

Regio- and diastereocontrolled C–H insertion of chiral γ - and δ -lactam diazoacetates. Application to the asymmetric synthesis of (8*S*,8*aS*)-8-hydroxyindolizidine†

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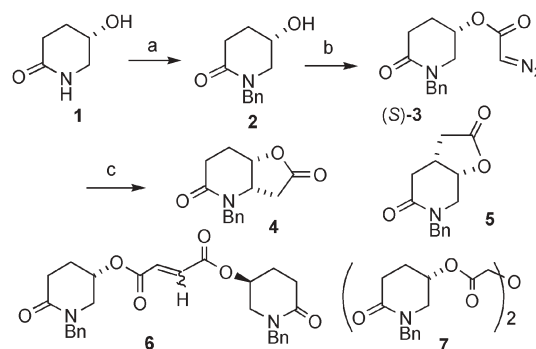
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γ - and δ -Lactam diazoacetates undergo efficient intramolecular C–H insertion catalyzed by $\text{Rh}_2(\text{MPPIM})_4$ with excellent regioselectivity and *cis*-diastereoselectivity to provide synthetically useful bicyclic lactam lactones.

The Rh(II)-catalyzed intramolecular carbon–hydrogen insertion reaction continues to attract considerable attention due to the high levels of regio-, chemo- and diastereoselectivity that can be achieved.¹ A decade ago, Doyle reported the intramolecular C–H insertion reactions of chiral non-racemic alkyl substituted cyclohexyl diazoacetates catalyzed by dirhodium(II) carboxamides.^{2a} The catalysts showed a matched/mismatched relationship to the diazo substrates; $\text{Rh}_2(\text{MEPY})_4$ and $\text{Rh}_2(\text{MEOX})_4$ emerged as effective catalysts, which promoted highly regioselective C–H insertion into equatorial secondary and tertiary C–H bonds to give lactone products. The regioselectivity in $\text{Rh}_2(\text{MPPIM})_4$ -catalyzed reactions, however, was found to be substrate dependent.² The regio- and diastereoselectivity of C–H insertion in equivalent heterocyclic diazoacetates have not been extensively examined. Previously, we showed the Rh(II)-carboxamidate-catalyzed C–H insertion of 3-(*N*-Cbz-pyrrolidinyl)diazoacetate did not exhibit a matched/mismatched relationship, and also demonstrated the use of the method in the synthesis of (–)-turneforcidine.³ In keeping with our ongoing interest in the synthesis of piperidine- and pyrrolidine-containing alkaloids, we needed access to functionalized piperidine and pyrrolidine building blocks that would permit the facile assembly of a wide variety of substituents and stereochemical diversity around the pyrrolidine and piperidine framework. We investigated the rhodium(II)-catalyzed diazo decomposition of γ - and δ -lactam diazoacetates and, herein, report the results of our study.

δ -Lactam diazoacetate (*S*)-**3** was readily obtained (Scheme 1) from the known⁴ (*S*)-5-hydroxy-2-piperidinone (**1**) via hydroxyl group protection (TBDMSCl) and *N*-benzylation. *O*-Desilylation (HCl, MeOH) then afforded the alcohol **2** $\{[\alpha]_{\text{D}}^{22} -16.7^\circ$ (*c* 3.30, CHCl_3), 89% over three steps}. Treatment of **2** with *p*-TSHACl⁶ gave an excellent yield (98%) of (*S*)-**3** $\{[\alpha]_{\text{D}}^{25} +25.0^\circ$ (*c* 5.90, CHCl_3)}. The diazoacetate (*S*)-**3** was evaluated against achiral and chiral Rh(II) carboxylate and carboxamidate catalysts to delineate



Scheme 1 Reagents and conditions: a. (i) TBDMSCl, imidazole, DMAP, DMF, 40 °C; (ii) BnBr, NaH, DMF; (iii) HCl, MeOH; 89%; b. *p*-TSHACl, PhNMe₂, *i*Pr₂NEt, CH₂Cl₂, 0 °C, 98%; c. Rh(II) cat. (2 mol%), CH₂Cl₂, reflux (see Table 1 for details).

optimal reaction conditions for C–H insertion reaction and to determine product distribution.

In general, it was found that chiral Rh(II) catalysts were better than achiral ones at promoting C–H insertion reaction (Table 1). Carbon–hydrogen insertion was inefficient with $\text{Rh}_2(\text{OAc})_4$ and the less electrophilic $\text{Rh}_2(\text{cap})_4$ as catalysts. The use of $\text{Rh}_2(\text{S-PTTL})_4$ led to a noticeable improvement on the yield (28%) of **4**, however, the yield of **4** was synthetically unacceptable. We then turned our attention to three enantiomeric pairs of Rh(II) carboxamides and evaluated their efficiency in catalyzing the C–H insertion reaction of (*S*)-**3**.

With $\text{Rh}_2(\text{5S-MEPY})_4$, a modest yield (45%) of **4** was obtained and the outcome was encouraging. However, the enantiomeric $\text{Rh}_2(\text{5R-MEPY})_4$ gave a significantly lower yield of **4** (14%). In all the cases (entries 1–5) studied thus far, the regioisomer **5** was not

Table 1 Rh(II)-catalyzed reaction of (*S*)-**3**^a

Entry	Rh_2L_4	4 (%)	5 (%)	6 (%) (<i>E</i> : <i>Z</i>) ^b	7 (%)
1	$\text{Rh}_2(\text{OAc})_4$	6	0	14 (1 : 1)	21
2	$\text{Rh}_2(\text{cap})_4$	11	0	64 (1 : 3)	23
3	$\text{Rh}_2(\text{S-PTTL})_4$	28	0	11 (1 : 3)	0
4	$\text{Rh}_2(\text{5S-MEPY})_4$	45	0	28 (1 : 3)	13
5	$\text{Rh}_2(\text{5R-MEPY})_4$	14	0	12 (1 : 3)	3
6	$\text{Rh}_2(\text{4S-MEOX})_4$	44	0	28 (1 : 3)	9
7	$\text{Rh}_2(\text{4R-MEOX})_4$	16	23	0	12
8	$\text{Rh}_2(\text{4S-MPPIM})_4$	87	0	0	3
9	$\text{Rh}_2(\text{4R-MPPIM})_4$	14	72	0	10

^a Product yields are isolated yields. ^b Ratio of *E* : *Z* isomers was based on the integration of the singlets due to the olefinic hydrogens centered at δ 6.12 (*Z*) and δ 6.64 (*E*).

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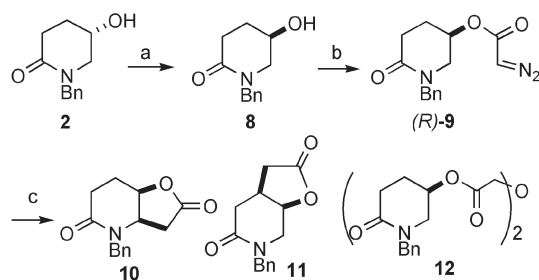
detected. The results from the reactions catalyzed by the $\text{Rh}_2(4S/R\text{-MEOX})_4$ and $\text{Rh}_2(4S/R\text{-MPPIM})_4$ were especially interesting and displayed important differences from those obtained from $\text{Rh}_2(S\text{-PTTL})_4$ and $\text{Rh}_2(5R/S\text{-MEPY})_4$. Although the result obtained for $\text{Rh}_2(4S\text{-MEOX})_4$ mirrored that for $\text{Rh}_2(5S\text{-MEPY})_4$ (see entries 4 and 6), the reaction catalyzed by $\text{Rh}_2(4R\text{-MEOX})_4$ gave a 1 : 1.4 ratio of **4** : **5** in a combined yield of 39% (entry 7). The use of the hindered $\text{Rh}_2(4S\text{-MPPIM})_4$ resulted in the highest yield (87%) of **4**, whereas with $\text{Rh}_2(4R\text{-MPPIM})_4$, the regioisomer **5** was formed as the major product (72%). The C–H insertion reaction proceeded with excellent regioselectivity and *cis*-diastereoselectivity, which was confirmed by NOESY1D. Neither the *trans*-fused γ - nor spirocyclic β -lactones were detected, in contrast to the results from $\text{Rh}_2(\text{MPPIM})_4$ -catalyzed intramolecular C–H insertion reaction of cyclohexyl diazoacetates.^{2a}

To confirm the above outcome, the enantiomeric diazoacetate (*R*)-**9** was synthesized (Scheme 2). (*S*)-Alcohol **2** was transformed to its enantiomer **8** $\{[\alpha]_{\text{D}}^{22} +17.4^\circ$ (*c* 3.30, CHCl_3)}, via Mitsunobu inversion⁷ ($\text{ClCH}_2\text{CO}_2\text{H}$, DEAD, Ph_3P) and subsequent base hydrolysis. Alcohol **8** was treated with *p*-TSHACl⁶ to give the desired diazoacetate (*R*)-**9** $\{[\alpha]_{\text{D}}^{25} -22.0^\circ$ (*c* 5.90, CHCl_3)}. The $\text{Rh}_2(4R\text{-MPPIM})_4$ -catalyzed reaction of (*R*)-**9** gave a high yield (85%) of bicyclic lactam lactone **10**, but with $\text{Rh}_2(4S\text{-MPPIM})_4$, the major product obtained was the regioisomer **11** (68%).

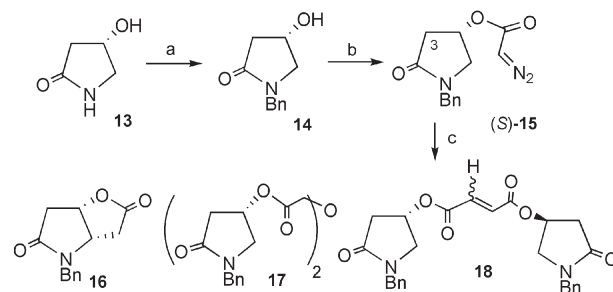
These results show that the optimal catalyst for achieving high regioselectivity in the formation of bicyclic lactam lactone is the use of $\text{Rh}_2(\text{MPPIM})_4$ as catalyst; (*S*)-**3**/ $\text{Rh}_2(4S\text{-MPPIM})_4$ and (*R*)-**9**/ $\text{Rh}_2(4R\text{-MPPIM})_4$ represent the matched pairs for highly regioselective C–H insertion reaction.

Next, the efficiency and regioselectivity of the C–H insertion reaction of the γ -lactam diazoacetate **15** were studied. Compound **15** was synthesized (Scheme 3) from commercially available (*S*)-4-hydroxy-2-pyrrolidinone (**13**)⁸ in the manner described for compound (*S*)-**3**.

On the basis of the results obtained for (*S*)-**3**, we chose $\text{Rh}_2(4S/4R\text{-MEOX})_4$ and $\text{Rh}_2(4S/4R\text{-MPPIM})_4$ as catalysts. The results in Table 2 clearly show that reaction temperature has a definite influence on the efficiency of the reaction. In refluxing CH_2Cl_2 , which was found to be effective for (*S*)-**3**, poor to moderate yields of the C–H insertion product **16** were obtained (entries 1, 3). Gratifyingly, a significantly higher yield (70%) of **16** was realized when the $\text{Rh}_2(4S\text{-MPPIM})_4$ -catalyzed reaction of (*S*)-**15** was



Scheme 2 Reagents and conditions: a. (i) $\text{ClCH}_2\text{CO}_2\text{H}$, Ph_3P , DEAD, CH_2Cl_2 ; (ii) K_2CO_3 , MeOH; 70%; b. *p*-TSHACl, PhNMe_2 , $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 0 °C, 98%; c. $\text{Rh}_2(4R\text{-MPPIM})_4$ (2 mol%), CH_2Cl_2 , reflux, **10** (85%), **11** (0%), **12** (4%); $\text{Rh}_2(4S\text{-MPPIM})_4$ (2 mol%), CH_2Cl_2 , reflux, **10** (17%), **11** (67%), **12** (14%).



Scheme 3 Reagents and conditions: a. (i) TBDMSCl, imidazole, DMAP, DMF, 40 °C; (ii) BnBr, BuLi, DMF, THF, -15 °C; (iii) HCl, MeOH; 82%; b. *p*-TSHACl, PhNMe_2 , $i\text{Pr}_2\text{NEt}$, DCM, 0 °C, 98%; c. Rh cat. (2 mol%), CH_2Cl_2 or 1,2-dichloroethane, reflux (see Table 2 for details).

Table 2 Rh(II)-catalyzed reaction of (*S*)-**15**

Entry	Rh_2L_4	Solvent	16 (%)	17 (%)	18 (%) (<i>E</i> : <i>Z</i>) ^b
1	$\text{Rh}_2(4S\text{-MEOX})_4$	CH_2Cl_2	17	21	20 (1 : 11)
2	$\text{Rh}_2(4R\text{-MEOX})_4$	CH_2Cl_2	0	13	11 (1 : 33)
3	$\text{Rh}_2(4S\text{-MPPIM})_4$	CH_2Cl_2	51	28	20 (2.4 : 1)
4	$\text{Rh}_2(4R\text{-MPPIM})_4$	CH_2Cl_2	0	37	30 (1.5 : 1)
5	$\text{Rh}_2(4S\text{-MPPIM})_4$	DCE ^a	70	11	7 (only <i>E</i>)
6	$\text{Rh}_2(4R\text{-MPPIM})_4$	DCE	0	19	0

^a DCE = 1,2-dichloroethane. ^b Ratio of *E* : *Z* isomers was based on the integration of the singlets due to the olefinic hydrogens centered at δ 6.23 (*Z*) and δ 6.77 (*E*).

conducted in refluxing 1,2-dichloroethane, whereas the corresponding *R*-catalysts failed to give any C–H insertion products. Further, unlike (*S*)-**3**, the *R*-catalysts did not lead to $\text{C}_3\text{--H}$ insertion to form the corresponding regioisomer of **16**. Neither *trans*-**16** nor the spirocyclic β -lactone was detected.

Using the $\text{Rh}_2(4S\text{- or }4R\text{-MPPIM})_4$ -catalyzed reaction of (*S*)-**3** as an example, we envisioned the formation of **4** and **5** to proceed via the rapidly interconverting reactive conformers^{9,10} **A**, **A'**, **B** and **B'** depicted in Fig. 1. In conformers **A** and **A'**, the Rh(II)-carbenoid moiety is oriented in the pseudoaxial and pseudoequatorial positions, respectively. Lactone **4** is formed

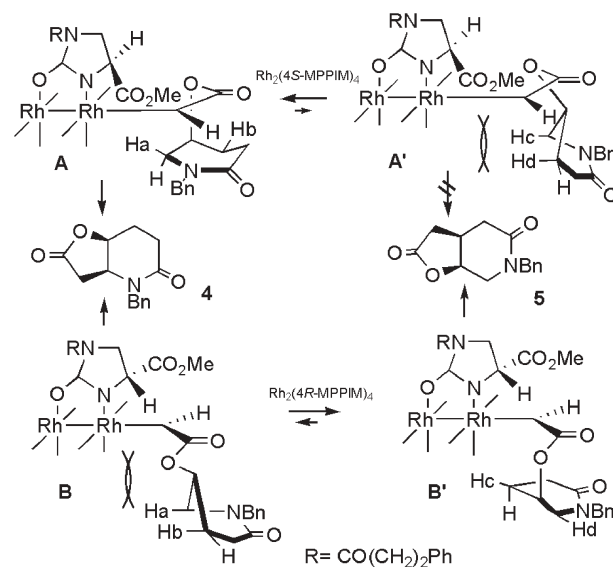
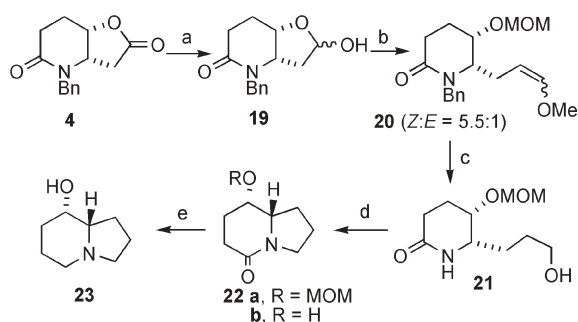


Fig. 1 Reactive conformer models for reaction of (*S*)-**3**.



Scheme 4 Reagents and conditions: a. Red-Al, THF–PhMe, -78°C , 94%; b. (i) $\text{Ph}_3\text{P}=\text{CHOMe}$, THF, -40°C , 74%, (ii) MOMCl, cat. Bu_4NI , $i\text{-Pr}_2\text{NEt}$, 89%; c. (i) Na, liq. NH_3 ; NH_4Cl , quant., (ii) 1 M aq. HCl then NaBH_4 , 76%; d. (i) TsCl, Et_3N , cat. DMAP, 91%, (ii) NaH, 95%; e. (i) 1 M aq. HCl, MeOH, 95%, (ii) $\text{BH}_3\cdot\text{SMe}_2$, THF; then EtOH, reflux, 88%.

preferentially through metalcarbenoid insertion into C–Ha (A) as the Rh(II)-carbene and C–Ha σ -bond are aligned parallel to each other and the insertion is also facilitated by the greater nucleophilicity of the σ -bond (early TS) due to the activating influence of the amide nitrogen atom.¹¹ Insertion of the Rh(II)-carbenoid into C–Hb (A) is prevented from occurring because the C–Hb σ -bond and the Rh(II)-carbenoid bond cannot adopt the proper alignment. Conformer A' is destabilized by steric interaction of the pseudoaxial C–Hc and C–Hd with the ligand wall/N–C(O)(CH₂)₂Ph of the Rh(II) catalyst. Thus, regioisomer 5 is not formed.

In the mismatched $\text{Rh}_2(4R\text{-MPPIM})_4$ -catalyzed reaction, conformer B is destabilized by the interaction of C–Ha and C–Hb with the ligand wall/N–C(O)(CH₂)₂Ph. However, because C–Ha is activated by the amide nitrogen, its interaction with the vacant p-orbital of the Rh(II)-carbenoid carbon can occur at a greater distance (early TS) resulting in the formation of the minor product 4. With B', the Rh(II)-carbenoid bond and the C–Hc bond are properly aligned and C–H insertion leads to the regioisomer 5 as the major product. Insertion into C–Hd, as with C–Hb in A, is unattainable for geometric reasons.

For (S)-15, the absence of the regioisomer of 16 suggests that the C₃–H bond in 15 is deactivated towards metalcarbenoid insertion by the amide carbonyl group. This outcome taken together with that obtained in the $\text{Rh}_2(4R\text{-MPPIM})_4$ -catalyzed reaction of (S)-3 to form 5 indicated that C–H bonds located α to an amide carbonyl group are deactivated towards Rh(II)-carbenoid insertion; β -C–H bonds are not deactivated.¹²

To demonstrate the utility of the bicyclic lactam lactone products, the enantioselective synthesis of (8S,8aS)-8-hydroxyoctahydroindolizidine¹³ (23) starting from 4 was conducted. Several syntheses^{13a–d} of ($\pm$)-23 have been described; only one asymmetric synthesis of (8S,8aS)-23, which was obtained in 13 steps and 17% overall yield from a chiral non-racemic 4-formyl- β -lactam intermediate,^{13e} was reported. Our building block 4 already has the correct configurations at the two stereocentres and seven of the eight carbons of the carbon framework in 23.

The synthesis began with the chemoselective reduction of 4 with Red-Al[®], which gave an excellent yield of the bicyclic lactam lactol 19 (Scheme 4). Wittig olefination ($\text{Ph}_3\text{P}=\text{CHOMe}$) followed by MOM protection of the secondary alcohol gave the ether 20 as a

mixture of Z/E diastereomers. N-Debenzylation¹⁴ of 20 was followed by hydrolysis of the enol ether unit and NaBH_4 reduction to provide the primary alcohol 21 in an overall yield of 76%. Tosylation of 21 and cyclization of the primary tosylate (NaH) yielded the bicyclic lactam 22a (95%). MOM ether deprotection of 22a gave 22b,^{13e} subsequent reduction of the lactam carbonyl group ($\text{BH}_3\cdot\text{SMe}_2$) afforded, initially, a very stable, non-polar 23 : borane complex as a white solid.¹⁵ The volatile indolizidine 23 was obtained only after refluxing the 23 : borane complex in 95% ethanol for 24 h. Compound 23 was purified (Dowex 50x2-400, H⁺ form) and characterized as its hydrochloride salt.

In summary, we have shown that the $\text{Rh}_2(\text{MPPIM})_4$ -catalyzed C–H insertion reaction of γ - and δ -lactam diazoacetates proceeded efficiently with excellent regioselectivity and *cis*-diastereoselectivity. Regioselectivity in the δ -lactam diazoacetate is dependent on the chirality of the Rh(II) catalyst. Reactive conformer models are proposed to explain product formation from (S)-3. The synthetic utility of the bicyclic lactam lactones is demonstrated by the concise asymmetric synthesis of 23 from 4 (9 steps, 34% overall yield). Applications to other alkaloid targets are in progress.

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Notes and references

- C. A. Merlic and A. L. Zechman, *Synthesis*, 2003, 1137.
- (a) M. P. Doyle, A. V. Kalinin and D. G. Ene, *J. Am. Chem. Soc.*, 1996, **118**, 8837; (b) M. P. Doyle, J. P. Morgan, J. C. Fetters, P. Y. Zavali, J. T. Colyer, D. J. Timmons and M. D. Carducci, *J. Org. Chem.*, 2005, **70**, 5291 and references cited.
- A. G. H. Wee, *J. Org. Chem.*, 2001, **66**, 8513.
- R. K. Olsen, K. L. Bhat, R. B. Wardle, W. J. Hennen and G. Kini, *J. Org. Chem.*, 1985, **50**, 896.
- Racemic 2: C. Herdeis, *Arch. Pharm.*, 1983, **316**, 719.
- (a) H. O. House and C. J. Blankley, *J. Org. Chem.*, 1968, **33**, 53; (b) E. J. Corey and A. G. Myers, *Tetrahedron Lett.*, 1984, **25**, 3559.
- Review: D. L. Hughes, *Org. React.*, 1983, **29**, 1.
- Purchased from Aldrich; can also be prepared: T. H. Park, S. Paik and S. H. Lee, *Bull. Korean Chem. Soc.*, 2003, **24**, 1227.
- (a) The minimum energy conformation about the Rh(II)-carbene carbon bond is based on: M. P. Doyle, W. R. Winchester, J. A. A. Hoorn, V. Lynch, S. H. Simonsen and R. Ghosh, *J. Am. Chem. Soc.*, 1993, **115**, 9968; (b) AM1 calculations (PC Spartan Pro, v.6.0.6) were performed on the δ -lactams with a pseudoaxial and pseudoequatorial diazoacetyl unit: ΔH_f (axial) = -31.822 kcal/mol, ΔH_f (equatorial) = -32.164 kcal/mol.
- Trajectory for C–H insertion, see: (a) D. F. Taber, K. K. You and A. L. Rheingold, *J. Am. Chem. Soc.*, 1996, **118**, 547; (b) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri and M. M. Pearson, *J. Am. Chem. Soc.*, 1993, **115**, 958; (c) E. Nakamura, N. Yoshikai and M. Yamanaka, *J. Am. Chem. Soc.*, 2002, **124**, 7181; (d) N. Yoshikai and E. Nakamura, *Adv. Synth. Catal.*, 2003, **345**, 1159.
- A. G. H. Wee and S. C. Duncan, *J. Org. Chem.*, 2005, **70**, 8372.
- For the deactivation of α - and β -C–H bonds in esters, see: G. Stork and K. Nakatani, *Tetrahedron Lett.*, 1988, **29**, 2283.
- Racemic synthesis: (a) D. H. R. Barton, M. M. M. A. Pereira and D. K. Taylor, *Tetrahedron Lett.*, 1994, **35**, 9157; (b) C. P. Rader, R. L. Young, Jr. and H. S. Aaron, *J. Org. Chem.*, 1965, **30**, 1536; (c) T. J. Bond, R. Jenkins, A. C. Ridley and P. C. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2241; (d) T. Shono, Y. Matsumura, K. Tsubata, K. Inoue and R. Nishida, *Chem. Lett.*, 1983, 21. Asymmetric synthesis: (e) H. K. Lee, J. S. Chun and C. S. Pak, *J. Org. Chem.*, 2003, **68**, 2471.
- A. J. Birch, *Pure Appl. Chem.*, 1996, **68**, 553.
- In ref. 13e, 23 was obtained as a white solid; we think that the product isolated is in fact the 23 : borane complex. IR ν_{max} (B–H): 2367 and 2320 cm^{-1} ; ^1H NMR of 23 : borane complex is identical to that reported.