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An Efficient 1,2-Chelation-Controlled Reduction of Protected Hydroxy Ketones via Red-Al

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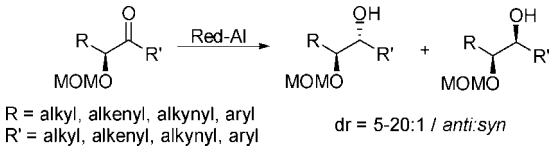
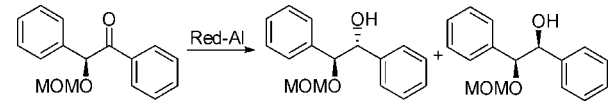


In this paper, we have demonstrated that Red-Al is an efficient chelation-controlled reducing reagent for acyclic acetal (i.e., MOM, MEM, SEM, and BOM) protected α-hydroxy ketones. Typically, diastereomeric ratios (dr) ranged from 5 to 20:1 for the 1,2-*anti*-diols in good to excellent yields.

The stereoselective reduction of the carbonyl moiety plays a pivotal role during the multistep synthesis of natural products. Typically, there are two characteristic approaches which utilize either a reagent- or substrate-controlled reaction process. The most efficient tactic is to exploit inherent chiralty to direct subsequent reactions via the substrate-controlled procedure. Numerous stereochemical induction models have been put forth helping to explain and further offer guidance for planning synthetic routes to targeted compounds via 1,2-asymmetric induction.[1–3] Generally, chelation-controlled reductions of protected hydroxyl carbonyls provide modest to very high diastereomeric ratios due to the rigid five-membered-ring formation prior to nucleophilic addition.[4] Along this line, there have been a variety of reagents that have been investigated for such a substrate-controlled hydride reduction protocol. For example, the most utilized hydride reagent for 1,2-chelation-controlled reduction is $Zn(BH_4)_2$ and frequently provides high levels of diastereoselective control.[5] However, $Zn(BH_4)_2$ has a couple of major drawbacks as a widespread reducing reagent such as lengthy preparation time, limited availability (i.e., not commercial), and lack of stability in ethereal solvents. An alternative reducing reagent to $Zn(BH_4)_2$ would be highly desirable. Other commercial reagents have been investigated and have revealed mixed results. Both $LiBH_4$ and $LiAlH_4$ have shown limited success as chelation-controlled reduction reagents.[6,7] In order to be a viable replacement to $Zn(BH_4)_2$, the reagent must be stable, commercially accessible, available in a variety of solvents, and provide yields and diastereoselectivities that are analogous (or greater) to that of $Zn(BH_4)_2$ or any other hydride reagent.

TABLE 1. Reduction of 1a with Red-Al[a,b]



no.	solvent	*T*, °C	anti	syn	yield (%)
1	toluene	0	>20	1	96
2	toluene	−25	>20	1	96
3	toluene	−50	>20	1	96
4	toluene	−78	>20	1	91
5	Et_2O	0	>20	1	94
6	THF	0	17	1	82
7	DME	0	8	1	37
8	MTBE	0	>20	1	92
9	CH_2Cl_2	0	>20	1	95
10	hexane	0	18	1	91

[a] Anti/syn ratios were determined on the crude product via a 360 or 500 MHz ^1H NMR. [b] Yields are of the isolated and purified compound.

It has been well-established that ethereal moieties can serve a dual purpose as both a hydroxyl protecting and directing group.[8] During our synthetic studies into the total synthesis of aigialomycin D, we required quick and chemoselective access to an *anti*-1,2-diol motif.[9] We envisaged that a 1,2-chelation-controlled reduction of a protected α-hydroxy ketone would furnish the desired *anti*-diol. Upon scanning through a variety of reducing reagents, we were surprised by the high level of anti diastereoselectivity (6 → 9:1 dr) that Red-Al (Vitride) provided when the directing group was a MOM ether. Based on this observation, we decided to further examine Red-Al as a chelation-controlled reducing reagent, and our results are presented herein.

We initially investigated the effect of both solvent and temperature on the chelation-controlled reduction of MOM-protected benzoin (**1a**) with Red-Al, and the results are presented in Table 1. As shown in entries 1–4, reduction of **1a** in toluene provided high levels of dr (>20:1) for the *anti*-diol **1b** in exceptional yields and exhibited little to no dependence on the reaction temperature. Based on this observation, we decided to investigate other solvents while maintaining the reaction temperature at 0 °C. Unfortunately, reduction of **1a** in ethereal solvents furnished mixed results. When either Et_2O or MTBE

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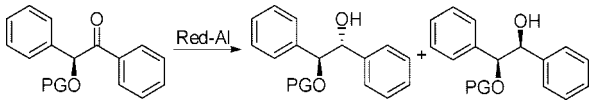
TABLE 2. Reduction of 2a–7a with Red-Al[a–c]



no.	protecting group	anti	syn	yield (%)
1	MOM (**1a**)	>20 (**1b**)	1	96
2	BOM (**2a**)	>20 (**2b**)	1	93
3	THP (**3a**)	7 (**3b**)	1	91
4	MEM (**4a**)	>20 (**4b**)	1	89
5	SEM (**5a**)	>20 (**5b**)	1	94
6	Me (**6a**)	>20 (**6b**)	1	89
7	TBS (**7a**)	2 (**7b**)	1	92[d]

[a] Anti/syn ratios were determined on the crude product via a 360 or 500 MHz ^{1}H NMR. [b] Yields are of the isolated and purified compound. [c] All reductions ran at 0 °C in toluene. [d] Desilylation was observed under reaction conditions.

were utilized as the solvent, high levels of dr for **1b** (>20:1) were observed with yields comparable to that of toluene. However, more Lewis basic ethers such as THF and DME led to inferior yields (82 and 37%, respectively) and lower levels of dr (8→17:1) for **1b**. These two results are not surprising as one can envision that the more Lewis basic ethers would compete with the MOM group of **1a** for chelation of the Na cation and lower the probability of the five-membered ring chelate prior to reduction.

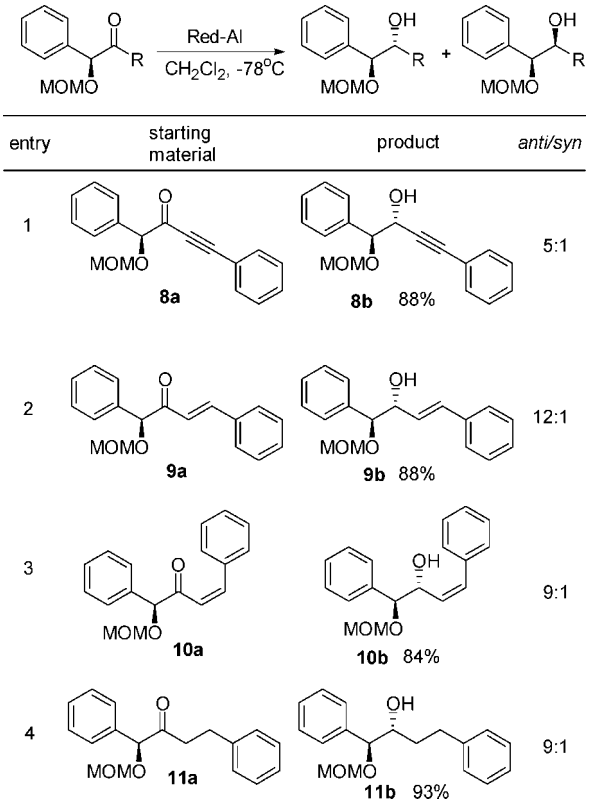
Similar to that of toluene, reduction of **1a** with Red-Al in CH_2Cl_2 and hexane led to high levels of dr (20:1 and 18:1 anti/syn, respectively) with excellent isolated yields as shown in entries 9 and 10 in Table 1.

With the observation that either toluene or CH_2Cl_2 as solvents provide the highest levels of dr and isolated yields for the *anti*-diol **1b** via Red-Al reduction of **1a**, the next phase of the investigation focused on the role of the directing group in providing high levels of dr. As delineated in Table 2, we chose to examine the Red-Al reduction of a variety of protected benzoins (**2a**–**7a**) under the optimized reaction conditions of 0 °C and toluene as the solvent from Table 1. Similar to that of **1a**, the linear acetal protected ketones **2a** (BOM), **4a** (MEM), and **5a** (SEM) provided the corresponding *anti*-diols (**2b**, **4b**, and **5b**) in excellent yields with high levels of dr (>20:1).

Similar to the acetal-protected benzoins **2a**, **4a**, and **5a**, the reduction of the simple α-methyl ether ketone **6a** under the standardized conditions furnished a virtually identical yield and dr for the *anti*-diol **6b**. However, the cyclic acetal THP-protected ketone **3a** provided a lower dr for the *anti*-diol (7:1) with yields comparable to that of its acyclic acetal counterparts **2b**, **4b**, and **5b**. These results were not unexpected due to the literature precedence that acyclic acetals (i.e., MOM, MEM, BOM, etc.) generally undergo efficient 1,2-chelation-controlled reactions, while the THP acetal typically affords inferior levels of dr.[8] Likewise, the TBS-protected benzoin (**7a**) furnished low levels of dr (2:1) for the *anti*-diol in excellent yield, and concomitant desilylation was observed under the reaction conditions. Based on the results of Tables 1 and 2, it appeared that a combination of an acyclic acetal protecting group α to the ketone carbonyl, Red-Al, and toluene or CH_2Cl_2 as the solvent afforded excellent yields and high levels of dr for the resultant *anti*-diol products derived from benzoin.

While the chelation-controlled Red-Al reduction of protected benzoins led us to standardized conditions for high levels of dr and isolated yields for the *anti*-diols, we were more interested

TABLE 3. Reduction of 8a–11a with Red-Al[a,b]



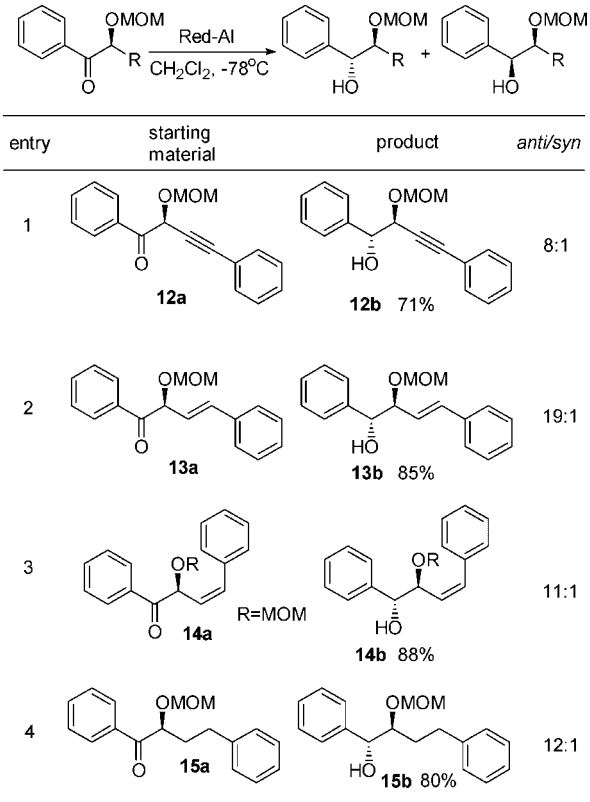
[a] Anti/syn ratios were determined on the crude product via a 360 or 500 MHz ^{1}H NMR. [b] Yields are of the isolated and purified compound.

in exploring the scope and limitations of this reaction protocol. As shown in Table 3, we chose to investigate MOM-protected α-hydroxy ketones which were diversified by carbon hybridization. Thus, reduction of the acetylenic ketone **8a** at 0 °C in toluene furnished the *anti*-diol **8b** in good yield, but with limited dr (~2:1). Further lowering the reaction temperature to −78 °C and exchanging the solvent from toluene to CH_2Cl_2 led to higher levels of dr (5:1) for **8b** in 88% yield. Based on these new reaction conditions, we investigated the Red-Al reduction of both *E*- and *Z*-α,β-unsaturated ketones **9a** and **10a**. Much to our delight, both **9a** and **10a** provided excellent yields of 88 and 84% coupled with high levels of dr for the *anti*-diols **9b** and **10b** (12:1 and 9:1, respectively). Lastly, the fully saturated MOM-protected α-hydroxy ketone **11a** readily underwent reduction with Red-Al at −78 °C and afforded the *anti*-diol **11b** in a 93% yield and a dr of 9:1.

It should be noted that all of the diastereomeric ratios were of the crude, unpurified products. The relative stereochemical relationships of **8b**–**11b** (anti versus syn) were determined by MOM group removal followed by acetonide formation of the subsequent diol. Final ^{1}H NMR experiments (1D NOE) were performed and in all cases enhancements were observed for the *cis*-hydroxyl methine protons.

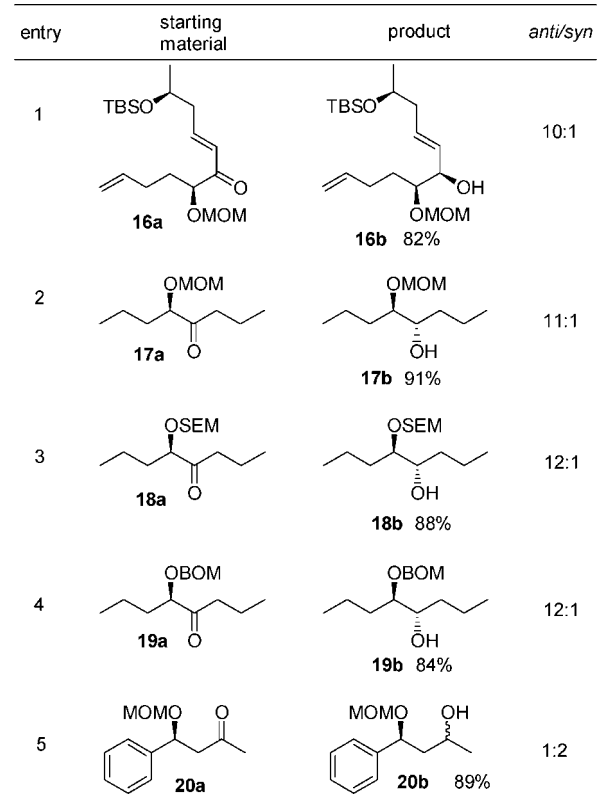
With the promising results of Table 3, the next phase of our investigation into defining the scope and limitations of Red-Al as a chelating reducing reagent led us to diversifying the carbon hybridization adjacent to the directing MOM group. As delineated in Table 4, the four investigated structures were similar to those as shown above, and identical reaction conditions were also employed (−78 °C and CH_2Cl_2 as the solvent). Thus, the

TABLE 4. Reduction of 12a–15a with Red-Al[a,b]



[a] Anti/syn ratios were determined on the crude product via a 360 or 500 MHz ^{1}H NMR. [b] Yields are of the isolated and purified compound.

TABLE 5. Reduction of 16a–20a with Red-Al[a,b]



[a] Anti/syn ratios were determined on the crude product via a 360 or 500 MHz ^{1}H NMR. [b] Yields are of the isolated and purified compound.

Red-Al reduction of the acetylenic ketone **12a** provided a modest dr of 8:1 for the *anti*-diol **12b** in a 71% yield. The diastereomeric ratio for the Red-Al reduction of **12a** was higher than that of **8a** (8:1 versus 5:1) for the *anti*-diols **12b** and **8b**, but one limitation of Red-Al as a chelation-controlled reducing reagent that emerged was the proximity of sp-hybridized carbons.[10] Much to our delight, reduction of the *E*- and *Z*-MOM protected-α-hydroxy ketones **13a** and **14a** afforded very high levels of dr of 19:1 for the *E*-*anti*-diol (**13b**) and 11:1 for the *Z* counterpart (**14b**), both in very high yields of 85 and 88%, respectively.

Similar to that of **11a** in Table 3, reduction of the saturated ketone **15a** with Red-Al furnished a yield of 80% with a dr for the resulting protected *anti*-diol **15b** of 12:1. Based on the results from Tables 3 and 4, Red-Al has emerged as a very efficient 1,2-chelation controlled reducing agent for benzoin related structural analogues by providing high levels of dr for the corresponding *anti*-diols. The resultant monoprotected homoallylic alcohols derived from these reductions are extremely useful synthons in contemporary synthetic organic chemistry.

The final aspect of our investigation was to examine Red-Al as a chelation-controlled reducing reagent of nonaromatic MOM protected α-hydroxy ketones as described in Table 5. During our synthetic studies into the total synthesis of aigialomycin D, we required the *anti*-diol **16b** with high levels of dr as the aliphatic coupling portion en route to the natural product.[11]

Initially, treatment of **16a** with Red-Al in toluene at 0 °C readily afforded alcohol **16b** with a satisfactory level of dr (6:1 by ^{1}H NMR of the crude product) in a very acceptable 84% yield. Based on the reaction conditions of Tables 3 and 4, we reinvestigated the reduction of ketone **16a** at −78 °C with CH_2Cl_2 as the solvent and observed an increase in dr from 6:1 to 10:1 in a virtually identical yield for the *anti*-diol **16b**. We were very pleased from this outcome as it greatly expanded the scope of this reaction beyond that of aromatic ketones. Keeping with the theme of nonaromatic substrates, we also examined the Red-Al reduction of three very simple acetal protected α-hydroxy ketones. Much to our delight, reduction of the MOM-, SEM-, and BOM-protected ketones **17a**–**19a** with Red-Al provided the three corresponding *anti*-diol products **17b**–**19b** with high levels of dr (11 → 12:1) in good to excellent yields of 84–91%. As mentioned before, the relative stereochemical relationship of **16b** (anti versus syn) was determined by protecting group removal followed by acetonide formation of the subsequent diol. Final ^{1}H NMR experiments (1D NOE) were performed, and enhancements were observed for the *cis*-hydroxyl methine protons. For diols **17b**–**19b**, the protecting groups were removed and NMR experiments (both ^{1}H and ^{13}C) confirmed that the products were indeed symmetric, as predicted.

While Red-Al has proven to be very successful at chelation controlled reduction for the synthesis of 1,2-*anti*-diols, we were interested in examining the reduction of a MOM-protected β-hydroxy ketone. Along this line, stereoselective synthesis of the resultant *anti*- or *syn*-1,3-diol motif is very significant due to its ubiquitous nature in many bioactive natural products.[12] Unfortunately, Red-Al reduction of the known ketone **20a** under

(10) In the paper by Takahashi and Tsuji, they report ~5:1 anti/syn selectivity for the reduction of a single benzyl-protected α-hydroxy acetylenic ketone with Red-Al. For more details, see: Takahashi, T.; Miyazawa, Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 5139.

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the standard reaction conditions (−78 °C in CH_2Cl_2) furnished a 2:1 ratio of *syn/anti*-diol **20b** in 89% yield.[13] Thus, one major limitation of Red-Al was that it provided low levels of dr for the chelation-controlled reduction of a β-hydroxy ketone leading to the 1,3-diol motif.

In conclusion, we have shown that Red-Al is an efficient chelation controlled reducing reagent for acyclic acetal (i.e., MOM, MEM, SEM, and BOM) protected α-hydroxy ketones. Typically, diastereomeric ratios ranged from 5 to 20:1 for the 1,2-*anti*-diols in good to excellent yields. Unfortunately, the high levels of dr could not be extended to 1,3-diols via the reduction of β-hydroxy ketones. Based on the various ketones investigated, the described reduction protocol should be quite useful in the stereoselective synthesis of natural product subunits and/or the production of valuable organic synthons.

Experimental Section

Reduction of 1a in Various Solvents. General Procedure for Table 1. To a stirred solution of MOM-protected benzoin (**1a**) (0.790 g, 3.1 mmol) dissolved in various solvents such as toluene, Et_2O, THF, DME, MTBE, CH_2Cl_2, or hexane at temperatures ranging from 0 to −78 °C as listed in Table 1 was added Red-Al in toluene (65 wt % in toluene, 0.96 mL, 3.1 mmol, 1 equiv). The resulting solution was stirred at the respective temperature for 2 h, and then 50 mL of saturated sodium potassium tartrate (Rochelle's salt) was added. The clear organic layer was washed with saturated Rochelle's salt, and the combined aqueous layers were extracted with ether. The ether layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography afforded 1,2-*anti*-diol product **1b** as the major product.

Reduction of 1a–7a in Toluene. General Procedure for Table 2. To a stirred solution of **1a–7a** in toluene at 0 °C was added Red-Al in toluene (1 equiv). The resulting solution was maintained at 0 °C for 2 h, and then 50 mL of saturated sodium potassium tartrate (Rochelle's salt) was added followed by extraction with Et_2O. The clear organic layer was washed three times with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography afforded the reduced 1,2-*anti*-diol products **1b–7b** as the major product in good yields ranging from 89 to 96%.

General Procedure for Tables 3−5. To a stirred solution of **8a–20a** in CH_2Cl_2 at −78 °C was added Red-Al in toluene (1 equiv). The resulting solution was maintained at −78 °C for 2 h, and then saturated sodium potassium tartrate (Rochelle's salt) was added followed by extraction with Et_2O. The clear organic layer was washed three times with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography afforded the 1,2-*anti*-diol products **8b–19b**.

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Supporting Information Available: General experimental procedures for all of the reduction protocols, synthesis of starting materials, and full characterization data for all new compounds is provided. In addition, ^{1}H NMR spectral data for the previously reported compounds are also available. This material is available free of charge via the Internet at http://pubs.acs.org.

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