Diastereoselective Intermolecular [4 + 3] Cycloadditions via an Extended Transition State: A Route to Enantiomerically Enriched Cycloadducts

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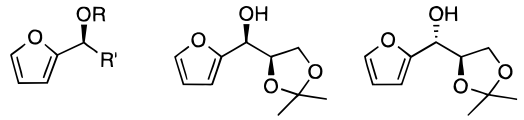
The synthesis of oxabicyclo[3.2.1]octenes via the [4 + 3] cycloaddition reaction between oxyallyl cations and furans has attracted considerable interest since its discovery more than 20 years ago.[1] Stereo- and regioselective cleavage of the C−O bond in symmetrical and unsymmetrical oxabicyclic compounds has also been reported.[2−4]

In order to expand the scope and utility of oxabicyclic compounds in organic synthesis, two limitations of the existing methods for the preparation of the starting materials must be overcome. The most pressing requirement is for methods to prepare unsymmetrical oxabicyclo[3.2.1]octenes as single enantiomers.[5] In addition, if the methodology is to be applicable to the synthesis of stereochemically complex acyclic "pentads", diastereomeric cycloadducts must be available. Herein, we report our success in identifying highly diastereoselective intermolecular [4 + 3] cycloadditions.[6] We also report that previously unavailable diastereomeric cycloadducts can now be made in good yields.

Our studies began by investigating the diastereoselectivity of intermolecular [4 + 3] cycloaddition reactions between chiral furyl alcohols or ethers and 1,3-dimethyl-2-oxyallyl cation. Most of the furans that were selected are available as single enantiomers.[7]



1a R=Me, R'=t-Bu
1b R=H, R'=t-Bu
1c R=H, R'=c-hexyl
1d R=H, R'=n-heptyl

1e **2**

(1) For reviews on [4 + 3] cycloadditions, see: (a) Hosomi, A.; Tominaga, Y. [4 + 3] Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, Chapter 5.1, p 593. (b) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (c) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (d) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.

(2) Nucleophilic ring opening on oxabicyclo[3.2.1] systems: (a) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. (b) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954. (c) Arjona, O.; de Dios, A.; Fernandez de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906 and references therein. (d) Lautens, M.; Chiu, P.; Colucci, J. T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281. (e) Lautens, M.; Abd-El-Aziz, A. S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305.

(3) For recent reviews on S_N2' and "S_N2' like" ring openings of oxa-n-cyclo systems, see: (a) Keay, B. A.; Woo, S. *Synthesis* **1996**, 669. (b) Lautens, M. *Synlett* **1993**, 177.

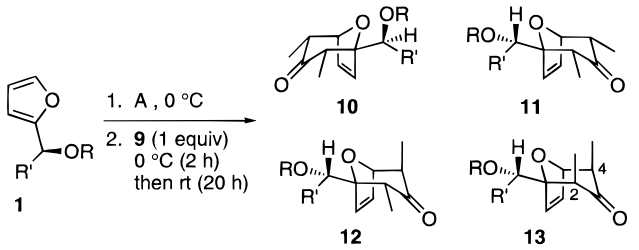
(4) Lautens, M.; Klute, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442.

(5) For an alternative approach to enantiomerically enriched oxabicyclo-[3.2.1]octenes via a tandem cyclopropanation/Cope rearrangement, see: Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.

(6) For stereoselective intramolecular [4 + 3] cycloadditions, see: (a) Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860. (b) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795.

(7) For the kinetic resolution of **1b**−**d**, see: (a) Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085. For the preparation of **1e** and **2**, see: (b) Schmid, C. R.; Bryant, J. D. In *Organic Syntheses*; Coffen, D. L., Ed.; Wiley: New York, 1993; Vol. 72, p 6. (c) Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 1529. (d) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636.

Table 1. [4 + 3] Cycloadditions Using Zn−Ag Couple

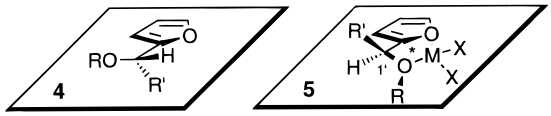


1 **10** **11** **12** **13**

entry	furan	conditions, A[a]	yield,[b] %	**10:11:12:13**[c]
1	**1a**	Zn−Ag, DMF	26	92:8:0:0
2	**1b**	Zn−Ag, THF	45−60	27:57:0:16
3	**1b**	EtMgCl then Zn−Ag, THF	50	11:30:0:59
4	**1b**	*n*-PrZnI then Zn−Ag, THF	49	0:3:3:94

[a] Typical conditions: 1.4 equiv of furan, 1.4 equiv of RMX (entries 3 and 4), 2.5 equiv of Zn−Ag couple, 1 equiv of **9**. Deprotonations were carried out at 0 °C (10 min) and subsequent reductive debrominations were done at 0 °C (2 h) then room temperature (20 h). All reactions were done at 0.8 M with respect to the furan. [b] Combined isolated yield. [c] Measured by capillary GC (HP 5 column).

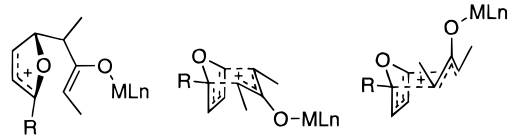
The choice of side chain was selected based on the notion that a metal ion (such as divalent zinc or magnesium) could chelate with the furan and side-chain oxygens thus restricting rotation around the $C_*-C_{1'}$ bond (e.g. **5**, Figure 1). The steric bulk of the R′ group would then dictate the sense and level of facial selectivity in the cycloaddition. Approach of the oxyallyl cation from the side opposite the bulky R′ group of **5** would be expected and the relative stereochemistry at the bridgehead carbons would be ultimately controlled by the stereochemistry at $C_{1'}$. "Non-chelated" cycloadducts would arise from rotamer **4**.



4 **5**

Figure 1. Diastereofacial selectivity in the [4 + 3] cycloadditions.

High diastereoselectivity also requires control of the mode of attack of the oxyallyl cation which is responsible for setting the stereochemistry at C_2 and C_4. As illustrated in Figure 2, [4π(4C) + 2π(3C)] cycloadditions leading to 1-substituted-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ones could occur in either a stepwise, **6**, or concerted manner, the latter case being further subdivided into compact, **7**, or extended modes, **8**.[1,8]



6 **7** **8**

Figure 2. The possible modes in the [4 + 3] cycloaddition.

In our initial studies, we employed reaction conditions first described by Noyori and Sato (Zn−Ag couple)[9] for the generation of the oxyallyl cation from 2,4-dibromopentan-3-one, **9** (Table 1). Contrary to our expectations, when the methyl ether **1a** was used, **10a** was the major diastereomer produced (entry 1) in accord with reaction via rotamer **4**.[10]

(8) Configurational assignments of the methyl groups at C_2 and C_4 in oxabicyclo[3.2.1] systems is possible by ^{1}H NMR analyses of the coupling constants. See: Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3940.

(9) Noyori, R.; Sato, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2745.

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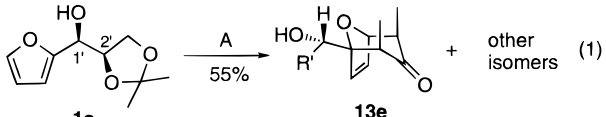
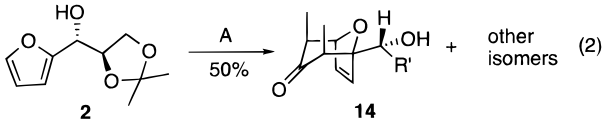
Conversely, cycloaddition with the free alcohol **1b** gave predominantly "chelate controlled" adducts in moderate yield but lower diastereoselectivity (entry 2).[11] In order to enhance the diastereofacial selectivity, the hydroxyl group was deprotonated with a divalent organometallic reagent followed by cycloaddition with **9** (entries 3 and 4). The best diastereoselectivity was observed using zinc salts.

An interesting consequence of the use of a magnesium or zinc alkoxide was the preferential formation of the product with methyl groups situated at C_2 and C_4 in a diaxial orientation.[12,17] This appears to be the first instance of diaxial products predominating in a [4 + 3] intermolecular cycloaddition with a furan.

In order to determine the effect of an additional oxygen moiety on the diastereomeric ratio, furan **1e** and its diastereomer **2** were prepared from glyceraldehyde acetonide.[7b−d] We found that the presence of the $C_{2'}$ oxygen either enhanced or reduced the diastereoselectivity but the reaction nonetheless gave diaxial adducts for both furans indicating that the furyl alkoxide (i.e. at $C_{1'}$) was the dominant control element in the cycloaddition (eqs 1 and 2).[13]

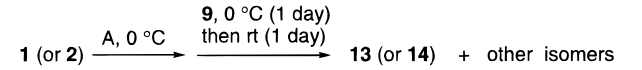




(A) (i) EtMgCl (1 equiv), THF then Zn-Ag (1.4 equiv), 0 °C. (ii) **9** (0.7 equiv), 0 °C (2 h) then rt (20 h).

The influence of the counterion on the diastereoselectivity was equally dramatic when the reaction was carried out in the presence of Et_2Zn under conditions first described by Mann[14] (Table 2). High diastereomeric excess (≥90%) and yields of up to 80% of crystalline adducts **13b** or **13c** were consistently obtained when a two-fold excess of dibromopentanone and Et_2Zn were used (entries 2 and 3).[15,16] The major product can be rationalized by invoking an extended transition state and a chelation-controlled mechanism.[17,18]

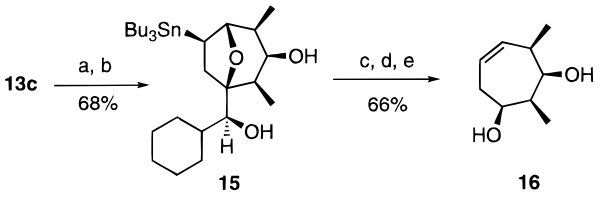
Table 2. [4 + 3] Cycloadditions Using Diethylzinc



entry	furan	A (equiv)	9 (equiv)	yield,[a] %	ratio[b]
1	**1b**	$ZnEt_2$ (1), THF	(2)	54	98:2[c]
2	**1b**	$ZnEt_2$ (2), THF	(1−3)	70−80	96:4[c]
3	**1c**	$ZnEt_2$ (2), THF	(1−3)	60−80	95:5
4	**1d**	$ZnEt_2$ (2), THF	(3)	48	95:5[d]
5	**1e**	$ZnEt_2$ (1), THF	(2)	40	95:5
6	**2**	$ZnEt_2$ (1), THF	(2)	40	88:12[e]

[a] Combined isolated yields. [b] Determined by ^1H NMR (400 MHz) unless otherwise indicated. Ratios correspond to **13**:all other isomers. [c] Measured by capillary GC (HP 5 column). [d] Along with 47% unreacted starting material. [e] Ratio corresponds to **14**:all other isomers.

Scheme 1



(a) THF, $LiBH_4$, 0 °C - rt (4h). (b) Bu_3SnH, cat. $Pd(OH)_2/C$, THF, rt. (c) BuLi, THF, rt. (d) H_5IO_6, THF, H_2O. (e) THF, DIBAL-H, -78 °C.

In order to demonstrate that the side chain could serve as a "chiral auxiliary", ketone **13c** was reduced selectively with $LiBH_4$ and the resulting alcohol hydrostannylated with excellent regioselectivity using our heterogeneous hydrostannylation reaction[19] to give **15**. The resulting tetraalkylstannane was then treated with *n*-BuLi to induce transmetallation followed by elimination. Oxidative cleavage of the resulting vicinal diol and stereospecific reduction of the ketone with DIBAL-H gave **16** which was identical to a subunit of ionomycin we previously prepared in racemic form (Scheme 1).[2d]

In summary, we have developed a route to enantiomerically pure oxabicyclo[3.2.1]octenes using a "chelate-controlled" facially selective [4 + 3] cycloaddition reaction. Furthermore, we have developed a route to previously unavailable diastereomers. A chiral side chain serves as a diastereocontrol element which is easily removed by oxidative cleavage thereby providing access to enantiomerically pure cycloheptenones.

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Supporting Information Available: Experimental procedures and tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates, as well as X-ray structures (25 pages). See any current masthead page for ordering and Internet access instructions.

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(10) Structural proof of **10a** and **11a** was achieved chemically by methylation of **10b** and **11b**[11] at the $C_{1'}$ hydroxyl respectively (NaH, THF, 0 °C then MeI).

(11) X-ray analysis of **11b** proved the structure of the cycloadduct (unpublished results). Moreover, an independant oxidation of **10b** and **11b** (TPAP (10 mol %), NMO (2.5 equiv), 4 Å MS, MeCN) gave the same diketone, indicating that **10b** and **11b** were epimeric at the $C_{1'}$ hydroxyl.

(12) Compound **13b** was epimerized using base (^{t}BuOK in ^{t}BuOH, 6 h, room temperature) to give the known compounds **11b**[11] and **12b**[18] confirming the diaxial orientation of the methyl groups at C_2 and C_4.

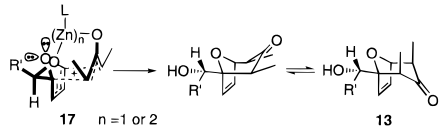
(13) X-ray crystallographic analyses of the major products resulting from **1e** and **2**, to be published by Lautens, M.; Colucci, J. T.; Lough, A. J.

(14) (a) Mann, J.; Barbosa, L. C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 787. (b) Mann, J.; Barbosa L. C. A. *Synthesis* **1996**, 31.

(15) Typically, the furyl alcohol and $ZnEt_2$ were premixed and stirred at 0 °C for 10 min in THF (0.3 M with respect to the furan) prior to the addition of **9**. The reaction was then stirred at 0 °C (1 day) then room temperature (1 day) followed by a saturated Na_2EDTA/EtOAc quench (1:1).

(16) Contrary to some recent findings,[14b] THF proved to be the best solvent for our cycloadditions. Furthermore, Mann observed predominant formation of diequatorial cycloadducts with 3-(2-furyl)propanol in benzene. Further investigations are required to determine why the diastereoselectivity changes as a function of the position of the hydroxyl group on the side chain.

(17) A complex related to **17** may be invoked to explain the observed facial selectivity and stereoselectivity. Divalent zinc (or perhaps an aggregate containing zinc ions) may act as a tether between the furyl alkoxide and the oxyallyl cation.



(18) In THF, the diastereoselectivity remained nearly constant regardless of the number of equivalents of Et_2Zn used (entries 1 and 2 in Table 2). However, in Et_2O, addition of a second equivalent of Et_2Zn resulted in a change in product from **13b** to **12b** (1:6 ratio of **13b**:**12b**, 26% combined isolated yield along with 52% unreacted starting material). Moreover, only one of the two adducts with axial−equatorial orientation of the methyl groups was observed (X-ray analysis of the reduced adduct of **12b** ($LiAlH_4$, THF, 0 °C) proved the structure of the cycloadduct−unpublished results).

(19) Lautens, M; Kumanovic, S.; Meyer, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1329.