ORGANIC LETTERS

2004
Vol. 6, No. 3
445−448

Diastereoselective Additions of Chiral Vinylzinc Reagents to α-Chiral Aldehydes

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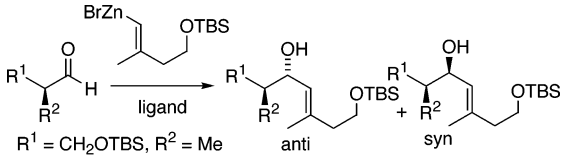
Received December 3, 2003

ABSTRACT



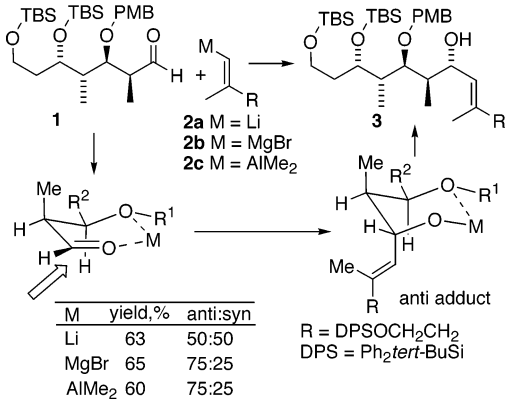
ligand	yield, %	anti:syn
none	74	45:55
Li(1*R*,2*S*)-NME*	70	>90:10
Li(1*S*,2*R*)-NME*	70	<10:90

* NME = *N*-methylephedrine

Additions of vinylic zinc bromide reagents to α-chiral aldehydes (R^1 = CH_2OTBS, R^2 = Me; R^1 = Me, R^2 = OTBS) in the presence of lithiated (+)- or (−)-*N*-methylephedrine proceed with predominant reagent control to afford anti or syn adducts stereoselectively, except when the aldehydes possess an alkoxy substituent at the α- or *β*-positions (R^1 = Me, R^2 = OBn; R^1 = CH_2OBn, R^2 = Me), in which case chelation-controlled adducts predominate.

In connection with a projected synthesis of callipeltoside[1,2] and related polyketide natural products, we were interested in effecting the chelation-controlled addition of a vinylmetal reagent such as **2** to an aldehyde **1**[3] to afford the anti adduct **3** (Scheme 1). Addition of the vinyllithium reagent **2a**, prepared by carboalumination−iodinolysis−lithiation as shown in Scheme 2,[4] was nonselective, affording a 1:1 mixture of the anti adduct **3** and the syn diastereomer. Although the Grignard reagent **2b**, prepared through transmetalation of reagent **2a** with $MgBr_2$, led to a significantly improved ratio of adducts favoring the anti isomer, the selectivity was less than desired. The most efficient route to

Scheme 1. Chelation-Controlled Additions of Vinylmetal Reagents **2a**−**c** to Aldehyde **1**



M	yield,%	anti:syn
Li	63	50:50
MgBr	65	75:25
$AlMe_2$	60	75:25

(1) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085.

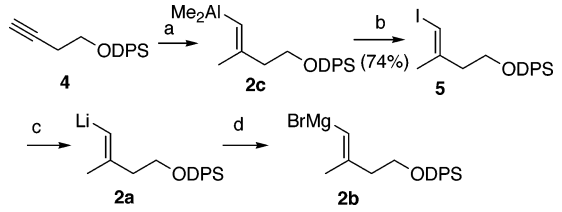
(2) Total syntheses: Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603. Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654. Trost, B. M.; Gunzer, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396. Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R.; Meyer, A. *Org. Lett.* **2003**, *5*, 4477.

(3) Aldehyde **1** was prepared by a route analogous to that described in Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Am. Chem. Soc.* **1998**, *63*, 817. Full details will be disclosed in due course.

(4) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

10.1021/ol0363568 CCC: $27.50
Published on Web 01/03/2004

Scheme 2. Preparation of Vinylmetal Reagents **2a**−**c**[a]



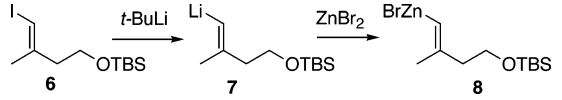
[a] (a) Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2, H_2O; (b) I_2 (74%, 2-steps); (c) *t*-BuLi; (d) $MgBr_2$.

3 involved in situ addition of aldehyde **1** to the carboalumination product, vinylalane **2c**. However, the selectivity of this process was no better than that observed with the Grignard reagent **2b**.

At this stage in our investigation, hoping to enhance the substrate preference for anti addition to aldehyde **1**, we decided to explore the use of a chiral ligand in the addition reaction. Additions of diorganozinc reagents to aldehydes catalyzed by chiral ligands have been extensively studied since Noyori's original discovery of the reaction in 1986.[5] The overwhelming majority of those studies were directed toward chiral ligand development with diethyl or dimethylzinc and simple achiral aldehydes.[6] In 1991 Oppolzer and Radinov reported a more synthetically useful variant of this reaction employing vinylzinc bromide reagents in which the lithium alkoxide derived from (1*S*,2*R*)-*N*-methylephedrine serves as a chiral ligand.[7] These reactions proceed through a chiral zinc complex and require a stoichiometric amount of the ligand. However, recovery of the chiral ligand is easily achieved through extraction of the reaction mixture with acid. Furthermore both enantiomers of *N*-methylephedrine are readily available in high optical purity.

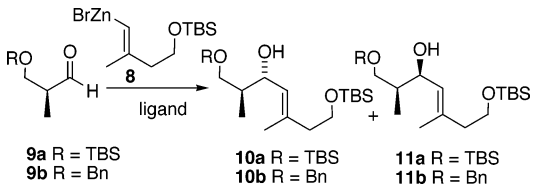
To date additions of this type have not generally been utilized in natural product synthesis despite the relative simplicity of the methodology and the reported high levels of enantioselectivity.[8] Moreover, only a few studies have addressed the issue of diastereoselectivity resulting from additions of organozinc reagents *of any kind* to chiral aldehydes.[9] In view of the potential of this methodology for applications in complex synthesis, we decided to examine reactions of vinylzinc reagents related to **2** with prototype chiral aldehydes. Our initial studies were conducted with the vinylzinc reagent **8**, prepared as shown in Scheme 3, from the TBS ether analogue **6** of vinyl iodide **5**.

Scheme 3. Preparation of the Vinylzinc Reagent **8**



Addition of the zinc reagent **8** to TBS-protected (*S*)-3-hydroxy-2-methylpropanal **9a**[10] proceeded with a slight Felkin−Anh preference, affording a 55:45 mixture of the syn and anti adducts **11a** and **10a** (Table 1). When the addition was conducted in the presence of the lithio derivative of (1*R*,2*S*)-*N*-methylephedrine, the anti adduct **10a** predominated by >90:10. Use of the enantiomeric *N*-methylephedrine reversed this product ratio in favor of the syn adduct **11a**. Addition of the zinc reagent **8** to the (*S*)-benzyloxy propanal **9b**[11] in the absence of chiral ligand afforded mainly the chelation-controlled anti adduct **10b** (75:25). This preference was increased to 95:5 when the addition was conducted in the presence of the (1*R*,2*S*) ligand (matched case). In the presence of the enantiomeric ligand the addition afforded a 75:25 mixture favoring the chelation-derived anti isomer **10b**. The stereochemistry of the foregoing adducts was confirmed by ^{1}H NMR analysis of the *O*-methyl mandelic esters.[12] Reactions of the vinylzinc reagent **8** with the chiral aldehydes **12a** and **12b**, derived from (*S*)-ethyl lactate, were examined next. The TBS-protected aldehyde **12a**[13] afforded a 65:35 mixture of adducts favoring the Felkin−Anh/Cornforth

Table 1. Additions of Vinylzinc Reagent **8** to the (*S*)-Aldehydes **9a** and **9b**

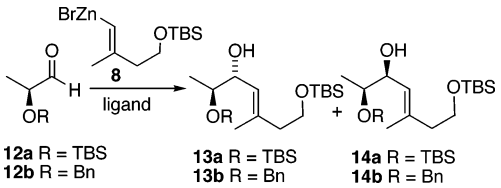


R	ligand	yield, %	**10**:**11**[a]
TBS (**9a**)	none	74	45:55
TBS (**9a**)	Li(1*R*,2*S*)-NME[b]	70	>90:10
TBS (**9a**)	Li(1*S*,2*R*)-NME[b]	70	<10:90
Bn(**9b**)	none	77	75:25
Bn (**9b**)	Li(1*R*,2*S*)-NME[b]	68	95:5
Bn (**9b**)	Li(1*S*,2*R*)-NME[b]	70	75:25

[a] ^{1}H NMR integration. [b] Li−NME = lithio *N*-methylephedrine ($PhCH(OLi)CH(NMe_2)CH_3$).

(5) Kitamura, M.; Suga, S.; Kawal, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
(6) For a recent comprehensive review, see: Pu. L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
(7) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.
(8) An intramolecular version of the reaction was employed by Oppolzer in reported syntheses of (*R*)-(−)-muscone and (+)-aspercilin, two relatively simple macrocylic natural products. Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593. Oppolzer, W.; Radinov, R. N.; De Brabander, J. *Tetrahedron Lett.* **1995**, *36*, 2607. See also: Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773.
(9) Soai, K.; Hatanaka, T.; Yamashita, T. J. *Chem. Soc., Chem. Commun.* **1992**, 927. Soai, K.; Shimada, C.; Takeuchi, M.; Itabashi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 567. Watanabe, M.; Komota, M.; Nishimura, M.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2193.
(10) Roush, W. R.; Palkowitz , A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(11) Marshall, J. A.; Yu, R. H.; Perkins, J. H. *J. Org. Chem.* **1995**, *60*, 5550.
(12) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.
(13) Massad, S.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5188.

Table 2. Additions of the Vinylzinc Reagent **8** to the (*S*)-Aldehydes **12a** and **12b**



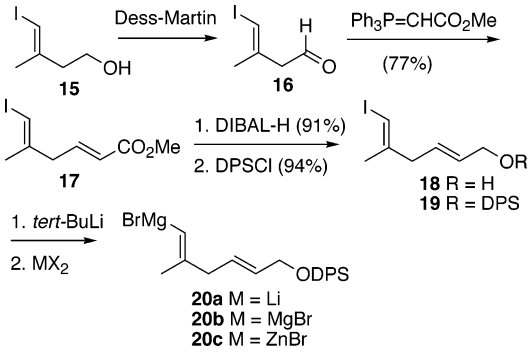
R	ligand	yield, %	**13**:**14**[a]
TBS (**12a**)	none	80	65:35
TBS (**12a**)	Li(1*R*,2*S*)-NME[b]	75	95:5
TBS (**12a**)	Li(1*S*,2*R*)-NME[b]	72	5:95
Bn(**12b**)	none	82	<5:95
Bn (**12b**)	Li(1*R*,2*S*)-NME[b]	72	15:85
Bn (**12b**)	Li(1*S*,2*R*)-NME[b]	76	<5:95

[a] ^{1}H NMR integration. [b] Li-NME = lithio *N*-methylephedrine (PhCH(OLi)CH(NMe$_2$)CH$_3$).

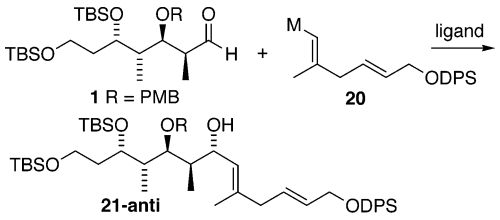
isomer **13a** in the absence of the chiral ligand. This ratio increased to 95:5 when the addition was conducted in the presence of the (1*R*,2*S*)-*N*-methylephedrine ligand. Use of the (1*S*,2*R*) ligand resulted in a predominance of the anti-Felkin−Anh adduct **14a** by an equal amount, indicative of a reagent-controlled process. Reactions conducted on the benzyl-protected aldehyde **12b**,[14] on the other hand, showed significant chelation control. In the absence of chiral ligand the addition led to a >95:5 mixture favoring the syn adduct **14b**. The (1*R*,2*S*) ligand was unable to overcome this substrate bias (mismatched pairing) as evidenced by the 85:15 ratio of adducts **14b**:**13b** in the presence of this ligand. As expected, the matched pairing strongly favored the syn adduct **14b**. Stereochemical assignments for these adducts are based upon ^{1}H NMR analysis of the *O*-methyl mandelic esters.[12]

Returning to our projected callipeltoside synthesis, to increase the convergency of our planned route we prepared the vinyl iodide **19**, a homologue of **6**, by the sequence outlined in Scheme 4. Addition of the lithio reagent **20a** to aldehyde **1** gave rise to a 1:1 mixture of adducts **21-anti** and **21-syn** (not shown, Scheme 5). As expected, the

Scheme 4. Preparation of Vinylmetal Reagents **20**



Scheme 5. Addition of Vinylmetal Reagents **20** to Aldehyde **1**



M	ligand	yield,%	anti:syn
Li	none	63	50:50
MgBr	none	63	75:25
ZnBr	none	68	80:20
ZnBr	Li(1*R*,2*S*)-NME	73	>90:10

Grignard reagent **20b** was more selective, affording a 3:1 mixture of anti and syn adducts. This ratio was slightly improved when the vinylzinc reagent **20c** was employed in the addition. Further improvement to >90:10 was realized in the presence of the (1*R*,2*S*) ligand.

To rationalize the enantioselectivity of their additions, Oppolzer and Radinov suggested the cyclic Zimmerman−Traxler-type transition state illustrated in Figure 1.[7] Although

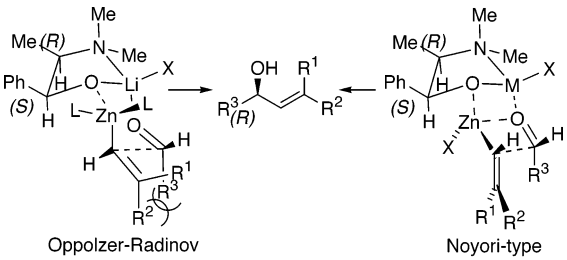


Figure 1. Proposed transition states for *N*-methylephedrine-directed addition reactions.

this arrangement accounts for the enantioselectivity, it is not compatible with their finding that the addition of (*E*)-1-propenylzinc bromide (R^1 = H, R^2 = CH$_3$) to pivaldehyde (R^3 = *t*-Bu) affords an adduct of higher ee than the corresponding addition of (*Z*)-1-propenylzinc bromide (R^1 = CH$_3$, R^2 = H). This observation is better accommodated by the currently accepted Noyori transition state for ligand-catalyzed additions of dialkylzinc compounds to aldehydes.[5,15]

In conclusion, the Oppolzer methodology appears well-suited for reagent-directed additions to chiral aldehydes except when a basic oxygen substituent resides at the α- or *β*-positions, whereupon chelation-controlled addition is highly favored. Although a stoichiometric amount of *N*-

(14) Ireland, R. E.; Thaisrivongs, S.; Dussalt, P. H. *J. Am. Chem. Soc.* **1998** *110*, 5768.

(15) For a recent application of this transition state to alkynylzinc reagents, see Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274.

methylephedrine is required, this ligand is easily recovered through acid extraction of the reaction mixture.

Acknowledgment. Funding for this research was provided by Grant R01 CA90383 from the National Cancer Institute.

Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0363568