Pergamon

Tetrahedron Letters 42 (2001) 1269–1271

TETRAHEDRON LETTERS

# Vinylogous Mukaiyama aldol reactions with triarylboranes

Mathias Christmann and Markus Kalesse*

*Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany*

Received 6 December 2000; accepted 7 December 2000

**Abstract**—The first vinylogous Mukaiyama aldol reactions with tris(pentafluorophenyl)borane and triphenylborane are described. Both Lewis acids diastereoselectively generate the C19–C21 all-*syn* stereo triad of ratjadone, and in the case of tris(pentafluorophenyl)borane the reaction proceeds with substoichiometric amounts. © 2001 Elsevier Science Ltd. All rights reserved.

The vinylogous Mukaiyama aldol reaction (VMAR) is a powerful carbon–carbon bond forming reaction since two stereocenters and one double bond can be generated at the same time.[1] The resulting δ-hydroxy-α,β-unsaturated carbonyl compounds are important intermediates in the synthesis of polyketide natural products.[2] In our retrosynthetic approach the α,β-unsaturated ester **3** serves as a precursor for epoxide **2** which has been converted to the tetrahydropyran moiety of ratjadone (**1**).[3] We therefore investigated the VMAR between aldehyde **4** and diene **5**. The reaction mediated by $BF_3{\cdot}OEt_2$ afforded **6** with a moderate Felkin–Anh selectivity of 3:1 in 92% yield (Scheme 1).[3d,4]

After having finished the first total synthesis of ratjadone[5] we studied this particular reaction in more depth after it became clear that it is one of the pivotal steps. In contrast to the classical Mukaiyama aldol reaction,[6] little is known about the diastereoselection in its vinylogous extension. Paterson et al.[2b] have shown that the stereochemical outcome of these reactions is very sensitive to the conditions employed (Lewis acid, temperature, solvent). From Evans' merged 1,2- and

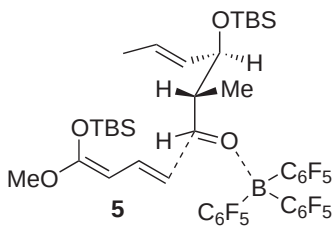
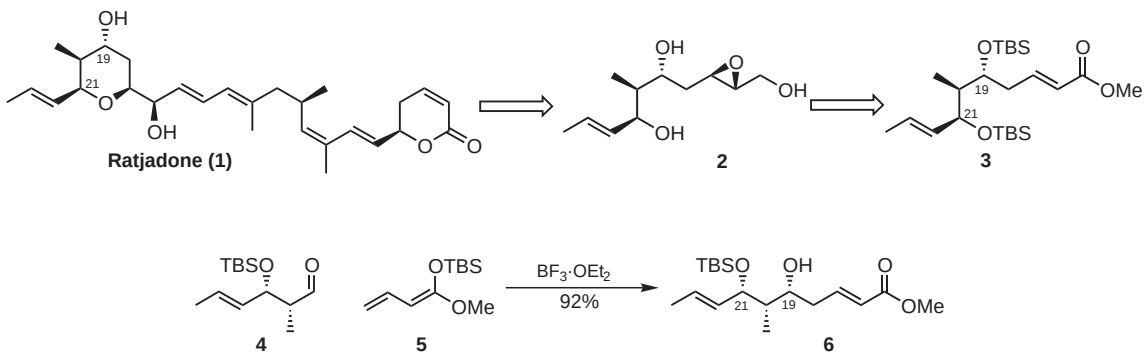



**Figure 1.** *Antiperiplanar* Felkin–Anh transition state.

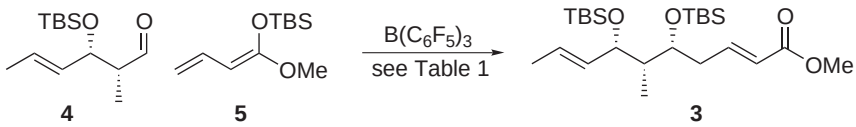



**Scheme 1.**

*Keywords*: vinylogous Mukaiyama aldol reaction; polyketide synthesis; ratjadone.

* Corresponding author. Fax: (+49)511-762-3011; e-mail: kalesse@mbox.oci.uni-hannover.de


PII: S0040-4039(00)02254-1




**Scheme 2.**

**Table 1.** Vinylogous Mukaiyama aldol reactions with different Lewis acids[10]

| Run | Lewis acid | Equiv. | Solvent | de (%) | Product (Yield %) | Temperature |
|---|---|---|---|---|---|---|
| 1 | $BF_3{\cdot}OEt_2$[a] | 1.5 | $CH_2Cl_2/Et_2O$ (9:1) | 50 | **6** (92) | −78°C |
| 2 | $Ti(OiPr)_4$ | 1.2 | $CH_2Cl_2$ | –[b] | – | 0°C→rt |
| 3 | $Ti(OiPr)_4$/BINOL | 1.2 | $CH_2Cl_2$ | –[b] | – | 0°C→rt |
| 4 | $TiCl_2(OiPr)_2$ | 2.0 | $CH_2Cl_2$ | –[b] | – | −78°C→rt |
| 5 | $TiCl_4$ | 1.0 | $CH_2Cl_2$ | –[c] | – | −78°C |
| 6 | $B(C_6H_5)_3$ | 1.0 | $CH_2Cl_2/Et_2O$ (9:1) | >90 | **6** (85) | −78°C |
| 7 | $B(C_6F_5)_3$ | 1.0 | $CH_2Cl_2/Et_2O$ (9:1) | >90 | **3** (81) | −78°C |
| 8 | $B(C_6F_5)_3$ | 0.5 | $CH_2Cl_2/Et_2O$ (9:1) | >90 | **3** (78) | −78°C |
| 9 | $B(C_6F_5)_3$ | 0.2 | $CH_2Cl_2/Et_2O$ (9:1) | >90 | **3** (74) | −78°C |
| 10 | $B(C_6F_5)_3$ | 0.1 | $CH_2Cl_2/Et_2O$ (9:1) | >90 | **3** (15) | −78°C |
| 11 | $B(C_6F_5)_3$ | 0.2 | $CH_2Cl_2$ | >90 | **3** (61), **6** (8) | −78°C |

[a] $BF_3{\cdot}OEt_2$ was distilled from $CaH_2$.
[b] No reaction.
[c] Decomposition.

1,3-asymmetric induction model[7] it can be deduced that a steric interaction between the nucleophile and the Lewis acid enhances the Felkin–Anh selectivity. Since diene **5** is—with respect to its reacting terminus—a small nucleophile we decided to use tris(pentafluorophenyl)borane as a bulky equivalent of $BF_3{\cdot}OEt_2$ (Fig. 1). This air-stable and water-tolerant Lewis acid was introduced by Yamamoto et al.[8] and is used for mild conversions in aldol-type reactions.

When we performed the reaction with $B(C_6F_5)_3$ under the same conditions as before for $BF_3{\cdot}OEt_2$, diastereoselective addition (de>90%) to aldehyde **4** was observed (Scheme 2). Additionally, we found complete transfer of the TBS group from the ketene acetal to the newly formed hydroxy group (**3**).

For a complete transfer of the TBS groups it was absolutely crucial to use a solvent mixture of $CH_2Cl_2$:$Et_2O$ (9:1). When the reaction was carried out in just $CH_2Cl_2$ a mixture of **3** (61%) and **6** (8%) was obtained (entry 11). $B(C_6F_5)_3$ can also be used in substoichiometric amounts (entries 8–10). Decreasing the amount of Lewis acid to 10 mol% causes a significant drop in the yield (entry 10). Interestingly, the use of the commercially less expensive triphenylborane gave the same selectivity but without transfer of the TBS group (entry 6). This is a remarkable finding since it was reported that classical Mukaiyama aldol reactions are not catalyzed by this Lewis acid.[8b] These two reagents can now be used alternatively depending on whether a free hydroxy group or, as in our case, a TBS ether is required. The use of other Lewis acids in this reaction such as $Ti(OiPr)_4$, $Ti(OiPr)_4$/BINOL,[9] $TiCl_2(OiPr)_2$, and $TiCl_4$ (entries 2–5) gave either no reaction or just decomposition (Table 1).

It could be demonstrated that the use of $B(C_6F_5)_3$ and $B(C_6H_5)_3$ in Lewis acid-mediated VMAR is a very promising alternative to $BF_3{\cdot}OEt_2$. By just changing the Lewis acid we could improve the diastereoselectivity from 50% de to over 90% de. Additionally, one has the option of whether the newly generated hydroxyl will be TBS-protected or remains unprotected for the subsequent introduction of a complementary protecting group. The excellent diastereoselectivity together with good yields make this variation of the Mukaiyama aldol reaction a very useful transformation in natural products syntheses.

## Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft, the Volkswagenstiftung (Meeresbiotechnologie) and the Fonds der Chemischen Industrie.

## References

1. Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972.
2. (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513; (b) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413–9436; (c) Mutou, T.; Suenaga, K.; Fujita, T.; Itoh, T.; Takada, N.; Hayamizu, K.; Kigoshi, H.; Yamada, K. *Synlett* **1997**, 199–201; (d) Bluet, G.; Campagne, J.-M. *Synlett* **2000**, 221–222.
3. (a) Schummer, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1995**, 685–688; (b) Gerth, K.; Schummer, D.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 973–976; (c) Claus, E.; Kalesse, M. *Tetrahedron*

*Lett*. **1999**, *40*, 4157–4160; (d) Christmann, M.; Kalesse, M. *Tetrahedron Lett*. **1999**, *40*, 7201–7204.
4. The diastereomeric ratio was determined by $^1$H NMR spectroscopy. The relative configuration at C19 was assigned by the conversion of the epimeric alcohols **6** into their corresponding acetonides. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett*. **1990**, *31*, 945–948; (b) Evans, D. A.; Rieger, D. L. *Tetrahedron Lett*. **1990**, *31*, 7099–7100; (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem*. **1993**, *58*, 3511–3515.
5. Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem*. **2000**, *112*, 4535–4538; *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 4364–4366.
6. Mahrwald, R. *Chem. Rev*. **1999**, *99*, 1095–1120.
7. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc*. **1996**, *118*, 4322–4343.
8. (a) Ishihara, K.; Hananki, N.; Yamamoto, H. *Synlett* **1993**, 577–579; (b) For a review, see: Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem*. **1999**, 527–538.
9. Bluet, G.; Campagne, J.-M. *Tetrahedron Lett*. **1999**, *40*, 5507–5509.
10. Synthesis of **3**: To the stirred solution (−78°C) of aldehyde **4** (24.2 mg, 0.1 mmol) and ketene acetal **5** (42.9 mg, 0.2 mmol) in 1 ml $CH_2Cl_2/Et_2O$ (9:1) was added tris(pentafluorophenyl)borane (10.2 mg, 0.02 mmol). The solution was allowed to warm to ambient temperature and evaporated in vacuo. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (18:1) to afford **3** (33.8 mg, 74% yield) as a colorless oil: $[\alpha]_D^{20} = -3.8$ (*c* 0.5, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.89 (dt, $J=15.7$, 7.5 Hz, 1H), 5.81 (dt, $J=15.7$, 1.5 Hz, 1H), 5.49 (ddq, $J=15.3$, 6.3, 0.6 Hz, 1H), 5.36 (ddq, $J=15.3$, 7.8, 1.1 Hz, 1H), 4.04 (dd, $J=7.8$, 5.9 Hz, 1H), 3.79 (dt, $J=5.9$, 4.4 Hz, 1H), 3.71 (s, 3H), 2.40 (m, 2H), 1.65 (dd, $J=6.4$, 1.6 Hz, 3H), 1.49 (ddq, $J=6.9$, 5.9, 4.4 Hz, 1H), 0.87 (d, $J=6.9$ Hz, 3H), 0.84–0.87 (2s, 9H), −0.03 to 0.02 (4s, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.8, 146.5, 133.8, 126.5, 122.7, 74.6, 71.7, 51.4, 44.6, 38.2, 25.9 (2C), 18.1, 17.6, 9.7, −3.7, −3.9, −4.5, −4.8; IR ($CHCl_3$): $\nu=$ 2995, 2930, 2886, 2857, 1716, 1255, 1075, 1035 cm$^{-1}$; MS (EI): $m/z$ (%) = 441 (1) $[M-CH_3]^+$, 399 (29) $[M-t\text{Bu}]^+$, 317 (35), 243 (46), 185 (100), 147 (24), 73 (71); HRMS (EI): $C_{23}H_{45}O_4Si_2$: calcd 441.2856; found 441.2855 $[M-CH_3]^+$.