had spectral properties fully consistent with those reported in the literature.[15,21]

In conclusion, we have described an asymmetric, catalytic transannular aldol reaction that provides polycyclic products in good yields (53−84%) and high enantioselectivities (er = 95:5−98:2) for 1,4-cyclooctanediones. Further work to elucidate the observed fluorine effect is underway. The enantioselectivities for larger macrocyclic diones currently participating in this proline-derived-catalyzed reaction are, at the moment, only moderate (41−82% ee) offering the prospect for further improvement. The potential of our methodology for natural product synthesis was illustrated with the shortest asymmetric total synthesis of (+)-hirsutene reported to date. Our observations contribute to a further advancement of catalytic, asymmetric transannular transformations and complement a recently discovered transannular Diels−Alder reaction by Jacobsen et al.[25]

Acknowledgment. We thank Linh Hoang for her contributions at the early stage of this project (2001). Generous support by the Max-Planck-Society, the DFG (SPP1179, *Organocatalysis*), Novartis (Young Investigator Award to B.L.), AstraZeneca (Award in Organic Chemistry to B.L.), and the Fond der Chemischen Industrie is gratefully acknowledged. We also thank our GC and NMR departments for their support.

Supporting Information Available: Experimental procedures, compound characterization, NMR-spectra, and GC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.
(2) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.
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(5) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
(6) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem.* **2003**, *115*, 2891.
(7) For examples of nonasymmetric catalysis and reagent-based asymmetric transannular aldolizations see: (a) Knopff, O.; Kuhne, J.; Fehr, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1307. (b) Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y. *J. Org. Chem.* **2007**, *72*, 3065.
(8) See Supporting Information.
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(10) The S value was calculated to be 11.7 using the KinRes program, see : Goodman, J. M.; Köhler, A.-K.; Alderton, S. C. M. *Tetrahedron Lett.* **1999**, *40*, 8715.
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