Platinum-Catalyzed Tandem Diboration/Intramolecular Allylboration: Diastereoselective Access to Cyclohexanes Bearing 1,3-Diols

C. Eric Ballard, James P. Morken*

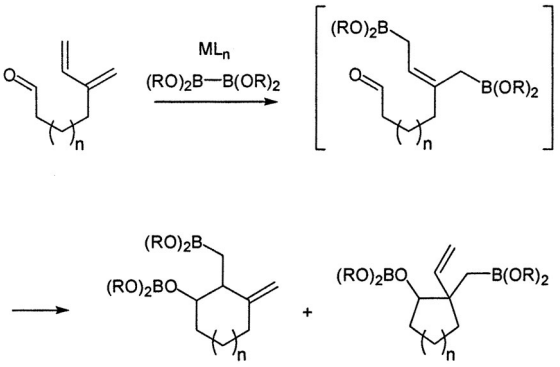
Department of Chemistry, Venable and Kenan Laboratories, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, 27599-3290, USA
Fax +1(919)9622388; E-mail: morken@unc.edu
Received 15 April 2004

Abstract: A tandem reaction sequence consisting of platinum-catalyzed diboration of 1,3-dienes followed by intramolecular allylboration and oxidative hydrolysis has been developed for constructing cyclic structures that bear a 1,3-diol. This methodology has proven effective for synthesizing cyclohexanes from dienals in good yields (44–64%) to generate diols containing two new vicinal stereocenters, one of which is quaternary. The products are obtained in high regio- and diastereomeric ratios (>19:1). A preexisting stereocenter on the substrate can provide high levels of asymmetric induction in the product.

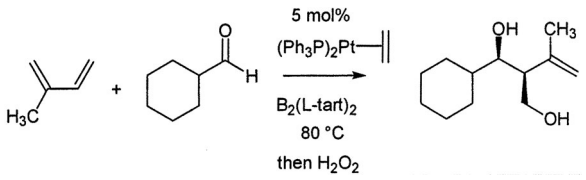
Key words: diboration, diene, platinum, allylboration, quaternary stereocenter

Addition of intermetallic reagents across the multiple bonds of organic substrates generates synthetically useful dimetallic species. To date, intermetallic reagents have been added across alkynes, enones, imines, alkenes, and dienes.[1] Recently our laboratory began a program in this area and demonstrated the first enantioselective addition of a diboron reagent across a simple olefin.[2] In addition, we have investigated the tandem 1,4-diboration/allylation involving chiral diborons and 1,3-dienes.[3–5] This reaction proceeds though the intermediacy of an allyl(bis)metal intermediate and we considered that if the precursor diene were tethered to the carbonyl, a useful carbocyclic ring-forming reaction may result (Scheme 1).[6] This reaction would provide two new stereocenters and, depending on the connectivity of the tether and the regioselectivity of the allylation, may introduce a quaternary stereocenter as well.

Concerned that the tethered aldehyde may react faster than the diene under diboration conditions thereby precluding development of the tandem reaction process, we first examined the diene diboration in the presence of an aldehyde. Exposure of isoprene, cyclohexanecarboxaldehyde and bis(diethyl-L-tartrateglycolato)diboron to 5 mol% $(Ph_3P)_2Pt$(ethylene) for 14 hours at 80 °C smoothly provided the derived tandem diboration/allylation product (75% conversion), indicating that the aldehyde does not interfere with diboration but will undergo allylation reactions with the allyl(bis)metal intermediate (Scheme 2).



Scheme 1

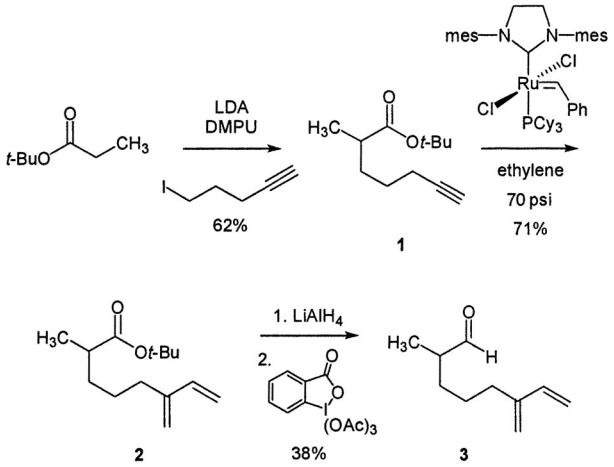


Scheme 2

Dienal **3** was chosen to initiate investigation on the tandem diboration/stereoselective intramolecular allylation reaction. Synthesis of the substrate proceeded as shown in Scheme 3. Finkelstein reaction of commercially available 5-chloropentyne followed by enolate alkylation gave ester **1**.[7] The alkyne was converted to the 1,3-diene by enyne metathesis using conditions developed by Diver.[8] Reduction of the ester followed by oxidation to the aldehyde provided **3** in reasonable yield.

With **3** in hand, development of the tandem reaction sequence was commenced. Initial investigations surveyed four diboron reagents: bis(diethyltartrato)diboron, bis(pinacolato)diboron, bis(neopentylglycolato)diboron and bis(catecholato)diboron [$B_2(cat)_2$]. We also surveyed a number of late transition metal complexes which are known to catalyze diboration and silaboration (see Table 1). Catalyst **4** has proven effective for addition of silaboranes across dienes[5b] while complex **5** is known for the diboration of simple olefins.[2] Complexes **6**–**8** have proven effective for diboration of dienes.[3,4b] Among the four diboron reagents investigated, only bis(catecholato)diboron exhibited reactivity with any of the transition metal complexes. As shown in Table 1, catalysts **7** and **8** were effective for the transformation of model substrate **3**

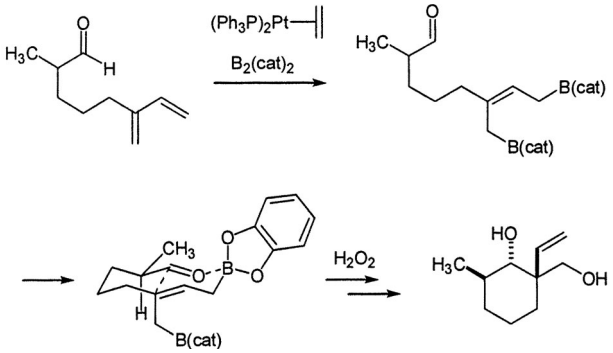
SYNTHESIS 2004, No. 9, pp 1321–1324
Advanced online publication: 18.05.2004
DOI: 10.1055/s-2004-822379; Art ID: C02304ST



Scheme 3

into diol **9** (entries 4 and 5) in the presence of bis(catecholato)diboron. Notably, in both cases the six-membered cyclic diol was produced to the exclusion of the seven-membered ring product and the level of stereoinduction was >19:1 as determined by ^{1}H NMR analysis. Optimization of reaction conditions indicated that the reaction proceeded equally well in THF at 60 °C and with 1.1 equivalents of bis(catecholato)diboron.

The major diastereomer produced in the tandem diboration/intramolecular allylation reaction is as depicted in Scheme 4. The assignment was determined by analysis of ^{1}H NMR coupling constants in conjunction with NOESY data. The major product diastereomer appears to arise from a *Z*-selective [1,4]-diboration of the 1,3-diene followed by allylation through a six-membered transition structure wherein the methyl group occupies an equatorial position. The relative stereochemistry of product **9** was assigned as follows (Figure 1). The coupling constant between H_a and H_b was 10.0 Hz, implying that they lie in an axial-axial orientation.[9] A NOESY experiment indicated there was a shorter distance between H_a and the protons of



Scheme 4

the methyl group than between H_a and H_b. These observations indicate that the methyl group and the vicinal alcohol bear a *trans* relationship. The NOESY experiment indicated closer proximity between H_a and the protons of the vinyl group than between H_a and the carbinol protons of the hydroxymethyl group. This indicates a *cis* relationship between the secondary hydroxyl group and the hydroxymethyl group.

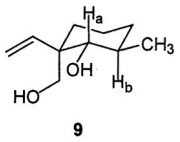
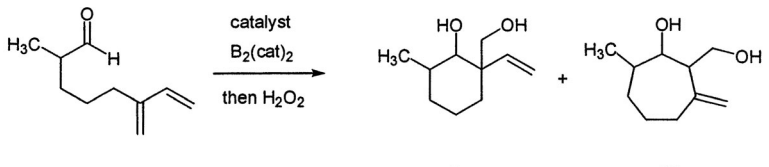


Figure 1

In order to determine the effect of substitution at an alternate location and the effect of alternate tether lengths, we examined other substrates. Using a similar reaction sequence as described in Scheme 2, the substrates depicted in Scheme 5 were prepared. Compounds **11**, **13** and **15**, which have the same tether length between the aldehyde and the diene as the model substrate **3**, were each efficient substrates for the reaction and all provided the six-membered carbocycle with a high level of stereoselection. The

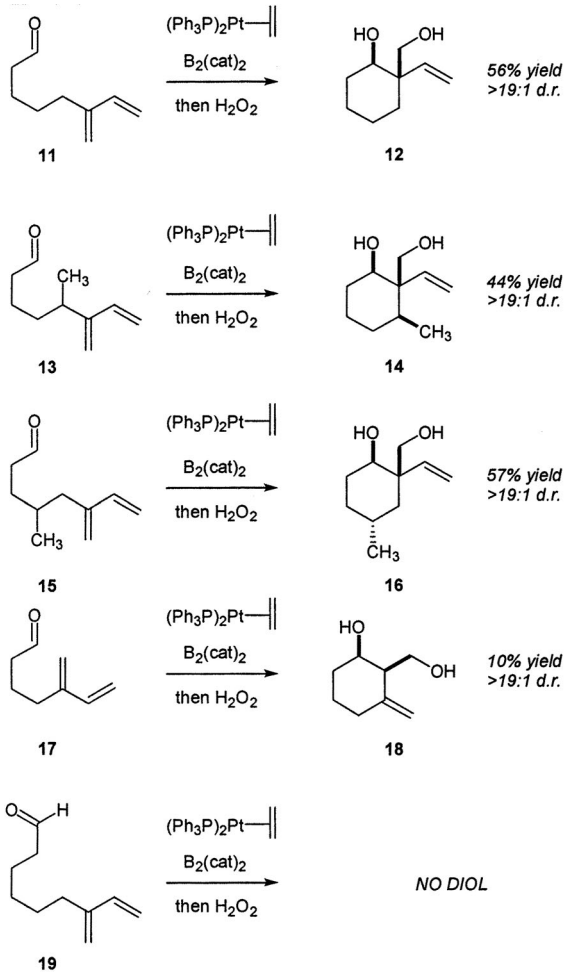
Table 1 [a] Screening of Catalysts for the Diene Diboration/Intramolecular Allylboration



Entry	Catalyst	Conditions	% Yield	**9**:**10** (dr)
1	$Ni(acac)_2$/DIBAL (**4**)	toluene, 80 °C, 20 h	0	–
2	(nbd)Rh(acac)/quinap (**5**)	THF, r.t., 14 h	0	–
3	$Pt(dba)_2$ (**6**)	benzene, 80 °C, 24 h	0	–
4	$Pt(dba)_2/PCy_3$ (**7**)	benzene, 80 °C, 24 h	30	>19:1 (>19:1)
5	$(Ph_3P)_2Pt(CH_2{=}CH_2)$ (**8**)	benzene, 80 °C, 24 h	64	>19:1 (>19:1)

[a] Experiments were conducted with 1.5 equiv of bis(catecholato)diboron.

stereoinduction from the existing stereocenter in substrates **13** and **15** was also high (>19:1). The sense of induction was ascertained for compound **16** by X-ray structure analysis and for **14** by analogy with the chair-like transition state model as described above. Dienal **17**, with one less carbon in the tether, may react to form either a five-membered or six-membered ring product and appears to provide exclusively the cyclohexyl derivative. While the yield for this transformation is low, the stereoselection still remains high. When the tether length is increased such that either a seven-membered or eight-membered ring may result, the reaction fails to provide the tandem reaction product.



Scheme 5

In conclusion, we have developed a tandem diene diboration/intramolecular allylboration that allows stereoselective access to cyclohexanes bearing 1,3-diols from linear dienals. Preexisting stereocenters on the tether can be used to control the stereochemistry of the new chiral centers. Efforts directed toward catalytic asymmetric dimetalation reactions continue in our laboratory

^{1}H NMR spectra were recorded on Bruker DRX (400 MHz or 300 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. ^{13}C NMR spectra were recorded on a Bruker 400 MHz (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). IR spectra were obtained of solutions of analytes dissolved in CH_2Cl_2 using a Nicolet 560 infrared spectrometer.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 32–63 μm) purchased from Scientific Absorbents or Sorbent Technologies. TLC was performed on EM science 0.25 mm silica gel 60 plates. Visualization was achieved with phosphomolybdic acid in EtOH followed by heating. All reactions were conducted in oven and flame dried glassware under an inert atmosphere of dry nitrogen or dry argon. Deuterated solvents were used as received. Benzene was distilled from CaH_2 and freeze-pump-thaw degassed. Toluene was passed through activated basic alumina. Anhydrous THF was purchased from Aldrich Chemical Companies and used as received. $Pt(dba)_2$ was synthesized by a literature procedure.[10] All other reagents were purchased from Aldrich Chemical Companies and used directly.

Diboration/Intramolecular Allylboration; General Procedure

Under an atmosphere of argon, the dienal (0.1 mmol) was dissolved in anhyd THF (0.8 mL). Bis(catecholato)diboron (1.1 equiv) and ethylenebis(triphenylphosphine)platinum(0) (0.05 equiv) were added. The reaction vial was capped and magnetically stirred in a 60 °C oil bath for 24 h. The reaction mixture was diluted with anhyd THF (2 mL) and NaOH (3 M, 0.4 mL) and H_2O_2 (30%, 0.4 mL) were added dropwise. The mixture was stirred at r.t. for 3 h. The oxidation was quenched by cautious addition of sat. $Na_2S_2O_3$ (3 mL). The presence of peroxide was checked with starch/KI paper. This mixture was diluted with deionized water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with NaOH (0.5 M, 2 × 5 mL), dried ($MgSO_4$), filtered, rotary evaporated, and purified by flash chromatography (EtOAc–hexanes, 1:1).

Compound 9

IR: 3614, 3502, 2931, 2858, 2871, 2339, 1721, 1636, 1480, 1463, 1437, 1395, 1378, 1368, 1339, 1152, 1098, 1048, 1005 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.05 (dd, *J* = 17.6, 11.0 Hz, 1 H), 5.28 (dd, *J* = 17.6, 1.0 Hz, 1 H), 5.23 (dd, *J* = 11.0, 1.0 Hz, 1 H), 4.21 (d, *J* = 11.4 Hz, 1 H), 3.62 (d, *J* = 11.4 Hz, 1 H), 3.21 (d, *J* = 10.0 Hz, 1 H), 2.91 (br s, 1 H), 2.73 (br s, 1 H), 1.98–1.85 (m, 2 H), 1.79–1.72 (m, 1 H), 1.63–1.35 (m, 3 H), 1.22–1.11 (m, 1 H), 1.17 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 144.0, 114.2, 82.1, 64.9, 45.5, 34.6, 33.9, 33.7, 21.0, 19.0.

HRMS–FAB: *m/z* [M + Li] calcd for $C_{10}H_{18}O_2Li$: 177.1467; found: 177.1462.

Compound 12

IR: 3610, 3498, 3083, 3056, 2939, 2865, 2667, 2358, 2341, 2254, 1733, 1636, 1451, 1418, 1376, 1046, 1000, 990, 924, 911 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.81 (dd, *J* = 17.8, 11.4 Hz, 1 H), 5.26 (dd, *J* = 11.4, 1.0 Hz, 1 H), 5.21 (dd, *J* = 17.8, 1.0 Hz, 1 H), 3.88 (dd, *J* = 6.4, 3.0 Hz, 1 H), 3.92–3.86 (m, 1 H), 3.82 (d, *J* = 11.4 Hz, 1 H), 3.57 (d, *J* = 11.4 Hz, 1 H), 2.48 (s, 2 H), 1.81–1.58 (m, 3 H), 1.50–1.21 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 142.4, 115.4, 74.3, 67.6, 45.4, 30.2, 29.5, 21.9, 21.1.

HRMS–FAB: *m/z* [M + Li] calcd for $C_9H_{16}O_2Li$: 163.1310; found: 163.1306.

Compound 14

IR: 3606, 3491, 3083, 3054, 2939, 2865, 2362, 2342, 2331, 1731, 1636, 1609, 1463, 1451, 1434, 1422, 1380, 1345, 1326, 1194, 1138, 1065, 1042, 1001, 990, 947, 919 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 5.81 (ddd, *J* = 17.9, 11.0, 1.0 Hz, 1 H), 5.46 (dd, *J* = 17.9, 1.0 Hz, 1 H), 5.40 (dd, *J* = 11.0, 1.0 Hz, 1 H), 4.23 (d, *J* = 11.4 Hz, 1 H), 3.86 (d, *J* = 11.4 Hz, 1 H), 3.69–3.63 (m, 1 H), 3.12 (br s, 1 H), 2.81 (br s, 1 H), 1.99–1.62 (m, 3 H), 1.50–1.16 (m, 4 H), 0.80 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 143.0, 116.4, 78.7, 61.5, 48.4, 39.0, 29.6, 29.3, 24.0, 16.0.

HRMS–FAB: *m*/*z* [M + Li] calcd for $C_{10}H_{18}O_2Li$: 177.1467; found: 177.1461.

Compound 16

IR: 3946, 3755, 3693, 3157, 3054, 2987, 2686, 2522, 2306, 2256, 1794, 1638, 1561, 1422, 1272, 1158, 1096 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.04 (dd, *J* = 17.6, 11.0 Hz, 1 H), 5.28 (dd, *J* = 17.6, 1.0 Hz, 1 H), 5.23 (dd, *J* = 11.0, 1.0 Hz, 1 H), 4.26 (dd, *J* = 11.6, 3.4 Hz, 1 H), 3.72–3.61 (m, 2 H), 2.50 (d, *J* = 4.7 Hz, 1 H), 2.33–2.32 (m, 1 H), 1.88–1.87 (m, 1 H), 1.79–1.52 (m, 3 H), 1.25 (s, 1 H), 0.95–0.84 (m, 2 H), 0.85 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 143.8, 114.5, 76.7, 64.7, 45.9, 42.2, 33.5, 30.6, 27.2, 22.2.

Compound 18

IR: 3610, 3502, 3076, 3054, 2939, 2867, 2362, 2342, 2323, 1733, 1684, 1646, 1449, 1439, 1420, 1391, 1200, 1171, 1154, 1048, 1013, 984 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.91 (s, 1 H), 4.79 (s, 1 H), 4.13–4.01 (m, 2 H), 3.78 (dd, *J* = 11.1, 5.6 Hz, 1 H), 2.58–2.52 (m, 1 H), 2.37 (br s, 2 H), 2.17–2.02 (m, 2 H), 1.86–1.66 (m, 4 H), 1.58–1.47 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 146.2, 110.5, 71.4, 62.3, 50.1, 33.9, 31.8, 23.2.

HRMS–FAB: *m*/*z* [M + Li] calcd for $C_8H_{14}O_2Li$: 149.1154; found: 149.1157.

Acknowledgment

This work was supported by the NIH (GM 59417-03). JPM is an Alfred P. Sloan Research Fellow and a Packard Foundation Fellow and thanks AstraZeneca, Bristol-Myers Squib and GlaxoSmithKline for support.

References

(1) Reviews with representative reactions: (a) Marder, T. B.; Norman, N. C. *Top. Catal.* **1998**, *5*, 63. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. (c) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392.
(2) (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702. (b) Miller, S. P.; Morgan, J. B.; Nepveux, F. J. V.; Morken, J. P. *Org. Lett.* **2004**, *6*, 131.
(3) Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, *5*, 2573.
(4) (a) Ishiyama, T.; Masafumi, Y.; Miyaura, N. *Chem. Commun.* **1996**, 2073. (b) Clegg, W.; Thorsten, J.; Marder, T. B.; Noman, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc., Dalton Trans.* **1998**, 1431.
(5) Examples of diastereoselective silaboration/allylboration: (a) Suginome, M.; Nakamura, H.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4248. (b) Suginome, M.; Matsuda, T.; Yoshimoto, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1567.
(6) (a) Hoffmann, R. W.; Sander, T.; Hense, A. *Liebigs Ann. Chem.* **1993**, 771. (b) Hoffmann, R. W.; Sander, T. *Liebigs Ann. Chem.* **1993**, 1185. (c) Watanabe, T.; Sakai, M.; Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1994**, 467. (d) Ahiko, T.-a.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **1997**, 811.
(7) Cookson, R. C.; Liverton, N. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1589.
(8) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271.
(9) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. In *Spectrometric Identification of Organic Compounds*, 5th ed.; New York: Wiley, **1991**, 221.
(10) Cherwinski, W. J.; Johnson, B.; Lewis, J. *J. Chem. Soc., Dalton Trans.* **1974**, 1404.