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Catalytic Asymmetric Synthesis of Ferrocenes and *P*-Stereogenic Bisphosphines

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Chiral ferrocenes[1] and *P*-stereogenic bisphosphines[2] are two of the most important classes of chiral ligands for transition metal-catalyzed asymmetric processes. Surprisingly, however, almost all of the methods used to prepare such chiral ligands use *stoichiometric* quantities of a chiral reagent or auxiliary.[3,4] Two recent reports on catalytic asymmetric synthesis of *P*-stereogenic phosphines[5,6] have prompted us to disclose our results. In this paper, efficient asymmetric deprotonation−electrophilic trapping reactions of a ferrocene amide **1** (→ **2**)[7] and a phosphine borane **3** (→ **4**)[8,9] using *n*-BuLi or *s*-BuLi in conjunction with *substoichiometric* quantities (0.1−0.5 equiv) of chiral diamines are described (Scheme 1). We were particularly attracted to developing catalytic asymmetric variants of such reactions since they each deliver products that are precursors to important chiral catalysts in their own right.[10−12] In addition, either enantiomer of the products **2** and **4** can be accessed using (−)-sparteine or the (+)-sparteine surrogate **5**.[13]

Since the reactivity of *n*-BuLi or *s*-BuLi is increased by complexation to (−)-sparteine, we reasoned that it should be possible to successfully use substoichiometric amounts of the chiral diamine in ligand-accelerated asymmetric deprotonation. We refer to this as *one-ligand catalysis*[14] to distinguish it from our recently developed ligand-exchange approach to catalytic deprotonation (*two-ligand catalysis*).[15]

To start with, we confirmed that (−)-sparteine and (+)-sparteine surrogate **5** gave enantiocomplementary results in the stoichiometric conversion of ferrocene **1** into **2**. Thus, ferrocene amide **1** was lithiated using *n*-BuLi/(−)-sparteine and then reacted with methyl iodide to deliver a 77% yield of adduct (*S*)-**2** of 98:2 er (Table 1, entry 1).[7b] Pleasingly, use of (+)-sparteine surrogate **5** led to the formation of the antipode (*R*)-**2** of 96:4 er (78% yield) (Table 1, entry 5). Next, we examined the use of substoichiometric amounts of the chiral diamines. With 0.4 equiv of (−)-sparteine, ferrocene amide (*S*)-**2** of 92:8 er was produced in 78% yield (entry 2). This result is strikingly similar to that obtained using 1.2 equiv of (−)-sparteine (77%, 98:2 er, Table 1, entry 1) and demonstrates that (−)-sparteine is being recycled. Lower loadings of (−)-sparteine led to reduced enantioselectivity (Table 1, entries 3 and 4), presumably due to background deprotonation by *n*-BuLi alone (which was verified by a 41% yield of *rac*-**2** from a reaction in the absence of diamine ligand, Table 1, entry 8). Notably, even better results were obtained using the (+)-sparteine surrogate **5**: with 0.4 equiv of diamine **5**, a 75% yield of ferrocene amide (*R*)-**2** of 94:6 er was generated (Table 1, entry 6), which is almost identical to the stoichiometric result (78%, 96:4 er, Table 1, entry 5). In addition, use of only 0.2 equiv of diamine **5** produced adduct (*R*)-**2** with high enantioselectivity (84%, 89:11 er, Table 1, entry 7).

A similarly successful set of catalytic results was obtained in the lithiation−oxygenation of phosphine borane **3**.[9b] Using *s*-BuLi and stoichiometric (−)-sparteine followed by reaction with air, we isolated alcohol (*R*)-**4** of 92:8 er (65% yield) (Table 2, entry 1), a result that could be nearly matched using 0.5 equiv of (−)-sparteine (61%, 87:13 er, Table 2, entry 2).[16] With 0.2 equiv of (−)-sparteine, the enantioselectivity was lower (77:23 er, Table 2, entry 4). In contrast, and in line with the results obtained with ferrocene amide **1**, the (+)-sparteine surrogate **5** proved to be a superior catalyst. Thus, the enantioselectivity was essentially the same using 1.2 and 0.5 equiv of diamine **5** (Table 2, entries 4 and 5), and even using 0.2 equiv of (+)-sparteine surrogate **5**, alcohol (*S*)-**4** was generated with high selectivity (54%, 86:14 er, Table 2, entry 6). We believe that the higher enantioselectivity observed with the (+)-sparteine surrogate **5** compared to (−)-sparteine is a result of a faster deprotonation by the *n*-BuLi or *s*-BuLi/diamine **5** complex compared to that with the (−)-sparteine complex.[17]

To further demonstrate the usefulness of these catalytic reactions, we carried out catalytic asymmetric lithiation−dimerization of

Scheme 1

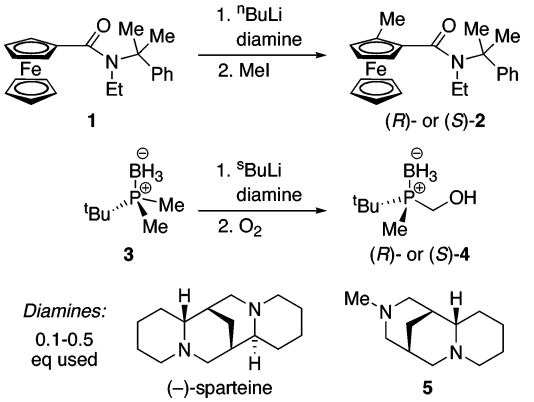

Table 1. Asymmetric Directed Ortho-Metalation of Ferrocene Amide **1** (→ **2**) Using Substoichiometric Quantities of Chiral Diamines

entry	diamine[a]	equiv of diamine	yield of **2** (%)[b]	er (*S*:*R*)[c]
1	(−)-sparteine	1.2	77	98:2
2	(−)-sparteine	0.4	78	92:8
3	(−)-sparteine	0.3	77	84:16
4	(−)-sparteine	0.2	72	75:25
5	**5**	1.2	78	4:96
6	**5**	0.4	75	6:94
7	**5**	0.2	84	11:89
8			41[d]	

[a] Reaction conditions: (i) 1.2 equiv of *n*-BuLi, 6:1 Et_2O−toluene, −78 °C, 2 h; (ii) MeI, −78 °C, 1 h then to room temperature over 4 h and room temperature, 12 h. [b] Isolated yield of **2** after chromatography. [c] Enantiomer ratio (er) determined by chiral HPLC (Chiralcel OD) of the decumylated ferrocene amide (see Supporting Information and ref 7b). [d] Reaction carried out in the absence of diamine ligand; 25% of ferrocene amide **1** also recovered.

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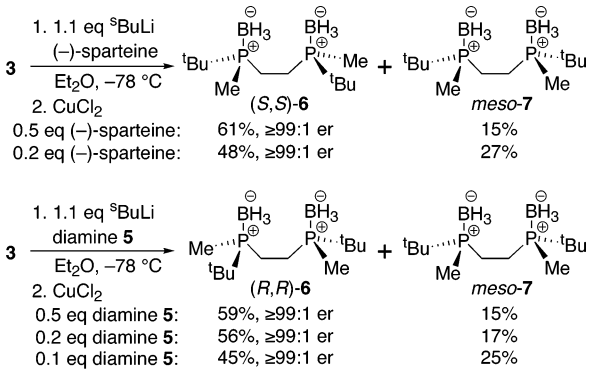
Table 2. Asymmetric Lithiation−Trapping of Phosphine Borane **3** (→ **4**) Using Substoichiometric Quantities of Chiral Diamines

entry	diamine[a]	equiv of diamine	yield of **4** (%)[b]	er (*R*:*S*)[c]
1	(−)-sparteine	1.2	65	92:8
2	(−)-sparteine	0.5	61	87:13
3	(−)-sparteine	0.2	57	77:23
4	**5**	1.2	63	9:91
5	**5**	0.5	60	8:92
6	**5**	0.2	54	14:86
7			57[d]	

[a] Reaction conditions: (i) 1.1 equiv of *s*-BuLi, Et_2O, −78 °C, 3 h; (ii) air, −78 °C, 1 h then room temperature, 16 h. [b] Isolated yield of **4** after chromatography. [c] Enantiomer ratio (er) determined by chiral HPLC (Chiralcel AD) of the benzoate (see Supporting Information). [d] Reaction carried out in the absence of diamine ligand.

Scheme 2



phosphine borane **3** to either bisphosphine (*S*,*S*)-**6** or (*R*,*R*)-**6**. To our delight, good yields (45−61%) of bisphosphine (*S*,*S*)-**6** or (*R*,*R*)-**6** (each ≥99:1 er) were obtained using substoichiometric amounts of the chiral diamine (Scheme 2). These dimerizations benefit from asymmetric amplification[18] (an under-utilized approach to enantiopure compounds), and the isolated yield of (*S*,*S*)- or (*R*,*R*)-**6** compared to that of *meso*-**7** is an indication of the efficiency of the catalysis. Significantly, use of just 0.1 equiv of (+)-sparteine surrogate **5** directly gave a 45% yield of (*R*,*R*)-**6** of ≥99:1 er.

In conclusion, we demonstrate that it is not necessary to use stoichiometric amounts of (−)-sparteine or (+)-sparteine surrogate **5** in the asymmetric deprotonation of ferrocene amide **1** and phosphine borane **3**. Instead, one-ligand catalytic asymmetric deprotonation is a viable and effective method for the synthesis of planar chiral ferrocenes and *P*-stereogenic bisphosphines, two important classes of chiral ligands for metal-catalyzed asymmetric processes. It is also of note that *n*-BuLi or *s*-BuLi and the (+)-sparteine surrogate **5** are more efficient catalysts than the corresponding (−)-sparteine complexes, which has important implications for catalytic asymmetric synthesis using organolithiums/diamine **5**.

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Supporting Information Available: Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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