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LETTERS

ENANTIOSPECIFIC GENERATION OF ANTI-ALDOL ADDUCTS VIA CONJUGATE ADDITION TO 5-METHYLENE-1,3-DIOXAN-4-ONES

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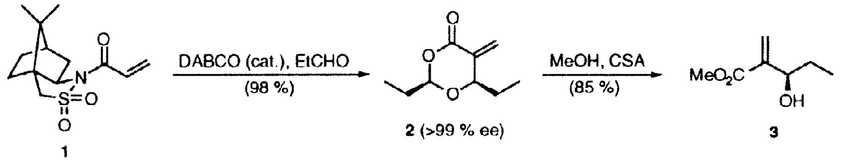
Abstract: Michael additions to the exocyclic olefins of optically pure dioxanones (prepared via the asymmetric Baylis-Hillman reaction) are studied. The products can be obtained in excellent diastereoselectivity to ultimately provide products equivalent to those derived via anti aldol additions. Quaternary centers can also be created with good selectivity via this protocol.

The issue of stereocontrol in the formation of carbon-carbon bonds is one that has attracted the interest of a large number of research groups.[1] In this regard, the use of preexisting stereochemistry has typically been the most prevalent source of control.[1]

Recently we reported an asymmetric variation of the Baylis-Hillman reaction.[2,3] The tertiary amine-catalyzed addition of acrylate **1** to aldehydes leads to the formation of dioxanones (**2**) in good yield and excellent enantiomeric purity (Scheme I).[2] We had previously found that these compounds could be easily opened and made to undergo directed reductions, providing facile access to propionates with the anti relationship.[2] Given the relative paucity of methods for the generation of these anti-aldol constructs in optically pure fashion,[4,5] we were interested in expanding this methodology based on our cyclic products.

Scheme I



Given the presence of the conjugated methylene that is generated in this asymmetric Baylis-Hillman reaction, we became interested in the prospects of expanding the utility of the initial reaction by studying addition reactions to this reactive moiety. Since our initial products from the asymmetric Baylis-Hillman reactions were dioxanones,[2] we decided to take advantage of the cyclic nature of the product by studying additions directly to these enoates. In this regard, we felt that cuprates held considerable promise.[6,7] Michael addition of cuprates would result in the formation of an enolate that should then pick up an electrophile in a stereocontrolled fashion to provide products with good selectivity (Scheme II). We therefore studied the addition of a variety of cuprates to dioxanone **4** with a protic workup in order to study the viability of these additions. In practice, the additions proceeded in fair yield to provide a mixture of diastereomeric products.[8] Apparently, protonation occurs preferentially from the top face (as drawn) of the enolate, leading to the formation of mostly the trans products (**5** - **7**). Unfortunately, the selectivity was only 4:1 for this isomer. Subsequent kinetic deprotonation/reprotonation of these products improved this selectivity considerably.[8,9] In a

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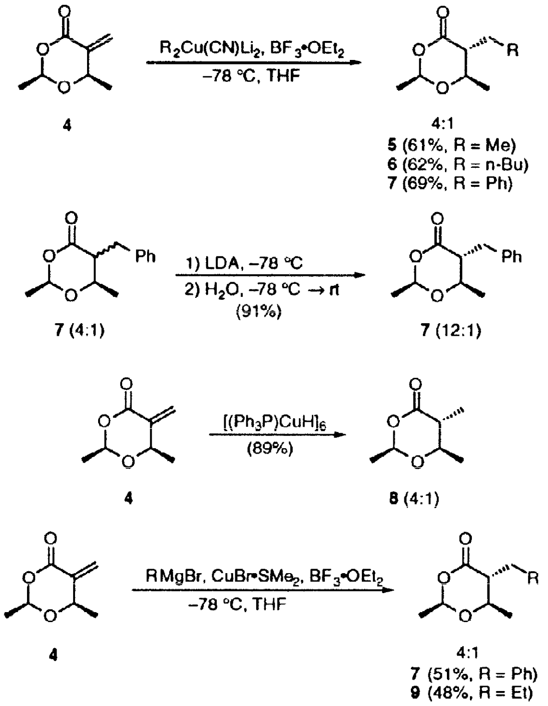
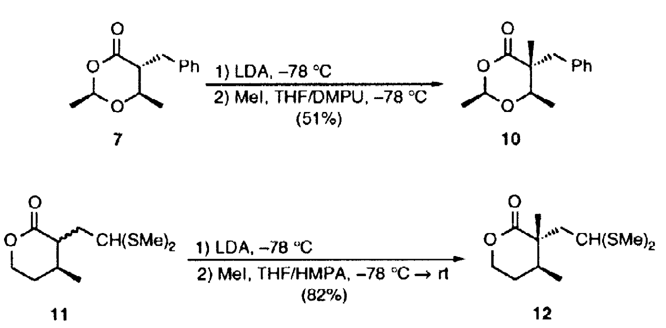
similar fashion, Stryker's reagent could also be added to the dioxanones,[10] again affording the products as a 4:1 mixture of diastereomers favoring the trans diastereomer (for example, **8**). Copper mediated addition of Grignard reagents also served as a viable method for the derivatization of the dioxanones.[6] Unfortunately, the selectivity was similarly poor.

Scheme II



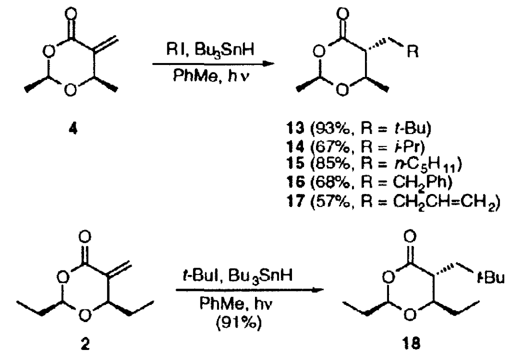
Given the success observed in the equilibration studies described above, we pursued the prospects of treating the enolates with other electrophiles. In this regard, we found that the enolates could be alkylated with methyl iodide to afford the corresponding quaternary products (Scheme III).[8] These compounds were obtained in diastereomerically pure form. However, the reaction is very sluggish and does not proceed to completion at the required low temperatures, typically returning as much as 60% of the unreacted starting material. Conversely, reaction at higher temperatures (−78 °C → rt) results in competitive decomposition. Given that lactones of similar configuration can be alkylated with little difficulty,[11] it seems likely that the presence of the labile acetal in the ring contributes to this decomposition, so low temperature alternatives are still under investigation.[12]

Scheme III



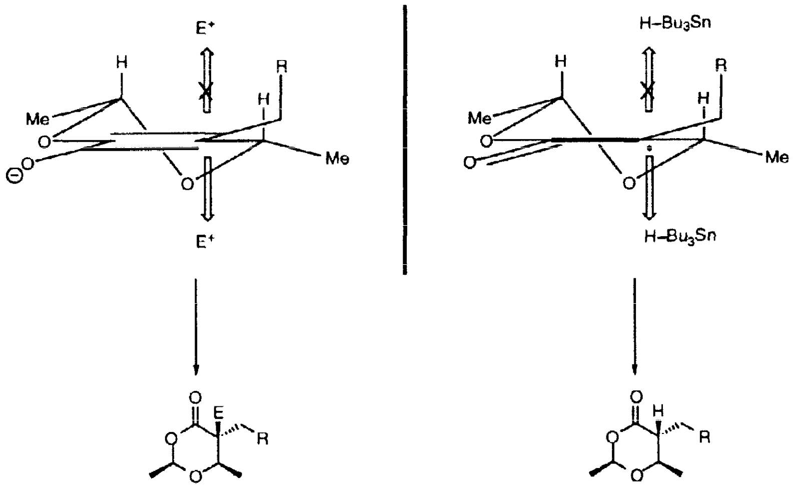
After the disappointing results from the aforementioned organometallic reagents to the dioxanones, we were delighted to find that radical additions were a vast improvement. Specifically, addition of a number of alkyl iodides in the presence of tributyltin hydride led to the trans products in excellent yields and with complete diastereoselectivity (Scheme IV).[8,13] While the bulk of our work has been done with readily available dioxanone **4**, it is readily adaptable to other Baylis-Hillman products as well.

Scheme IV



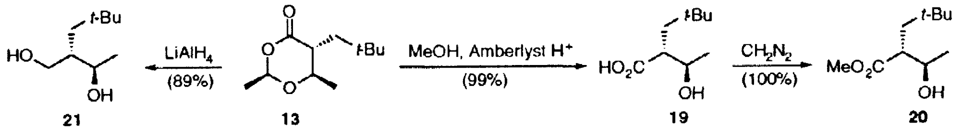
Rationale for the formation of the trans products from both of these processes arises from the likelihood that the reactive intermediates in both cases adopt a preferred conformation such as in Scheme V.[14] Such a conformation would minimize the steric repulsion between the newly introduced side chain (R) and the existing alkyl group at the adjacent position. From this conformation, approach of an electrophile or a hydrogen source should then occur preferentially from the lower face as drawn. This approach is cis to the two pseudoequatorial methyl groups, thereby avoiding an undesirable interaction with the newly added group. The bulky nature of tributyltin hydride probably enhances this selectivity compared with a proton.

Scheme V



The products from these additions could be easily opened up under acidic or reductive conditions to afford the products in good yield (Scheme VI).[8] In this regard, products corresponding to anti aldol adducts could be prepared in excellent optical purity in good overall yields.[8] It is noteworthy that basic treatment led to a complex mixture of products.

Scheme VI



In summary, additions to dioxanones prepared via the asymmetric Baylis-Hillman reaction provide the corresponding anti aldol adducts with excellent selectivity. Further investigations in this area are currently underway.

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6. For a recent review, see: Organocopper Reagents, Taylor, R. J. K., Ed.; Oxford University Press, UK, 1994.
7. For a similar study, see: Amberg, W.; Seebach, D. *Chem. Ber.* **1990**, *123*, 2413.
8. The structures assigned to each new compound were determined by their characteristic ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra. Configuration about the newly formed stereocenters was determined via analysis of coupling constants and the pertinent nuclear Overhauser enhancements.
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10. See Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237 and references cited within.
11. Tomioka, K.; Kawasaki, H.; Yasuda, K.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 3597.
12. Seebach has reported the use of a Schwesinger P4 base for the alkylation of similar dioxanones (Pietzonka, T.; Seebach, D. *Chem. Ber.* **1991**, *124*, 1837) and work is underway to examine this possibility with the corresponding products derived from the asymmetric Baylis-Hillman reaction.
13. For a similar study, see: Bulliard, M.; Zehnder, M.; Giese, B. *Helv. Chim. Acta* **1991**, *74*, 1600.
14. Alternatively, the referee suggested the possibility that the radical might exist in a more pyramidalized geometry, which could also explain the enhanced selectivity of this pathway. Radicals are known to exist in systems where they would need to adopt a pyramidal geometry such as in bridgehead positions.[15] In this system, such a geometry would result in all of the substituents adopting an equatorial orientation. We are grateful to the referee for making this alternative suggestion.

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