Development of a Catalytic Asymmetric Variant of Hoppe’s O-Alkyl Carbamate Deprotonation Methodology

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This paper is dedicated with much respect to Professor Dieter Hoppe on the occasion of his 65th birthday.

Abstract: The optimisation of a ligand-exchange approach to catalytic asymmetric deprotonation of O-alkyl carbamates and subsequent electrophilic trapping (the ‘Hoppe reaction’) is presented. The method uses s-BuLi and sub-stoichiometric amounts of a chiral diamine [(−)-sparteine or the (+)-sparteine surrogate] in conjunction with a chiral ‘regenerating’ diamine (bisisopropyl bispidine) for the deprotonation and proceeds with good yields (up to 84%) and high enantioselectivity (up to 94:6 er). The first applications of this catalytic asymmetric deprotonation methodology in natural product synthesis are also described.

Key words: asymmetric catalysis, synthesis, organometallic reagents, chiral bases, diamines

The asymmetric deprotonation of O-alkyl carbamates using s-BuLi/(-)-sparteine and subsequent electrophilic trapping to give α-substituted O-alkyl carbamates of high er values was first reported in 1990 by Hoppe and co-workers.1 During the last 16 years, this process has been extensively studied within the Hoppe group2,3 and has also been exploited in natural product total synthesis, with examples that include (S)-1-methyldeoxyacetate,4 (R)-pantolactone,5 an algae nonaether from Tolypothrix conglutinata6 and (R)-japonilure.7 Typically, the process, which is affectionately known in our group as the ‘Hoppe reaction’, utilises 1.4 equivalents each of s-BuLi and (-)-sparteine (Et2O, −78 °C) for the deprotonation of an O-alkyl carbamate 1 (Scheme 1). The reaction proceeds via a configurationally stable organolithium complex 2 which is trapped with an electrophile (Bu3SnCl in this case) to give α-substituted O-alkyl carbamate (S)-3 (73% yield, 99:1 er).8 Recently, the impressive level of enantiocontrol observed in the Hoppe reaction has been interpreted using quantum chemical DFT calculations.9

Given the synthetic utility of Hoppe’s O-alkyl carbamate methodology, we were intrigued by the prospect of developing a catalytic asymmetric variant in which sub-stoichiometric quantities of (-)-sparteine [or our (+)-sparteine surrogate10] would be employed. This seemed to be a realistic aim since lithiation trapping of 1 using s-BuLi alone (under otherwise identical conditions to those shown in Scheme 1) furnished only a 17% yield of rac-3. Clearly, (-)-sparteine provides ligand-accelerated catalysis of the s-BuLi-mediated deprotonation of O-alkyl carbamates. Disappointingly, however, use of 1.4 equivalents of s-BuLi in conjunction with 0.2 equivalents of (-)-sparteine and subsequent trapping gave only a 17% yield of (S)-3 with 85:15 er (Scheme 2). Taken together, the low yield and reduced enantioselectivity in this example suggest that the diamine does not readily dissociate from the organolithium complex 2. Thus, the reactive s-BuLi/(-)-sparteine complex is not regenerated and uneffective, slow deprotonation by uncomplexed s-BuLi probably occurs to account for the reduced enantioselectivity.

A similar situation was reported for N-Boc pyrrolidine deprotonation.11,12

To solve this problem, we devised a ligand-exchange process whereby the (-)-sparteine that is ‘trapped’ by chelation to lithium in organolithium complex 2 could be ‘freed’ by displacement by another diamine ligand and, in this way, the reactive s-BuLi/(-)-sparteine would be regenerated and could re-enter the catalytic cycle. The key features of our proposed approach are summarised in Scheme 3. Thus, we envisaged that an excess of another diamine 4 would displace (-)-sparteine from complex 2 to give a new organolithium complex 6 and the reactive s-

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BuLi/(-)-sparteine complex. In this way, it was hoped that, after electrophilic trapping, a >17% yield of (S)-3 in >85:15 er should be obtained (compare with Scheme 2). There are three important features of our approach: (i) ligand exchange of (-)-sparteine and 4 must occur to some extent;13 (ii) organolithiums 2 and 6 must be configurationally stable throughout the ligand-exchange process14 and (iii) deprotonation of O-alkyl carbamate 1 by s-BuLi/(-)-sparteine must be significantly faster than deprotonation by the organolithium complex 5 (formed from s-BuLi and diamine 4). Indeed, in a preliminary communication, we demonstrated that catalysis of the Hoppe reaction using such a ligand-exchange approach worked well.15 In this paper, we provide information on the relative rates of deprotonation of O-alkyl carbamates using s-BuLi complexed to different diamines together with optimisation of our ligand-exchange approach. In addition, an illustration of the use of catalytic asymmetric Hoppe reactions in the synthesis of two natural products is presented.

Scheme 3

In order to implement the proposed ligand-exchange approach to catalysis, we needed to identify a suitable regenerating diamine 4. Ideally, when s-BuLi is combined with diamine 4, it should produce a complex that does not deprotonate 1 to any extent. To probe this, we planned to study the conversion of 1 into 3 using s-BuLi and a range of diamines 7–12 with differently sized groups around the coordinating nitrogens (Figure 1).

Diamines 7,15 8,16 917 and 1118 were prepared according to the literature methods. For the synthesis of diamine 10, a three-step approach was preferred (Scheme 4). Thus, double Mannich19 reaction of N-Boc piperidone 13 with paraformaldehyde and isopropylamine afforded a 78% yield of 14. The carbonyl group in 14 was removed by formation of the tosylhydrazone and sodium borohydride reduction20 which gave 15 (82% yield). Finally, lithium aluminium hydride reduction generated a 58% yield of the required diamine 10. In contrast, a more direct two-step synthesis of diamine 12 was employed.21 In this case, double Mannich reaction of keto amine 16 with isopropylamine afforded ketone 17 in 69% yield. Diamine 12 was directly produced from 17 in moderate yield (38%) by Wolff–Kishner reduction (Scheme 4).

With diamines 7–12 in hand, we investigated the conversion of O-alkyl carbamate 1 into 3 using s-BuLi and the diamines (Table 1). It was intended to use the yield of these reactions as a guide to identifying an approximate reactivity series for the s-BuLi/diamine complexes. As shown in Table 1, use of (-)-sparteine and diamines 7 and (S,S)-8 (entries 1–3) all gave >70% yields of 3 indicating that their s-BuLi complexes are the most reactive. Diamines 9 and 10 showed moderate reactivity (~55% yield of 3; entries 4–5), whilst s-BuLi complexes of diamines 11 and 12 were the least reactive (entries 6–7). Not surprisingly, as the steric hindrance of the N-alkyl substituents on the diamines increased, the reactivity of the s-BuLi complexes decreased. These initial results suggested to us that diamines 11 and 12 would be better regenerating diamines than, for example, diamine 8.

Unfortunately, these results did not allow us to differentiate between the reactivity of s-BuLi/diamine complexes that gave >70% yield of O-alkyl carbamate 3. Therefore, we devised a competition experiment22 which would allow us to directly compare the reactivity of (-)-sparteine and the other diamines. Thus, we deprotonated O-alkyl carbamate 1 using 2.8 equivalents of s-BuLi in combination with 1.4 equivalents each of (-)-sparteine and diamine 7. After electrophilic trapping with Bu₃SnCl, adduct (R)-3 of 88:12 er was obtained in 83% yield (Table 2, entry 1). The major enantiomer results from
preferential reaction of the s-BuLi complex of diamine 7 over (+)-sparteine, i.e., the s-BuLi/diamine 7 complex deprotonates 1 faster than the s-BuLi/(-)-sparteine complex. Hence, based on this exciting competition result, we speculated that it might even be possible to use (-)-sparteine as a readily available regenerating diamine for asymmetric catalysis using the (+)-sparteine surrogate 7 (vide infra). Three other competition experiments were also carried out (Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diamine 1</th>
<th>Diamine 2</th>
<th>Yield (%)</th>
<th>er (S/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-)-sparteine</td>
<td>7</td>
<td>83</td>
<td>12:88</td>
</tr>
<tr>
<td>2</td>
<td>(-)-sparteine</td>
<td>rac-8</td>
<td>41</td>
<td>60:40</td>
</tr>
<tr>
<td>3</td>
<td>(-)-sparteine</td>
<td>12</td>
<td>60</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>12</td>
<td>86</td>
<td>4:96</td>
</tr>
</tbody>
</table>

Reaction conditions: (i) 2.8 equiv s-BuLi/diamine, Et₂O, –78 °C, 5 h; (ii) Bu₃SnCl.

Table 2 Competition Experiments: Conversion of O-Alkyl Carbamate 1 into 3 Using Excess s-BuLi and an Excess of a Mixture of Two Ligands

If s-BuLi complexes of diamines rac-8 and (-)-sparteine were of equal reactivity, then adduct 3 should be generated with ca. 75:25 er. In fact, using rac-8 and (-)-sparteine, adduct 3 was produced in 60:40 er (entry 2) indicating that the s-BuLi/diamine rac-8 complex also deprotonates 1 faster than the s-BuLi/(-)-sparteine complex. Clearly, diamine 8 (and the closely related TMEDA) should not be used for catalysing the Hoppe reaction using a ligand-exchange approach. Finally, we verified the low reactivity of the s-BuLi/diamine 12 complex using competition experiments with each of (-)-sparteine and diamine 7. The reaction essentially proceeded as if diamine 12 was not there so that adduct 3 was produced in 97:3 er (entry 3) or 96:4 (entry 4) with (-)-sparteine and diamine 7, respectively. Based on the results from Table 2, it is possible to establish the following reactivity order for s-BuLi/diamine complexes: 7 ~ 8 >> (-)-sparteine >> 12. A similar order of reactivity was also obtained for N-Boc pyrrolidine deprotonation using s-BuLi/diamines.

Our interpretation of the competition results presented in Table 2 assumes that we measure the relative rate of deprotonation from a pre-lithiation complex containing one of each of O-alkyl carbamate 1, s-BuLi and diamine (which is consistent with Würthwein and Hoppe’s computational model) rather than the relative rate of irreversible complexation of s-BuLi/diamines to carbamate 1. To verify that formation of the pre-lithiation complex was reversible, we devised the experiment presented in Scheme 5. Thus, a-bis-deuterated O-alkyl carbamate 18 (prepared according to the two-step route shown in Scheme 6, via known20 alcohol 21) was incubated with s-BuLi/(-)-sparteine in the usual way. A-Bis-deuterated O-alkyl carbamate 18 will complex to s-BuLi/(-)-sparteine to form the pre-lithiation complex but will not undergo deprotonation due to the high kinetic isotope effect for such reactions at –78 °C, as noted previously by Hoppe et al.21 Subsequent addition of a different substrate that can undergo deprotonation (e.g., N-Boc pyrrolidine 19) can be used to probe whether the initial pre-lithiation complex formation is reversible. When N-Boc pyrrolidine 19 was added and left for 5 h at –78 °C before quenching with Me₃SiCl, unreacted O-alkyl carbamate 18 was recovered in 76% yield together with trimethylsilyl adduct (S)-20 (64% yield) of 94:6 er. This clearly demonstrates that complexation of s-BuLi/(-)-sparteine to carbamate 18 (and by analogy 1) is reversible and we believe that the competition experiments are indeed a measure of relative rate of deprotonation from a pre-lithiation complex.

Our conclusions from the % yields for one-ligand stoichiometric reactions (Table 1) and the competition experiments (Table 2) are three-fold. First, (-)-sparteine and
diamine 7 should be the best chiral diamines to be used in sub-stoichiometric quantities (as their s-BuLi complexes are the most reactive and give the highest enantioselectivities). Second, for efficient catalysis with the very reactive s-BuLi/diamine 7 complex, it could be possible to use any diamine that gives a less reactive s-BuLi complex as the regenerating diamine. The same is true for catalysis due to the higher reactivity of s-BuLi/diamine 7.

Finally, to demonstrate the synthetic usefulness of this catalytic asymmetric variant of Hoppe’s O-alkyl carbamoyloxy-alkylboronates (e.g. (S)-26) with Grignard reagents, a process recently developed by Hoppe et al. 27 First of all, catalytic asymmetric deprotonation of O-alkyl carbamate 1 was accomplished using the optimised procedure with 0.2 equivalents of (-)-sparteine. Subsequent electrophilic trapping with trisopropylborate and conversion into the stoichiometric amounts (entries 8 and 9). Our preferred conditions used 0.2 equivalents of (-)-sparteine or diamine 7 and 1.2 equivalents of diamine 12 with 1.3 equivalents of s-BuLi. With diamine 7, a 72% yield of adduct (R)-3 of 94:6 er was obtained (entry 6) whereas (-)-sparteine generated its antipode (S)-3 of 92:8 er in 77% yield (entry 8). It is notable that diamine 7 engenders higher enantioselectivity than (-)-sparteine under identical conditions and may be a result of more efficient catalysis due to the higher reactivity of s-BuLi/diamine 7.

Thus, our attention switched to regenerating diamines 10 and 12 which produce less reactive s-BuLi complexes. In this way, improved results were obtained at lower loadings of diamine 7. As predicted, higher enantioselectivity was obtained using diamine 12 (compare entries 4 and 5). Even use of 0.06 equivalents of diamine 7 with 1.2 equivalents of diamine 12 and 1.3 equivalents of s-BuLi generated adduct (R)-3 of 85:15 er in 63% yield (entry 7), which clearly indicates that the chiral diamine 7 is being recycled, presumably via the proposed ligand exchange (Scheme 3). To access the opposite enantiomer of adduct 3, (-)-sparteine was also successfully employed in sub-stoichiometric amounts (entries 8 and 9). Our preferred conditions used 0.2 equivalents of (-)-sparteine or diamine 7 and 1.2 equivalents of diamine 12 with 1.3 equivalents of s-BuLi. With diamine 7, a 72% yield of adduct (R)-3 of 94:6 er was obtained (entry 6) whereas (-)-sparteine generated its antipode (S)-3 of 92:8 er in 77% yield (entry 8). It is notable that diamine 7 engenders higher enantioselectivity than (-)-sparteine under identical conditions and may be a result of more efficient catalysis due to the higher reactivity of s-BuLi/diamine 7.

Table 3: Catalytic Asymmetric Deprotonation of O-Alkyl Carbamate 1 → 3 Using s-BuLi and a Mixture of Two Ligands

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diamine 1 (equiv)</th>
<th>Diamine 2 (equiv)</th>
<th>s-BuLi (equiv)</th>
<th>Yield (%)</th>
<th>er (S:R)</th>
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<tbody>
<tr>
<td>1</td>
<td>7 (0.25)</td>
<td>(-)-sp (1.1)</td>
<td>1.7</td>
<td>57</td>
<td>63:37</td>
</tr>
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<td>2</td>
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<td>(-)-sp (0.8)</td>
<td>1.2</td>
<td>84</td>
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<td>3</td>
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<td>(-)-sp (1.11)</td>
<td>1.6</td>
<td>75</td>
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<td>7 (0.4)</td>
<td>10 (1.0)</td>
<td>1.4</td>
<td>65</td>
<td>12:88</td>
</tr>
<tr>
<td>5</td>
<td>7 (0.3)</td>
<td>12 (0.9)</td>
<td>1.3</td>
<td>47</td>
<td>6:94</td>
</tr>
<tr>
<td>6</td>
<td>7 (0.2)</td>
<td>12 (1.2)</td>
<td>1.3</td>
<td>72</td>
<td>6:94</td>
</tr>
<tr>
<td>7</td>
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<td>12 (1.2)</td>
<td>1.3</td>
<td>63</td>
<td>15:85</td>
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<tr>
<td>8</td>
<td>(-)-sp (0.2)</td>
<td>12 (1.2)</td>
<td>1.3</td>
<td>77</td>
<td>92:8</td>
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<tr>
<td>9</td>
<td>(-)-sp (0.1)</td>
<td>12 (1.2)</td>
<td>1.3</td>
<td>54</td>
<td>81:19</td>
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</table>

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<td>78%</td>
<td>91:9</td>
<td></td>
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<td>1.2 equiv diamine 12</td>
<td>72%</td>
<td>94:6</td>
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</tbody>
</table>

* Reaction conditions: (i) s-BuLi/diamine 1 and 2, Et3O, -78 °C, 5 h; (ii) Bu3SnCl.
* Isolated yield after chromatography.
* Enantiomeric ratio determined by chiral HPLC.

Scheme 7

For the synthesis of (R)-(+)1,3-diphenylpropan-1-ol 27, we planned to utilise the reaction of α-carbamoyloxy-alkylboronates (e.g. (S)-26) with Grignard reagents, a process recently developed by Hoppe et al. 27 First of all, catalytic asymmetric deprotonation of O-alkyl carbamate 1 was accomplished using the optimised procedure with 0.2 equivalents of (-)-sparteine. Subsequent electrophilic trapping with trisopropylborate and conversion into the...
pinacol borate ester was carried out following Hoppe’s protocol to give known 27 borate ester (S)-26 in 58% yield (Scheme 8). Then, reaction of borate ester (S)-26 first with phenylmagnesium bromide and then with alkaline hydrogen peroxide afforded alcohol (R)-27 of 87:13 er in 60% isolated yield after chromatography. This reaction proceeds via a 1,2-borate rearrangement with inversion of stereochemistry as depicted in Scheme 8. Hence, it was necessary to use (−)-sparteine to obtain the requisite (R)-stereochemistry of the natural product. Our synthesised alcohol (R)-27 was identical in all respects to the naturally occurring material. 26

Scheme 8

In conclusion, we have developed a catalytic asymmetric variant of the widely utilised ‘Hoppe reaction’. The key feature of our ligand-exchange approach is the use of substoichiometric quantities of a chiral diamine [(+] or (−)-sparteine surrogate 7 or (−)-sparteine) in conjunction with an achiral, sterically hindered ‘regenerating’ diamine 12. It is interesting to note that the (−)-sparteine surrogate leads to higher enantioselectivity than (−)-sparteine under identical catalytic conditions. The first examples of the use of our catalytic asymmetric deprotonation methodology in natural product synthesis have also been described.

General experimental details have been reported previously. 28 Et2O and THF were freshly distilled from benzophenone ketyl or dried after degassing with N2 by use of a MBraun solvent purification system in which the solvents were passed through a column of 3 Å molecular sieves under a positive pressure of N2. (−)-Sparteine and diamines 7, 8, 10, 11 and 12 were distilled from CaH2 before use. s-BuLi was titrated against N-benzylbenzamide before use. PE refers to the fraction of petroleum ether with a boiling point range of 40–60 °C. For Kugelrohr distillation, the temperatures quoted correspond to the oven temperatures. 1 H NMR (400 MHz, CDCl3; rotamers): δ = 4.58 (d, J = 14.0 Hz, 1 H, CHNBoc), 4.42 (d, J = 13.5 Hz, 1 H, CHNBoc), 3.31 (d, J = 14.5 Hz, 1 H), 3.22–3.18 (m, 2 H), 3.12 (d, J = 10.5 Hz, 1 H), 2.88 (d, J = 10.5, 1 H), 2.77–2.73 (m, 2 H), 2.42 (br s, 1 H), 2.38 (br s, 1 H), 1.48 (s, 9 H, CMe3), 1.03 (d, J = 6.5 Hz, 3 H, CHMe2(Me2)), 0.94 (d, J = 6.0 Hz, 3 H, CHMe2(Me2)).

IR (film): 2968, 2933, 1731 (C=O, ketone), 1695 (C=O, Boc), 1449, 1424, 1390, 1172, 1125 cm−1.


PAPER Catalytic Asymmetric Variant of Hoppe’s O-Alkyl Carbamate Deprotonation Methodology 2237

tert-Butyl 7-Isopropyl-3,7-diaza[bicyclo][3.3.1]nonane-3-carboxylate (14)

A stirred solution of isopropanol (4.3 mL, 50.5 mmol), tert-butyl 4-oxopiperidine-1-carboxylate 13 (10.0 g, 50.1 mmol), paraformaldehyde (4.5 g, 150 mmol) and AcOH (3.0 mL, 54.5 mmol) in EtOH (250 mL) was heated at reflux for 16 h. The resulting orange solution was allowed to cool to r.t. and the solvent was evaporated under reduced pressure. The residue was treated with 20% aq KOH (200 mL) and extracted with Et2O (3 × 150 mL). The combined Et2O extracts were dried (MgSO4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with PE–Et2O (1:1) as eluent gave biodipinone 14 (11.0 g, 78%) as a yellow oil; Rf = 0.4 (PE–Et2O, 1:1).

IR (film): 2968, 2933, 1731 (C=O, ketone), 1695 (C=O, Boc), 1449, 1424, 1390, 1172, 1125 cm−1.


tert-Butyl 7-Isopropyl-3,7-diaza[bicyclo][3.3.1]nonane-3-carboxylate (15)

p-Toluenesulfonyl hydrazide (8.00 g, 42.9 mmol) was added portionwise to a stirred solution of biodipinone 14 (11.0 g, 39.0 mmol) in EtOH (100 mL) at r.t. under N2. The resulting solution was stirred and heated at reflux for 4 h. After being allowed to cool to r.t., the solvent was evaporated under reduced pressure. The residue was dissolved in THF–H2O (9:1, 100 mL) and NaBH4 (5.00 g, 132.3 mmol) was added portionwise over 30 min. The resulting mixture was stirred at r.t. for 16 h and then heated at reflux for 4 h. After being allowed to cool to r.t., H2O (30 mL) was added and the layers were separated. The aqueous layer was extracted with Et2O (3 × 40 mL). Then, the combined organic extracts were dried (MgSO4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with PE–EtOAc (4:1) as eluent gave N-Boc biodipinone 15 (8.6 g, 82%) as a colourless oil; Rf = 0.2 (PE–Et2O, 7:3).

IR (film): 2967, 2931, 1692 (C=O), 1426, 1363, 1179, 1136 cm−1.

1 H NMR (400 MHz, CDCl3; rotamers): δ = 4.14 (d, J = 13.0 Hz, 1 H, CHNBoc), 4.01 (d, J = 14.0 Hz, 1 H, CHNBoc), 3.07 (dd, J = 13.0, 1.0 Hz, 1 H), 2.99 (dd, J = 13.0, 1.5 Hz, 1 H), 2.89 (d, J = 10.5 Hz, 1 H), 2.82 (d, J = 10.5, 1 H), 2.51 (sept, J = 6.5 Hz, 1 H, CHMe2(Me2)), 2.42 (d, J = 10.5 Hz, 1 H), 2.36 (d, J = 10.5 Hz, 1 H), 1.79 (br s, 1 H), 1.74 (br s, 1 H), 1.65 (d, J = 12.0 Hz, 1 H, CH2(H2)), 1.56 (d, J = 12.0 Hz, 1 H, CH2(H2)), 1.44 (s, 9 H, CMe3), 0.95 (d, J = 6.5 Hz, 3 H, CHMe2(Me2)), 0.91 (d, J = 6.5 Hz, 3 H, CHMe2(Me2)).

13C NMR (100 MHz, CDCl3; rotamers): δ = 121.4 (C=O), 138.2 (C=O), 79.7 (CMe3), 55.2 (CH2N), 53.2 (CHN and CHN), 50.4 (CH2N), 49.7 (CH2N), 48.2 (CH), 48.0 (CH), 28.5 (CMe3), 19.0 (CHMe2(Me2)), 16.7 (CHMe2(Me2)).

MS (CI, NH3): m/z (%) = 283 (100) [M + H+].


Synthesis 2006, No. 13, 2233–2241 © Thieme Stuttgart · New York
3-Isopropyl-7-methyl-3,7-diazabicyclo[3.3.1]nonane (10)
A solution of N-Boc bispidine 15 (6.00 g, 22.4 mmol) in THF (15 mL) was added dropwise via cannula to a stirred suspension of LiAlH₄ (4.20 g, 111 mmol) in THF (30 mL) at r.t. under N₂. The resulting suspension was stirred and heated at reflux for 16 h. After being allowed to cool to r.t., Na₂SO₄·10H₂O (10.0 g) was added portionwise over 10 min. The solids were removed by filtration through Celite and the filter cake was washed with CH₂Cl₂ (2 × 50 mL). The filtrate was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave bispidine 10 (0.90 g, 58%) as a colourless oil; bp 115–120 °C, 3 mmHg; Rₖ = 0.1 (PE–Et₂O, 1:1).

IR (film): 2983, 2962, 1460, 1358, 1150 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 2.71–2.62 (m, 5 H), 2.44–2.38 (m, 4 H), 2.18 (s, 3 H, NMe), 1.94 (br s, 2 H, CH), 1.59–1.55 (m, 1 H, CH₂N), 46.4 (NMe), 29.0 (CH₂), 28.8 (CH), 17.9 (CH₂).

13C NMR (100.6 MHz, CDCl₃): δ = 59.3 (CH₂N), 54.1 (CHN), 53.0 (CH₂), 46.4 (NMe), 29.0 (CH₂), 28.8 (CH), 17.9 (CH₂).

HRMS: m/z [M + H]⁺ calcd for C₁₅H₂₈N₂O₂: 269.2229; found: 269.2226.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane (12)
Anhydrous hydrazine (4.9 mL, 150 mmol) was added dropwise to a stirred solution of LiAlH₄ (4.10 g, 108 mmol) in THF (15 mL) at r.t. The resulting mixture was stirred and heated at reflux for 16 h. After being allowed to cool to r.t., H₂O (100 mL) was added and the mixture was extracted with Et₂O (4 × 50 mL). The combined Et₂O extracts were washed with 20% aq NaOH (6 × 80 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by Kugelrohr distillation gave bispidine 12 (2.2 g, 38%) as a colourless oil; bp 130–160 °C, 2 mmHg.

IR (film): 2983, 2962, 1460, 1358, 1150 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 2.70–2.58 (m, 2 H, CH₂Me), 2.55 (dd, J = 10.0, 5.5 Hz, 4 H) 2.49 (br d, J = 10.0 Hz, 4 H), 2.00–1.95 (m, 2 H, CH), 1.47–1.46 (m, 2 H, CH₂), 0.99 (dd, J = 6.5 Hz, 12 H, CH₂Me).

13C NMR (100.6 MHz); δ = 54.0 (CHN), 52.4 (CH₂N), 28.1 (CH₂), 27.7 (CH), 18.2 (CH₂Me).


Representative procedure for the results presented in Table 1 (Table 1, entry 1):

(R)-3-Phenyl-1-tributyltin-1-N,N-diisopropylcarbamoyloxyp propane ([R]-3)
A solution of 2-chloro-1-phenylethane (6.50 g, 20.7 mmol) in Et₂O (3 mL) was added dropwise to a stirred solution of s-BuLi (3.0 mL, 1.0 M soln in cyclohexane, 30 mmol) in Et₂O (3.0 mL) at −78 °C under Ar. After stirring for 10 min at −78 °C, a solution of O-alkyl carbamate 1 (512 mg, 2.10 mmol) in Et₂O (3 mL) was added dropwise and the resulting solution was stirred at −78 °C for 5 h. Then, Bu₃SnCl (0.8 mL, 2.94 mmol) was added dropwise and the solution was allowed to warm to r.t. over 16 h. Aq 2 M HCl (10 mL) was added, the layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined Et₂O layers were washed with sat. aq KF (10 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using PE–Et₂O 40:1 as eluent gave stannane ([R]-3 (827 mg, 71%, 52:48 er) as a colourless oil.

1H NMR (400 MHz, CDCl₃): δ = 7.30 (t, J = 7.0 Hz, 2 H, m-Ph), 7.21–7.18 (m, 3 H, Ph), 4.70 (dd, J = 9.5, 5.0 Hz, 1 H, OCH₂), 4.23–4.03 (m, 1 H, CH₂Me), 3.84–3.64 (m, 1 H, CH₂Me), 2.77 (ddd, J = 13.0, 11.0, 5.0 Hz, 1 H, PhCH₂), 2.65, (ddd, J = 13.0, 10.0, 6.0, 1 H, PhCH₂), 2.29–2.18 (m, 1 H), 2.10–2.01 (m, 1 H), 1.67–1.44 (m, 6 H), 1.38–1.11 (m, 18 H), 1.04–0.80 (m, 15 H).

CHIRAL HPLC: Daicel Chiralcel OD, hexane–i-PrOH (600:1), 0.5 mL min⁻¹, 226 nm, −6.5 min ([S]-3), −7.0 min ([R]-3).

Spectroscopic data are identical to those reported.

Representative procedure for the results presented in Table 2 (Table 2, entry 1):

(R)-3-Phenyl-1-tributyltin-1-N,N-diisopropylcarbamoyloxyp propane ([R]-3)
A solution of (+)-sparteine (197 mg, 0.84 mmol) and diamine 7 (163 mg, 0.84 mmol) in Et₂O (2.5 mL) was added dropwise to a stirred solution of s-BuLi (1.34 mL of 1.25 M soln in cyclohexane, 168 mmol) in Et₂O (2.5 mL) at −78 °C under Ar. After stirring for 10 min at −78 °C, a solution of O-alkyl carbamate 1 (158 mg, 0.60 mmol) in Et₂O (2 mL) was added dropwise and the resulting solution was stirred at −78 °C for 5 h. Then, Bu₃SnCl (0.34 mL, 1.68 mmol) was added dropwise and the solution was allowed to warm to r.t. over 16 h. Aq 2 M HCl (10 mL) was added, the layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined Et₂O layers were washed with sat. aq KF (10 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using PE–Et₂O 40:1 as eluent gave stannane ([R]-3 (277 mg, 83%, 88:12 er) as a colourless oil.

1H NMR (400 MHz, CDCl₃): δ = 1.20–1.10 (m, 8 H, 3 × 80 mL), 2.00–1.90 (m, 2 H, CH₂), 0.99 (dd, J = 6.5 Hz, 12 H, CH₂Me).

IR (film): 2963, 1734 (C=O) cm⁻¹.


Spectroscopic data are identical to those reported.

Synthesis 2006, No. 13, 2233–2241 © Thieme Stuttgart · New York
A solution of deuterated alcohol 21 (1.90 g, 13.7 mmol) in Et₂O (10 mL) was added dropwise to a stirred suspension of sodium hydride (680 mg of a 60% dispersion in mineral oil, 15.0 mmol) [which had been pre-reinsed with Et₂O (2 × 15 mL) in Et₂O (20 mL) at r.t. under N₂]. The resulting solution was stirred for 30 min at r.t. (during which time gas evolution took place). A solution of diisopropylcarbamoyl chloride (1.8 g, 11 mmol) in Et₂O (10 mL) was added dropwise. The resulting solution was stirred for 16 h at r.t. Then, aq 2 M HCl (20 mL) and Et₂O (20 mL) were added. The layers were separated and the aqueous layer was extracted with Et₂O (2 × 20 mL). The combined organic layers were dried (NaHCO₃/MgSO₄, 1:1 by weight) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using PE–EtOAc (6:1) as eluent gave stannane (1.9 g, 94%) of sufficient purity for use in the next step.

\[ \text{[1,1-}^2\text{H}_3\text{-3-Phenylpropanol (21)} \]

A solution of deuterated carbamate (2.66 g, 14.6 mmol) in Et₂O (20 mL) was added dropwise to a stirred suspension of LiAlD₄ (2.2 g, 52 mmol) at r.t. under N₂. The resulting suspension was stirred at r.t. for 1 h and then heated at reflux for 16 h. After being allowed to cool to r.t., Na₂SO₄/10H₂O was added portionwise over 10 min and stirred for 30 min. The solids were removed by filtration through Celite and the filter cake was washed with Et₂O (100 mL). The filtrate was dried (MgSO₄) and evaporated under reduced pressure to give the crude deuterated alcohol 21 (1.9 g, 94%) of sufficient purity for use in the next step.

\[ \text{[1H NMR (400 MHz, CDCl₃):} \delta = 7.33–7.19 \text{ (m, 5 H, Ph), 2.72 (t,} \text{ J = 7.0 Hz, 2 H, CH}_2\text{Ph), 1.90 (t,} \text{ J = 7.0 Hz, 2 H, CH}_2\text{CD}_2\text{).} \]

Spectroscopic data are identical to those reported.²³

\[ \text{[2H NMR (400 MHz, CDCl₃):} \delta = 7.31–7.20 \text{ (m, 5 H, Ph), 4.30–4.09} \text{ (m, 2 H, CH}_2\text{Ph), 1.98 (t,} \text{ J = 7.5 Hz, 2 H, CH}_2\text{CD}_2) \]

\[ \text{[3H NMR (400 MHz, CDCl₃):} \delta = 7.33–7.19 \text{ (m, 5 H, Ph), 2.72 (t,} \text{ J = 7.0 Hz, 2 H, CH}_2\text{Ph), 1.90 (t,} \text{ J = 7.0 Hz, 2 H, CH}_2\text{CD}_2) \]

\[ \text{[13C NMR (100.6 MHz, CDCl₃):} \delta = 34.0 \text{ (CH}_2\text{Ph), 32.0} \text{ (CH}_2\text{CD}_2) \]

N,N-Diisopropylcarbamoyloxy-[1,1-2H₂]-3-phenylpropanol (18)

A solution of 3-phenylpropionic acid (2.66 g, 14.6 mmol) in Et₂O (20 mL) was added dropwise to a stirred solution of diisopropylcarbamoyl chloride (1.8 g, 11 mmol) in Et₂O (10 mL) at r.t. under Ar. After stirring for 10 min at ~78 °C, a solution of O-alkyl carbamate 1 (628 mg, 2.58 mmol) in Et₂O (3 mL) was added dropwise and the resulting solution was stirred at ~78 °C for 5 h. Then, Bu₃SnCl (0.91 mL, 3.35 mmol) was added dropwise and the solution was allowed to warm to r.t. over 16 h. 2 M aq HCl (10 mL) was added, the layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined Et₂O layers were washed with sat. aq KF (10 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using PE–EtOAc (40:1) as eluent gave stannane (2.19 g, 94%) of sufficient purity for use in the next step.

\[ \text{[IR (film):} 3429 \text{ (OH), 2966, 2932, 2873, 1666} \text{ (C=O) cm}^{-1}. \]

\[ \text{[HRMS:} [M + H]^+ \text{ calcd for C}_{16}\text{H}_{23}\text{N}_2\text{O}_2\text{H}: 266.2087; \text{found:} 266.2089 \]

\[ \text{[Chiral GC: Betadex 120, 20 m} \times 0.25 mm i.d.} \text{ (β-cyclodextrin), } T \text{ 95 °C isothermal, H } \text{carrier gas at 14 psi constant pressure, ~100 min} [\delta{_20}] \text{ ~103 min} [\delta{_20}]. \]

Spectroscopic data are identical to those reported.¹¹

Representative procedure for the results presented in Table 3 (Table 3, entry 6):

\[ \text{[(R)-3-Phenyl-1-trIBUTYL-1-N,N-dio} \text{isopropylcarbamoyl ox} \text{o} \text{ynol [(R)-3]} \]

A solution of diamine 7 (100 mg, 0.515 mmol, 0.2 equiv) and bispiperidine 12 (650 mg, 3.10 mmol, 1.2 equiv) in Et₂O (4 mL) was added dropwise to a stirred solution of s-BuLi (3.0 mL of a 1.1 M soln in cyclohexane, 3.3 mmol) in Et₂O (4 mL) at ~78 °C under Ar. After stirring for 10 min at ~78 °C, a solution of O-alkyl carbamate 1 (628 mg, 2.58 mmol) in Et₂O (3 mL) was added dropwise and the resulting solution was stirred at ~78 °C for 5 h. Then, Bu₃SnCl (0.91 mL, 3.35 mmol) was added dropwise and the solution was allowed to warm to r.t. over 16 h. 2 M aq HCl (10 mL) was added, the layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined Et₂O layers were washed with sat. aq KF (10 mL), dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using PE–EtOAc (40:1) as eluent gave stannane (1.9 g, 94%, 72%, 94:6 er) as a colourless oil; [α]D ~22.0 (c 1.4, CHCl₃) [Lit.³¹ [α]D ~21.9 (c 1.0, CHCl₃) for (S)-3 of 98.5:1.5 er].

Chiral HPLC: Daicel Chiralcel OD, hexane–i–PrOH (600:1, 0.5 mL min⁻¹, 226 nm, ~6.5 min [S]-3, ~7.0 min [R]-3).

Spectroscopic data are identical to those reported.³¹

\[ \text{[(S)-3-Phenyl-1-hydroxymethyl-1-N,N-diisopropylcarbamoyloxy} \text{ynol [(S)-23]} \]

A solution of diamine 7 (86 mg, 0.44 mmol, 0.2 equiv) and bispiperidine 12 (531 mg, 2.52 mmol, 1.2 equiv) in Et₂O (2 mL) was added dropwise to a stirred solution of s-BuLi (2.73 mL of a 1.1 M soln in cyclohexane, 2.73 mmol) in Et₂O (3 mL) at ~78 °C under Ar. After stirring for 10 min at ~78 °C, a solution of O-alkyl carbamate 1 (555 mg, 2.11 mmol) in Et₂O (2 mL) was added dropwise and the resulting solution was stirred at ~78 °C for 5 h. Then, a stream of CO₂ gas was passed over the solution for 20 min. H₂O (5 mL) and 35% aq HCl (1 mL) were added and the solution was allowed to warm to r.t. over 10 min. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude carboxylic acid 22 (740 mg). To a stirred solution of this crude carboxylic acid 22 in THF (30 mL) at 0 °C under N₂ was added BH₃·SMES (10.0 mL of a 1.0 M soln in THF, 10.0 mmol). The resulting solution was stirred at r.t. for 16 h and MeOH (10 mL) was cautiously added over 15 min. The mixture was stirred at r.t. for 1 h and then heated at reflux for 1 h. After being allowed to cool to r.t., the solvent was evaporated under reduced pressure to give the crude product. Purification by flash chromatography using PE–EtOAc (9:1) as eluent gave alcohol (S)-23 (482 mg, 78% over two steps) as a white solid; mp 55–57 °C; [R] = 0.3 (PE–EtOAc, 1:1); [α]D ~25.1 (c 0.4, CHCl₃).

IR (film): 3429 (OH), 2966, 2932, 2873, 1666 (C=O) cm⁻¹.
1H NMR (400 MHz, CDCl3): δ = 7.32–7.28 (m, 2 H, Ph), 7.22–7.18 (m, 3 H, Ph), 4.93–4.86 (m, 1 H, CHO), 4.20–4.00 (m, 1 H, CHMe), 3.95–3.70 (m, 1 H, CHMe, 3.73 (dd, J = 12.0 Hz, 3.0, 1.1 H, CH₂H₂O), 3.70 (dd, J = 12.0, 7.0 Hz, 1 H, CH₂H₂O), 2.81–2.66 (m, 2 H, CH₂Ph), 2.05–1.85 (m, 2 H, CH₂), 1.25 (d, J = 7.0 Hz, 12 H, CH₂Me).

2.83–2.65 (m, 4 H), 1.79–1.72 (m, 2 H).

13C NMR (100.6 MHz, CDCl 3): δ = 128.58 (Ph), 128.3 (Ph), 126.0 (Ph), 76.4 (CHO), 66.2 (CH₂O), 46.3 (br, CHN), 45.6 (br, CHN), 33.1 (CH₃), 31.9 (CH₂), 21.3 (br, CHMe₂), 20.6 (br, CHMe₂).

HRMS: m/z [M + H⁺] = 294 (100) + 34.9 (M + H) × 0.4, CH₂Cl₂) {Lit.27 [D +36.7 (C, 0.97, CH₂Cl₂)}.

(S)-4-Phenyl-1,2-butanediol [S-(–)]

LiAlH₄ (632 mg, 16.6 mmol) was added portionwise over 10 min to a stirred solution of alcohol (S)-23 (410 mg, 1.40 mmol) in THF (20 mL) at r.t. under N₂. The resulting suspension was stirred and heated at reflux for 24 h. After being allowed to cool to r.t., Na₂SO₄-10H₂O (3.0 g) was added portwise and the mixture was stirred at r.t. for 1 h. The solids were removed by filtration through Celite and the filter cake was washed with Et₂O (20 mL), 9:1 CHCl₃–MeOH (100 mL) and MeOH (50 mL). The filtrate was dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography using CHCl₃–MeOH (19:1) as eluent gave diol (S)-24 (98 mg, 42%, 91:9 er) as a colourless oil, which crystallised at –24 °C [{Lit.26 [D +22.5 (c = 1.9, EtOH)]}].

Chiral HPLC: Daicel Chiralcel OD, hexane–PrOH (19:1), 0.5 mL min⁻¹, 254 nm, 87:13 er) as a colourless oil, which crystallised

Chiral HPLC: Daicel Chiralcel OD, hexane–PrOH (4:1), 0.5 mL min⁻¹, 254 nm, 14.5 min [{R-(–)}, 23].

1H NMR (400 MHz, CDCl 3): δ = 7.31–7.28 (m, 2 H, Ph), 7.23–7.19 (m, 3 H, Ph), 3.75–3.69 (m, 1 H, CHO), 3.65 (dd, J = 11.0, 3.0 Hz, 1 H, CH₂H₂O), 3.46 (dd, J = 11.0, 7.5 Hz, 1 H, CH₂H₂O), 2.83–2.65 (m, 4 H, 1.4 H, 1.79–1.72 (m, 2 H).

13C NMR (100.6 MHz, CDCl 3): δ = 124.2 (ipso-Ph), 128.4 (Ph), 128.38 (Ph), 126.0 (Ph), 71.5 (CH₂O), 66.8 (CHO), 34.6 (CH₂), 31.8 (CH₃).

Spectroscopic data are identical to those reported.

(S)-Diisopropylcarbamic Acid 1-(4,4,5,5-Tetramethyl[1,3,2]di-oxaborolan-2-yl)-3-phenylpropyl Ester [S-(–)]

s-BuLi (2.00 mL of a 1.1 M soln in cyclohexane, 2.20 mmol) was added dropwise to a stirred solution of (–)-sparteine (79 mg, 0.34 mmol) in THF (2.0 mL) as eluent. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash chromatography using CHCl₃–MeOH (19:1) as eluent gave borate ester (S)-26 (41 mg, 60%, 87:13 er) as a colourless oil, which crystallised at –24 °C [{Lit.26 [D +22.5 (c = 1.9, EtOH)]}].

Chiral HPLC: Daicel Chiralcel OD, hexane–PrOH (19:1), 0.5 mL min⁻¹, 254 nm, 38.2 min [{S-(–)}, 43.5 min [{R-(–)}.

1H NMR (400 MHz, CDCl 3): δ = 7.29–7.08 (m, 10 H, Ph), 4.61 (dd, J = 8.0, 5.5 Hz, 1 H, CHO), 2.72–2.54 (m, 2 H, PhCH₂), 2.10–1.91 (m, 2 H, CH₂CHO), 1.85 (br s, 1 H, OH).

13C NMR (100.6 MHz, CDCl 3): δ = 144.5 (ipso-Ph), 141.7 (ipso-Ph), 128.5 (Ph), 128.4 (Ph), 128.4 (Ph), 127.7 (Ph), 125.9 (Ph), 125.85 (Ph), 73.9 (CHO), 40.5 (CH₃), 32.1 (CH₃).

Spectroscopic data are identical to those reported.

References

Catalytic Asymmetric Variant of Hoppe’s O-Alkyl Carbamate Deprotonation Methodology


(13) For examples of ligand exchange with (−)-sparteine, see:


