detected by ESMS analysis of this mixture. Deprotonation of **1** with *n*-butyllithium/TMEDA at −78 °C followed by trapping with Ph_2PCl at −30 °C provided the product of *ortho* lithiation–trapping in low yield.

[15] Crystal structure analysis of **7**: Bruker CCD platform diffractomer, 168(2) K, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, the structure was solved by direct methods (SHELXTL; G. M. Sheldrick, SHELXTL Version 5.10, Bruker Analytical X-Ray Systems, Inc.; Madison, WI, **1999**); full-matrix least-squares refinement on F^2 (SHELXTL), structure presentation: crystal dimensions $0.22 \times 0.18 \times 0.08$ mm^3, orange crystals, space group $P2_12_12_1$, orthorhombic, $a = 10.0557(5)$ Å, $b = 17.7209(8)$ Å, $c = 19.4695(9)$ Å, $V = 3469.4(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.481$ Mg m^{-3}, $2\theta_{max} = 56.58°$, 42399 measured, 8460 independent reflections, $R = 0.0343$, $wR = 0.0667$, residual electron density = 0.652 e Å^{-3}, hydrogen atoms were included using a riding model. CCDC-187068 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[16] Diastereomers **10** and **16** could be separated by silica gel chromatography.

[17] Sequential treatment of **16** with a) MeOTf, b) $NaBH_4$, and c) aqueous oxalic acid[18a] provided (*S*p)-tricarbonyl(η^6–2-trimethylsilylbenzaldehyde)chromium(0), $[\alpha]_D^{23} = +151$ ($c = 0.14$ in $CHCl_3$).[18b,c]

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[19] Control experiments established that the selectivities reported in Tables 1 and 2 are largely the result of kinetic control in the lithiation step. For example, generation of the arenyllithium by reaction of iodide **7** with *s*BuLi in Et_2O followed by addition of 10 mol % of **2** and warming to −30 °C in the presence or absence of added TMEDA did not result in significant equilibration. Similarly, treatment of arene **2** with 0.7 equiv *s*BuLi in Et_2O followed by addition of TMEDA (1.5 equiv) also did not result in significant equilibration.

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[22] Although the lithium aggregate is depicted in **A** to be on the face of the *t*Bu substituent, it alternatively could be oriented towards the chromium tripod.

[23] The effective size of this fragment would obviously depend on the orientation of the Ph_3P ligand. It is interesting to note that the torsion angle measured from the center of the arene to C6 and Cr1 to P1 is 53.9° (see Figure 1).

Enantioselective Synthesis of Substituted Pyrrolidines by Dynamic Resolution**

Iain Coldham,* Samuel Dufour, Thomas F. N. Haxell, Steven Howard, and Graham P. Vennall

The formation of enantiomerically enriched products from chiral organolithium species is a highly efficient and selective approach for organic synthesis.[1] The majority of examples involve the selective asymmetric deprotonation of a prochiral hydrogen atom adjacent to an oxygen or nitrogen atom, such as the method developed by the groups of Hoppe and Beak in which *sec*-butyllithium and (−)-sparteine is used as the chiral base.[2] However, an alternative mode of asymmetric induction exists, in which the chiral, racemic organolithium species is formed and complexed with a chiral ligand to promote asymmetric substitution. We report here the first highly enantioselective substitution of nonactivated organolithium species at ambient temperature.

Asymmetric substitution requires, for high yields, a dynamic resolution[3] in which the reacting chiral center can invert under the reaction conditions. Success has been achieved with lithiated allylic or benzylic substrates in the presence of a chiral ligand through either a dynamic thermodynamic or a dynamic kinetic resolution pathway.[4–7] Examples with α-thio and α-seleno organolithium species have also been reported,[8] however, to our knowledge there are no reports of dynamic resolution, followed by addition of an electrophile, of other nonactivated lithiated species. This may be a consequence of the common perception that organolithium species should be generated and treated at low temperature (typically −78 °C); under these conditions, although allylic, benzylic, α-thio and α-seleno organolithium species undergo racemization,[9] nonactivated chiral organolithium species do not normally racemize. For example, α-amino organolithium species display configurational stability at low temperature.[10] We have found, however, that the formation of α-amino organolithium species and their racemization is possible at room temperature.[11] We therefore set out to substitute racemic α-amino organolithium species asymmetrically in the presence of a chiral ligand.

Extending our work on intramolecular carbolithiation,[11,12] we studied the dynamic resolution of chiral 2-lithiopyrrol-

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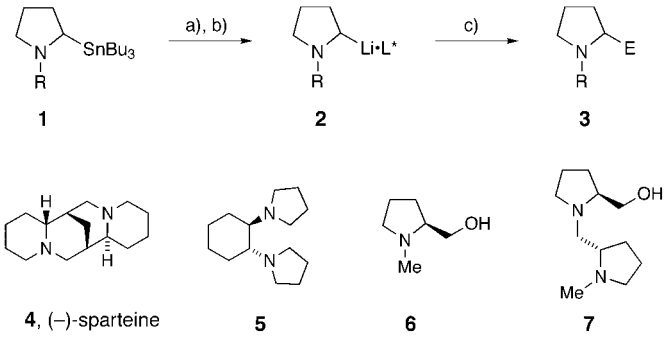
idines (Scheme 1). We tested a variety of N-substituted pyrrolidines and chiral ligands to effect the asymmetric substitution of the organolithium species **2**, generated at room temperature by transmetalation of the racemic stannanes **1**.

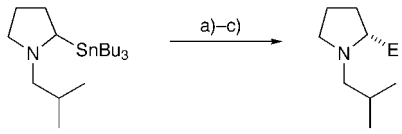


Scheme 1. a) *n*BuLi (1.2 equiv), hexane/Et_2O (4:1), 22 °C, 1 h; b) chiral ligand L* (1.5 equiv), 30 min; c) −10 °C, electrophile E^+, see Tables 1 and 2.

The stannanes **1** (R = alkyl) were prepared from the known stannane **1** (R = CO_2tBu).[10c,11,13] Treatment with *n*BuLi and addition of the chiral ligands **4**–**7** (ligands **6** and **7** were pretreated with *n*BuLi in Et_2O), followed by an electrophile, gave the products **3**, as described in Table 1. Regarding the various N-substituents, greater steric bulk enhanced the enantioselectivity, although the rate of transmetalation was noticeably reduced with larger substituents. There was no enantioselectivity when the derivative **1** (R = CO_2tBu) was used.

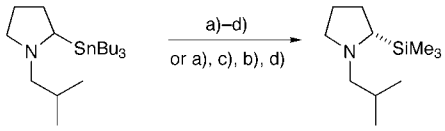
The ligand (−)-sparteine (**4**) provided the products **3** with reasonable enantioselectivity, but we have not yet been able to improve this selectivity with a variety of N-substituents. Interestingly, the major enantiomer has the configuration opposite from that formed by asymmetric deprotonation/electrophile addition of *N*-Boc pyrrolidine with (−)-sparteine (Boc = *tert*-butoxycarbonyl).[10c] Bis(oxazoline) ligands[14] gave no isolable products other than tetrabutyltin, so we turned to chiral diamine or amino alcohol ligands. The ligands **5** and **6** promoted low enantioselectivity (Table 1). However, the commercially available prolinol derivative **7** gave excellent asymmetric induction. Thus, by using the ligand **7**, a selection of 2-substituted pyrrolidines **3** was prepared (Scheme 2, Table 2). In each case the products were formed with > 95:5 enantiomeric ratio.

It is clear that an asymmetric substitution reaction is taking place with dynamic resolution of the intermediate organolithium species. Cooling the organolithium species to −78 °C



Scheme 2. a) *n*BuLi (1.2 equiv), hexane/Et_2O (4:1), 22 °C, 1 h; b) **7** (1.5 equiv, pretreated with *n*BuLi), Et_2O, 30 min; c) −10 °C, E^+.

prior to addition of the chiral ligand and then the electrophile results in the formation of a racemic mixture of the pyrrolidine products **3**. However, addition of the chiral ligand *before* cooling to −78 °C provides the products **3** with high enantioselectivity (Scheme 3). These results suggest that a dynamic thermodynamic resolution is operating.[3a]



Scheme 3. a) *n*BuLi (1.2 equiv), hexane/Et_2O (4:1), 22 °C, 1 h; b) −78 °C; c) **7** (1.5 equiv, pretreated with *n*BuLi, 1.8 equiv), Et_2O, 30 min; d) Me_3SiCl (4 equiv). Sequence a–d: product **3e**, yield 77 %, e.r. 50:50; sequence a,c,b,d: product (*S*)-**3e**, yield 74 %, e.r. ≥ 96:4

In dynamic thermodynamic resolution, the ratio of enantiomers of the product results from the ratio of the intermediate diastereomeric complexes, which interconvert slowly in comparison with the rate of reaction with the electrophile. To determine which of these complexes reacts faster with the electrophile, the organolithium–ligand complex **2** (50:50

Table 1. Formation of pyrrolidines **3** by using chiral ligands **4**–**7**.

R	Ligand	"E^+"	E	Product	Yield [%]	e.r.[a]	Config.[b]
Et	**4**	Me_3SiCl	$SiMe_3$	**3a**	81	73:27	(*R*)
*n*Pn	**4**	$CO_2/LiAlH_4$	CH_2OH	**3b**	83	81:19	(*S*)
*n*Oct	**4**	Me_3SiCl	$SiMe_3$	**3c**	50	75:25	(*R*)
CH_2tBu	**4**	Me_3SiCl	$SiMe_3$	**3d**	30	80:20	(*R*)
*i*Bu	**4**	Me_3SiCl	$SiMe_3$	**3e**	78	85:15	(*R*)
*i*Bu	**4**	PhNCO	CONHPh	**3f**	57	82:18	(*S*)
*i*Bu	**5**	Me_3SiCl	$SiMe_3$	**3e**	49	60:40	(*R*)
*i*Bu	**6**	PhNCO	CONHPh	**3f**	76	59:41	(*R*)
*i*Bu	**7**	PhNCO	CONHPh	**3f**	61	97:3	(*R*)

[a] The enantiomer ratio was determined by either HPLC or NMR spectroscopy. [b] The absolute configuration of the major enantiomer was determined by comparison with an authentic sample prepared from (*S*)-**1** (R = Boc).

Table 2. Formation of pyrrolidines **3** (R = *i*Bu) by using chiral ligand **7**.

"E^+"	E	Product	Yield [%]	e.r.[a]	Config.[b]
Me_3SiCl	$SiMe_3$	**3e**	75	≥ 96:4	(*S*)
PhNCO	CONHPh	**3f**	61	97:3	(*R*)
Me_2CO	$C(OH)Me_2$	**3g**	54	≥ 96:4	(*R*)
Bu_3SnCl	$SnBu_3$	**3h**	71	96:4	(*S*)
Me_2SO_4	Me	**3i**	65[c]	≥ 96:4	(*S*)
p-$MeOC_6H_4CHO$	$CH(OH)C_6H_4OMe$	**3j**	70[c,d]	97:3	(*anti*)
				97:3	(*syn*)

[a] The enantiomer ratio was determined by HPLC, NMR spectroscopy, or specific rotation. [b] The absolute configuration was determined by comparison with an authentic sample prepared from (*S*)-**1** (R = Boc). [c] E^+ added at −78 °C. [d] *anti*:*syn* = 1:1.

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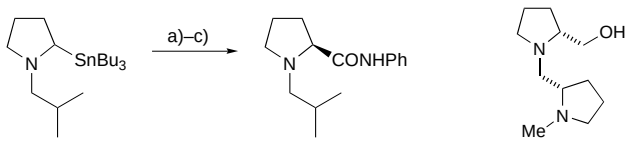
mixture of diastereomeric complexes, formed by adding the ligand **7** after cooling to −78 °C) was treated with 0.3 molar equivalents of the electrophile TMSCl. The product **3e** was formed as a mixture of enantiomers in the ratio 61:39 (*R*:*S*) (opposite enantioselectivity) which indicates that the minor diastereomeric complex reacts faster. Similar results were obtained with the ligand (−)-sparteine (**4**) in which case asymmetric substitution occured by a dynamic thermodynamic resolution with the minor diastereomeric complex reacting faster.

By employing the diastereomer **8** of the chiral ligand **7**,[15] the opposite major enantiomer of the 2-substituted pyrrolidine was formed (Scheme 4). It is possible, therefore, to prepare highly enantioenriched (*R*)- and (*S*)-2-substituted pyrrolidines, by starting from racemic organolithium species and using a dynamic resolution at ambient temperature with control of the absolute configuration by choice of the chiral ligand.



(±)-**1**, R = *i*Bu **3f** **8**

Scheme 4. a) *n*BuLi (1.2 equiv), hexane/Et_2O (4:1), 22 °C, 1 h; b) chiral ligand **8** (1.5 equiv, pretreated with *n*BuLi), 30 min; c) −10 °C, PhNCO. Product (*S*)-**3f**, yield 74 %, e.r. 96:4.

Experimental Section

General procedure: The racemic stannane **1**, R = *i*Bu,[13] (0.3 g, 0.72 mmol) in hexane/Et_2O (0.8 mL, 4:1) was treated with *n*BuLi (0.35 mL, 0.86 mmol, 2.5 M in hexanes) at room temperature. After 1 h, the deprotonated ligand **7** (prepared by adding *n*BuLi (0.52 mL, 1.3 mmol) to **7** (0.21 g, 1.3 mmol) in Et_2O (0.8 mL) at −30 °C, then warming to room temperature) was added. After 30 min at room temperature, the mixture was cooled to −10 °C and the electrophile PhNCO (0.33 mL, 3.0 mmol) was added. After 1 h, citric acid (30 mL, 10 % aqueous solution) was added and the aqueous layer was extracted with Et_2O (30 mL), basified with $NaHCO_3$ (30 mL, saturated solution) and extracted with Et_2O (30 mL). This latter organic layer was dried (Na_2SO_4), evaporated, and the residue was purified by column chromatography on silica, eluting with light petroleum (b.p. 40–60 °C)/EtOAc (4:1) to give the pyrrolidine **3f** (109 mg, 61 %), $[\alpha]_D^{25} = +154.8$ (c = 0.78, $CHCl_3$), e.r. 97:3 determined by chiral HPLC (Chiracel AD column, hexane/EtOH 90:10, flow rate 1.0 mL min^{-1}, detection at 235 nm, retention times: 6.7 and 10.4 min).

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