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Titanium(IV)-Promoted Mukaiyama Aldol–Prins Cyclizations

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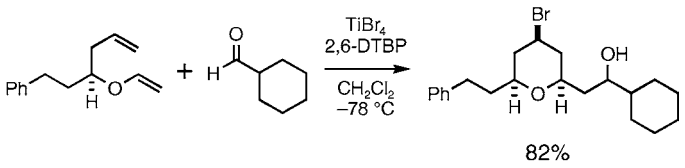
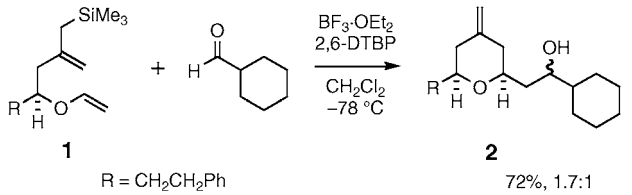
ABSTRACT



A new version of the Mukaiyama aldol–Prins (MAP) cyclization has been developed. Unsaturated enol ethers such as 3 were found to couple with aldehydes in the presence of $TiBr_4$ to give 4-bromotetrahydropyran products. This cascade reaction sequence leads to the formation of two new carbon–carbon bonds, a ring, and three new stereogenic centers. We expect this reaction to be a powerful new tool in synthesis.

Cascade reactions can be very powerful transformations in organic synthesis.[1] We recently reported the first examples of a Mukaiyama aldol−Prins (MAP) cascade cyclization reaction (Scheme 1).[2] In our initial work, a very reactive allylsilane was selected as the internal nucleophile to promote a rapid and clean Prins cyclization. The allylsilane substrate **1**, however, is more difficult to prepare than a simple alkene analogue such as **3**. In this paper, we describe the use of simple alkene substrates in MAP cyclizations and the importance of selecting the appropriate Lewis acid to promote the reaction.

Scheme 1. Mukaiyama Aldol−Prins (MAP) Cyclization Cascade with an Allylsilane Internal Nucleophile



Cationic cascade reactions are well-known in organic chemistry. Johnson's polyene cyclizations represent an important milestone in this area.[3] In most cases, the cyclization reaction is initiated by the addition of a proton or Lewis acid. Berrisford demonstrated that a silicon-tethered bis-nucleophile could add to an *external* aldehyde electrophile in a cascade reaction.[4] More recently, Leighton has developed a powerful strategy to prepare polyol segments using similar silicon-tethered bis-nucleophiles.[5] The Mukaiyama aldol-Prins cyclization developed in our lab uses the reaction of a bis-nucleophile and an aldehyde to couple two fragments and build a ring. A formal synthesis of leucascandrolide A demonstrated the potential of this method in synthesis.[2]

Synthesis of allylsilane substrates such as **1** requires several steps, and an important advantage of the unsubstituted alkene substrates such as **3** is that they are very simple to make. The alkene substrate **3** was prepared in two steps from dihydrocinnamaldehyde. Allyl Grignard addition followed

(1) (a) de Meijere, A.; von Zezschwitz, P.; Nuske, H.; Stulgies, B. *J. Organomet. Chem.* **2002**, *653*, 129−140. (b) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306. (c) Heumann, A.; Reglier, M. *Tetrahedron* **1996**, *52*, 9289−9346. (d) Tietze, L. F. *Chem. Ind.* **1995**, 453−457.

(2) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420−8421.

(3) (a) Johnson, W. S. *Angew. Chem.* **1976**, *88*, 33−41. (b) Bartlett, P. A. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341−409. (c) Johnson, W. S. *Tetrahedron* **1991**, *47*, R11−R50.

(4) Frost, L. M.; Smith, J. D.; Berrisford, D. J. *Tetrahedron Lett.* **1999**, *40*, 2183−2186.

(5) Wang, X.; Meng, Q.; Nation, A. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 10672−10673.

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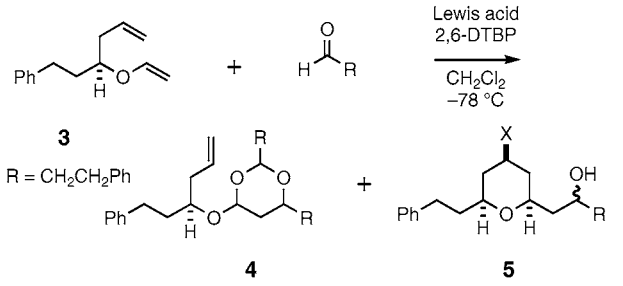
by $Hg(TFA)_2$-catalyzed exchange with ethyl vinyl ether[6] produced **3** reliably and in good overall yield.[7] The optically pure substrate (−)-**3** was prepared using an enantioselective Ti(BINOL)-catalyzed allylation[8] (ca. 97% ee) followed by the vinyl ether exchange. These procedures have been used in our laboratory to prepare half a dozen substrates using different aldehyde starting materials.

Initially, the Mukaiyama aldol addition and Prins cyclization with a simple alkene substrate **3** was evaluated using the optimized conditions from Scheme 1. Reaction of **3** with 2.5 equiv of dihydrocinnamaldehyde in the presence of $BF_3{\cdot}OEt_2$ and 2,6-di-*tert*-butylpyridine (2,6-DTBP) at −78 °C led to the unexpected product **4** in 82% yield, Table 1, entry

Table 1. Effect of Lewis Acid on the MAP Cyclization with an Unactivated Alkene

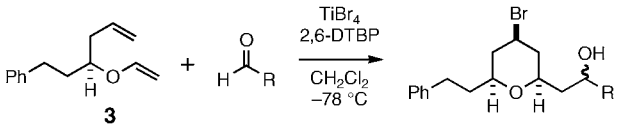


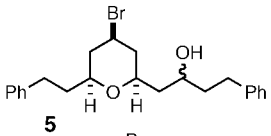
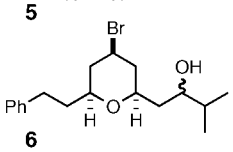
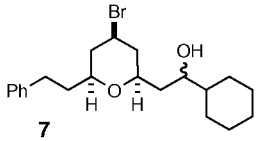
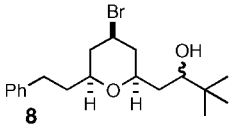
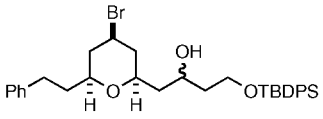
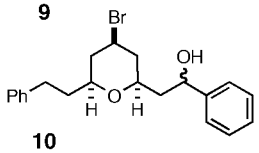
entry	Lewis acid	X	**4** (%)	**5** (%)
1	$BF_3{\cdot}OEt_2$		82	
2	$SnBr_4$	Br	58	11
3	$SnCl_4$	Cl	40	15
4	$TiCl_2(O^iPr)_2$	Cl	15	47
5	$TiCl_4$	Cl	0	62
6	**$TiBr_4$**	**Br**	**0**	**72**

1. The Mukaiyama aldol reaction has taken place but the oxocarbenium ion, rather than cyclizing onto the alkene, added a second equivalent of the aldehyde to produce the 1,3-dioxane structure **4**.[9] Compound **4** was not the desired product, but it was formed very cleanly. Other Lewis acids were used to promote the condensation with better success. Tin halides and titanium blend reagents led to a mixture of the MAP product **5** and the 1,3-dioxane **4**. The more powerful Lewis acids, $TiCl_4$ and $TiBr_4$, did not produce 1,3-dioxane **4** and gave the best yields of **5**, entries 5 and 6. The $TiBr_4$ is particularly effective and gave the adduct **5** in 72% isolated yield. In each of these experiments, compound **5** was produced as a ca. 1:1 mixture of diastereomers at the alcohol stereogenic center. The selectivity for the equatorial bromide was >95:5. Control experiments established that dioxane **4** was efficiently converted to **5** on treatment with $TiBr_4$ but not with $SnBr_4$. The combination of a powerful Lewis acid with a nucleophilic halide led to the best yields in the Mukaiyama aldol−Prins cyclization with unsubstituted alkenes.

The scope of the $TiBr_4$-promoted MAP reaction using optimized reaction conditions[10] is presented in Table 2.

Table 2. MAP Cyclization Promoted by $TiBr_4$



entry	product	yield(%)	dr
1	 **5**	80	1.1:1
2	 **6**	78	1.1:1
3	 **7**	82	1:1
4	 **8**	74	1.2:1
5	 **9**	70	1.2:1
6	 **10**	53	1.3:1

Entries 1−4 show the outcome with several aliphatic aldehydes. The yields clustered around 80% and the stereoselectivity at the bromide center favored equatorial by >95:

(6) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828−2833.

(7) Details are provided in the Supporting Information.

(8) (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001−7002. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468.

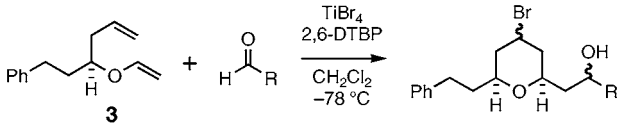
(9) (a) Hoaglin, R. I.; Hirsh, D. H. Production of Unsaturated Aldehydes, U.S. Patent 2,628,257, Feb 10, 1953. (b) Chretien-Bessiere, Y.; Leotte, H. *Compt. Rend.* **1962**, *255*, 723−724.

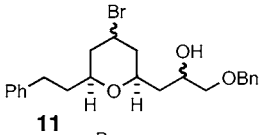
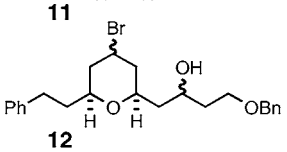
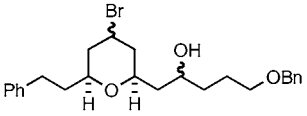
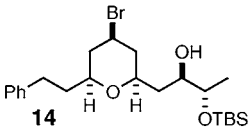
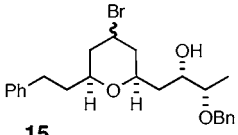
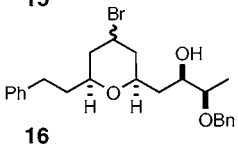
(10) **Tetrahydropyran (7).** Cyclohexanecarboxaldehyde (215 μL, 1.65 mmol, 2.0 equiv), enol ether **3** (167 mg, 0.826 mmol, 1.0 equiv), and 2,6-di-*tert*-butylpyridine (278 μL, 1.24 mmol, 1.5 equiv) were dissolved in methylene chloride and cooled to −78 °C. A solution of $TiBr_4$ in methylene chloride (3.2 mL, 0.52 M, 2.0 equiv) was added dropwise, and the dark red solution was allowed to stir at −78 °C. TLC analysis showed complete consumption of starting material in 5 min, at which point the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL) at −78 °C. The mixture was allowed to come to room temperature, and the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude oil was purified by flash column chromatography (5−30% diethyl ether/hexanes) to give a 1:1 isomeric mixture of **7** (268 mg, 0.678 mmol, 82%) as a clear, colorless oil. Characterization is included in the Supporting Information.

5. The alcohol stereogenic center was formed with essentially no preference in each case. For compounds **5** and **8**, the epimeric mixture of alcohols was oxidized to a single ketone to confirm the structure of the two diastereomeric products. Entry 5 demonstrates that a silyl-protected alcohol was tolerated in the reaction. Benzaldehyde led to a lower yield (53%) than any of the aliphatic aldehydes. The product was stable to the reaction conditions, and the origin of this reduced yield was not obvious. The reaction is successful with each of the aldehydes in Table 2, but the best yields were observed with aliphatic aldehydes.

Aldehydes with protected alcohols lead to interesting stereochemical consequences in the reaction, Table 3. The

Table 3. MAP Cyclization of Aldehydes with Protected Alcohols



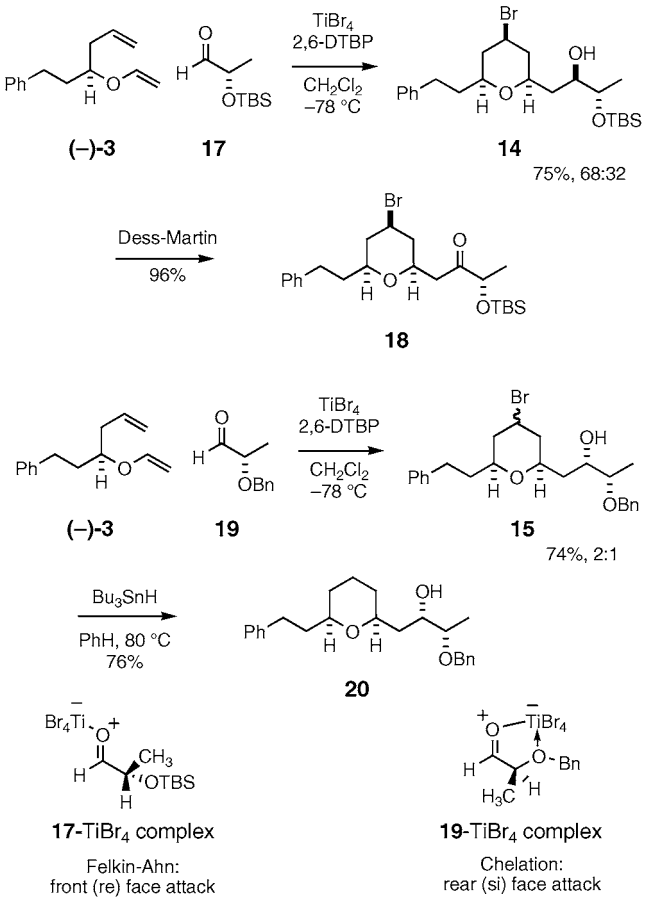
entry	product	yield(%)	dr(OH)	eq/ax
1	 **11**	71	~1:1	78::22
2	 **12**	75	~1:1	68:32
3	 **13**	75	~1.1	85:15
4[a]	 **14**	75	68:32	>95:5
5[a]	 **15**	74	>95:5	68:33
6[a]	 **16**	72	>95:5	66:34

[a] Optically pure (−)-(*S*)-**3** was used in these experiments.

TBDPS-protected aldehyde in Table 2, entry 5, reacted just like any other aliphatic aldehyde. However, the corresponding substrate with a benzyl protecting group (Table 3, entry 2) produced a THP product with 32% of the axial bromide.[11] Previous cases strongly favored equatorial bromides. In Table 3, five of the six entries lead to significant amounts of the axial bromide.[12] The exception is entry 4, where the TBS ether produces the expected equatorial bromide. The increase in axial bromide correlates with the presence of a benzyl ether in the aldehyde.

These MAP reactions are subject to the expected stereochemical influences of a chiral aldehyde. In three cases, optically pure enol ether (−)-**3** was coupled with optically pure aldehydes, Scheme 2 (and Table 3, entries 4−6). The

Scheme 2. MAP Cyclizations with Optically Pure Components



TBS ether aldehyde **17** derived from (*S*)-lactic acid coupled with (−)-**3** to give a 68:32 mixture of isomers in 75% yield. Oxidation with Dess−Martin's reagent produced ketone **18** as a single diastereomer, confirming that the alcohol center in **14** was epimeric. The benzyloxy aldehyde **19** coupled with (−)-**3** under standard conditions to produce a 2:1 mixture of diastereomers. Radical debromination of this mixture gave the alcohol **20** as a single diastereomer, confirming that the

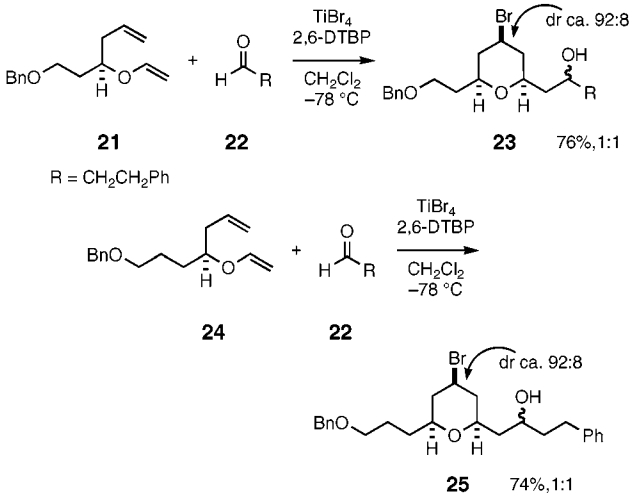
(11) The axial and equatorial bromides were assigned by ^{1}H NMR analysis. The equatorial isomer of compound **5** (X = Br) showed the expected NOE enhancements between the 2, 4, and 6 protons on the THP ring. For the other compounds, the distinctive chemical shift and coupling constants (ax-Br: ca. 4.7 ppm, (quint, J = 2.9, Hz); eq-Br: ca. 4.1 (tt, J = 4.4, 12.0 Hz)) were used to assign the axial and equatorial bromide isomers.

(12) Hart recently observed modest amounts of axial bromide in a $TiBr_4$-promoted Prins cyclization: Hart, D. J.; Bennet, C. E. *Org. Lett.* **2003**, *5*, 1499−1502.

bromide carbon in **15** was epimeric. The configuration of the major alcohol epimers for **14** and **15** were determined by advanced Mosher's analysis,[13] confirming the expected Felkin−Ahn and chelation-controlled selectivity, respectively. These experiments establish the stereochemical outcome of the coupling reactions but also demonstrate the utility of the MAP reaction to coupling optically pure and potentially complex components.

The formation of axial bromide in the benzyl ether substrates in Table 3 is puzzling. Entries 1−3 and 5−6 all lead to significant amounts of axial bromides. Scheme 3 shows a control experiment for the formation of axial bromide in the cyclization. Placing a benzyl ether on the other side of the tetrahydropyranyl ring, separated by either two or three carbon atoms, leads to 92:8 selectivity for the equatorial bromide. These substrates are less selective than the examples in Table 2, but they are better than the *O*-benzyl examples in Table 3. A stronger correlation is found between aldehydes that would be expected to chelate the Lewis acid (e.g., aldehyde **19**−$TiBr_4$ complex in Scheme 2) and the formation of the axial bromide. This chelation would place the Lewis acid adjacent to the carbon chain of the aldehyde rather than in the normally preferred geometry adjacent to the aldehyde hydrogen (e.g., aldehyde **17**−$TiBr_4$ complex in Scheme 2). The correlation is good but the details of the mechanism are not. The axial bromide ends up on the face of the THP ring opposite to the $TiBr_4$-coordinated alkoxide, and thus, a direct transfer of the bromide appears unlikely. The axial selectivity is independent of the secondary alcohol configuration, an observation that further undermines any intramolecular bromide transfer mechanism. For example, compounds **15** and **16** are generated with nearly identical equatorial to axial bromide ratios, but the relative configuration of the THP ring and the secondary alcohol are opposite. The geometries of the two diastereotopic Ti-chelates will be different, and an intramolecular bromide transfer would be affected by the change in geometry. We conclude that an intramolecular bromide transfer is not important in formation of the axial bromide products. We will continue to investigate the origin of the axial bromide in these cyclizations.

Scheme 3. MAP Cyclizations with *O*-Benzyl Enol Ether Components



The $TiBr_4$-promoted Mukaiyama aldol−Prins cyclization is a valuable reaction for rapidly building complexity in organic structures. The products of these MAP reactions are structurally related to segments of common oxygenated natural products. The reaction is suitable for coupling fragments and thus lends itself to convergent synthetic strategies. It is worth emphasizing that many of the MAP cyclization products described in this paper were formed in only three steps from commercially available precursors. Applications of the new MAP reaction in natural product synthesis are in progress.

Acknowledgment. The National Institutes of Health (CA-81635) provided financial support.

Supporting Information Available: Preparation and characterization of the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035303N

(13) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.