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

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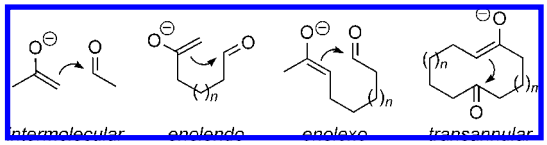
Few transformations have stimulated more research on the development of asymmetric processes than the aldol reaction. Indeed, a great variety of effective chiral auxiliaries, reagents, and catalysts have been introduced that efficiently control its relative and absolute stereochemistry.[1] Interestingly, 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.

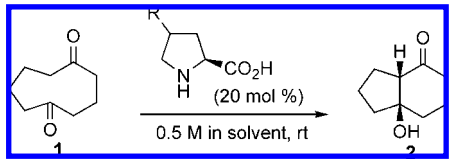


While proline-catalyzed enolendo and enolexo aldolizations have been developed with high enantioselectivities,[1] catalytic, asymmetric transannular aldolizations, which create two new rings and at least two new stereogenic centers, have previously been unknown with any type of catalysis.[7] Here we 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**

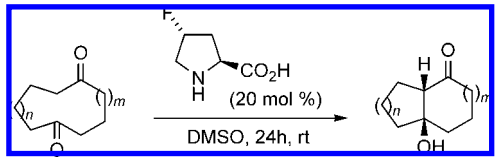


entry	R	solvent	time [h]	conversion [%][a]	er[b]
1	H	DMF	16	60	77:23
2	*trans*-OH	DMF	24	50	82:18
3	*trans*-OTBS	DMF	15	60	39:61
4	*trans*-O*t*-Bu	DMF	2	95	80:20
5	*trans*-F	DMF	24	75	90:10
6	*cis*-F	DMF	24	50	79:21
7	*trans*-F	CH_3CN	24	50	56:44
8	*trans*-F	DMSO	24	75	91:9

[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]

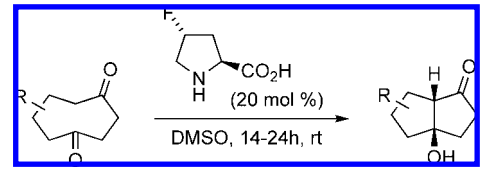
Table 2. Substrates Studied in Transannular Aldolizations[a]



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]



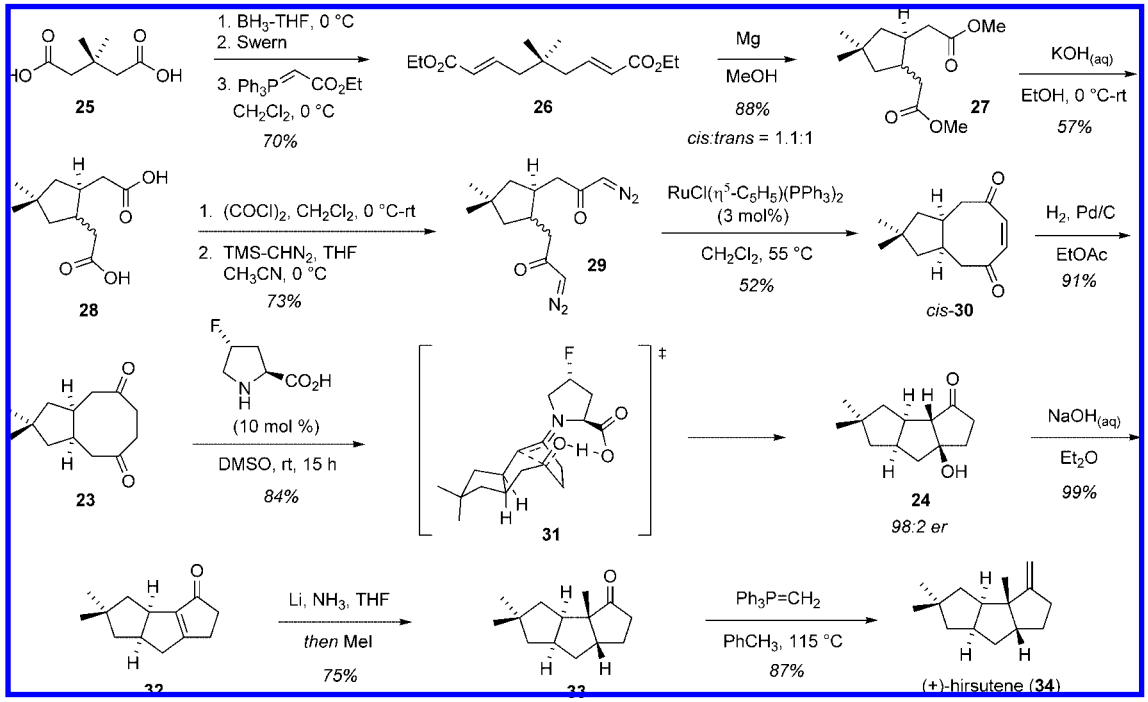
entry	substrate	product	yield [%][b]	er[c]	dr[c]
(1)	13	14	53(95)	97:3	-
(2)[d]	15	16	67(93)	97:3	-
(3)[e]	17	18	80	97:3	-
(4)	19	20	68(95)	97:3	>20:1
(5)[f]	*rac*-21	22	42(98)	95:5	>20:1
(6)[e,f]	23	24	84	98:2	>20:1

[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]

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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.

References

(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.
(3) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.
(4) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
(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.
(9) Determined on the basis of comparison with **24**.
(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.
(11) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, *17*, 195.
(12) Mehta, G.; Reddy, D. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 1153. and references cited therein.
(13) Schuda, P. F.; Phillips, J. L.; Morgan, T. M. *J. Org. Chem.* **1986**, *51*, 2742. and references cited therein.
(14) For reviews on syntheses of triquinane natural products see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647.
(15) For reports of asymmetric total syntheses of hirsutene see: (a) Hua, D. H.; Venkataraman, S.; Sinai-Zingde, G. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (b) Weinges, K.; Reichert, H.; Huber-Patz, U.; Irngartinger, H. *Liebegs Ann. Chem.* **1993**, 403. (c) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A. *Tetrahedron* **2004**, *60*, 535.
(16) For reports of asymmetric formal syntheses of hirsutene see: (a) Castro, J.; Sorensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericas, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388. (b) Inoue, T.; Hosomi, K.; Araki, M.; Nishide, K.; Node, M. *Tetrahedron: Asymmetry* **1995**, *6*, 31. (c) Anger, T.; Graalmann, O.; Schröder, H.; Gerke, R.; Kaiser, U.; Fitjer, L.; Noltemeyer, M. *Tetrahedron* **1998**, *54*, 10713. (d) Leonard, J.; Bennett, L.; Mahmood, A. *Tetrahedron Lett.* **1999**, *40*, 3965. (e) Singh, V.; Vedantham, P.; Sahu, P. K. *Tetrahedron Lett.* **2002**, *43*, 519. (f) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708.
(17) Berglund, R. A.; Braish, T. F.; Jakubowski, J. A.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 649.
(18) Chavan, S. P.; Ethiraj, K. S. *Tetrahedron Lett.* **1995**, *36*, 2281.
(19) Makhey, D.; Li, D.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L. F.; La Voie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 1809.
(20) Del Zotto, A.; Baratta, W.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* **2000**, 2795.
(21) Confirmed by ^{1}H and ^{13}C NMR comparison with the known compound, see : Jiao, L.; Yuan, C.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 4421.
(22) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.
(23) Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1049.
(24) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.
(25) Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736.

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