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Evaluation of (+)-Sparteine-like Diamines for Asymmetric Synthesis

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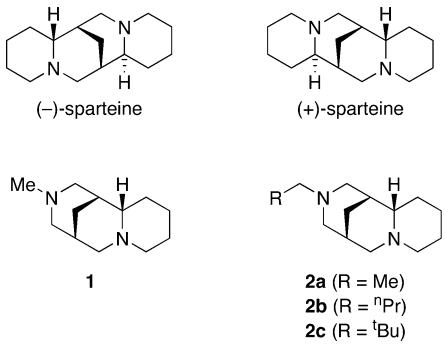
Abstract: Three new (+)-sparteine-like diamines were prepared from (−)-cytisine and evaluated as sparteine surrogates in the α-lithiation rearrangement of cyclooctene oxide and the palladium(II)/diamine catalyzed oxidative kinetic resolution of 1-indanol. The new diamines exhibited opposite enantioselectivity to that observed with (−)-sparteine but increasing the steric hindrance of the *N*-alkyl group beyond *N*-Et had a detrimental effect on enantioselectivity. The optimal *N*-Me diamine was evaluated with much success in five other (−)-sparteine-mediated processes involving different metals (lithium, magnesium, and copper) and different types of reaction mechanisms.

As part of our ongoing program of research into the development of new sparteine-like ligands for asymmetric synthesis, we recently described the synthesis of diamine **1** and its evaluation as a (+)-sparteine surrogate.[1,2] Diamine **1** can be readily prepared in three steps from (−)-cytisine (extracted from *Laburnum anagyroides* seeds[3]) and was shown to have good "(+)-sparteine-like" properties: essentially equal and opposite enantioselectivity was achieved with (−)-sparteine and diamine **1** in four different test reactions.[1] With these initial results in hand, we wanted to determine whether the *N*-Me substituent in diamine **1** was optimal for high enantioselectivity. Thus, three new diamines **2a**−**c** with *N*-alkyl groups of different steric demands (*N*-Et, *N*-^{n}Bu and *N*-$CH_2{}^t$Bu) were synthesized and have been evaluated in comparison with diamine **1** and (−)-sparteine in the α-lithiation rearrangement of cyclooctene oxide[5] and the palladium(II)/diamine catalyzed oxidative kinetic resolution of 1-indanol.[6,7] Recently, Kann et al. have reported a comparison between (−)-sparteine, diamine **1**, and a *N*-^{i}Pr-substituted analogue of **1** in the asymmetric lithiation of phosphine−borane complexes.[4] Furthermore, we have also evaluated the efficacy of diamine **1** as a (+)-sparteine surrogate in a wider range of (−)-sparteine-mediated asymmetric reactions: (i) carbolithiation of (*E*)-cinnamyl alcohol;[8] (ii) desymmetrization of a *meso* anhydride using phenylmagnesium chloride;[9] (iii) asymmetric substitution of *N*-pivaloyl-*o*-ethylaniline;[10] (iv) dynamic resolution of *tert*-butylphenylphosphine−borane,[11] and (v) copper(II)-mediated resolution of BINOL.[12] This study includes a variety of metals (lithium, magnesium, and copper) and, importantly, a range of different reaction mechanisms (i.e. not simply asymmetric deprotonation). Herein we describe the results of these studies.



Our previously described route to diamine **1** from extracted[3] (−)-cytisine was easily modified for the preparation of diamines **2a**−**c** (Scheme 1). Standard acylation of (−)-cytisine with aqueous sodium hydroxide and the appropriate acid chloride furnished *N*-acylated cytisines **3a**−**c** in 65−84% yield. Then, pyridone hydrogenation gave crude lactams **4a**−**c** (isolated but not purified) which were directly subjected to reduction with excess lithium aluminum hydride in refluxing THF to give diamines **2a**−**c**. After purification by Kugelrohr distillation, diamines **2a**−**c** were isolated as colorless oils in 81−89% yield over the two steps. As far as can be judged by ^{1}H NMR spectroscopy, diamines **2a**−**c** (and lactams **4a**−**c**, isolated and characterized in separate experiments) were obtained as single diastereoisomers and we have assigned their relative stereochemistry to be that shown in Scheme 1 based on preferential pyridone hydrogenation on the less hindered *exo* face of **3a**−**c** and by analogy with the synthesis of diamine **1** (the stereochemistry of which was secured by X-ray crystallography of an intermediate lactam[2]).

Over the past few years, the Hodgson group have extensively studied enantioselective epoxide desymmetrization using alkyllithiums/diamines (e.g. (−)-sparteine) and they have reported several pioneering contributions.[5,13−16] For the α-lithiation -rearrangement of medium-ring cycloalkene oxides with alkyllithiums,[5,15] the optimized reaction conditions (85:15−95:5 er) are 2.4 equiv

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SCHEME 1. Synthesis of Diamines 2a−c from (−)-Cytisine

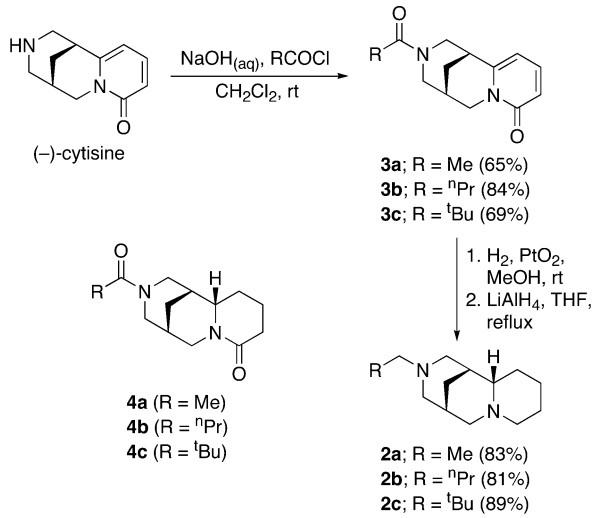
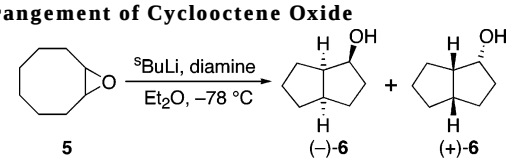


TABLE 1. Evaluation of Diamines in the α-Lithiation rearrangement of Cyclooctene Oxide



entry	diamine[a]	major product	yield (%)[b]	er[c]
1	(−)-sparteine	(−)-**6**	84	83:17 (85:15)
2	**1**	(+)-**6**	70	19:81
3	**2a**	(+)-**6**	72	18:82
4	**2b**	(+)-**6**	53	27:73
5	**2c**	(+)-**6**	53	34:66

[a] Reaction conditions: 2.4 equiv of ^{s}BuLi, 2.4 equiv of diamine, Et_2O, −78 °C, 5 h. [b] Isolated yield of (−)- or (+)-**6** after purification by column chromatography. [c] Enantiomer ratio determined by chiral HPLC (Daicel Chiralpak AD) of the 2,4-dinitrobenzoate (the value in parentheses is the literature er under essentially the same reaction conditions[5]).

of *sec*-butyllithium (or isopropyllithium) and 2.5 equiv of (−)-sparteine (or (−)-α-isosparteine) in Et_2O at −90 °C (or −98 °C). For the α-lithiation rearrangement of cyclooctene oxide **5** into bicyclic alcohol **6**, we carried out our comparative study using commercially available *sec*-butyllithium at the more convenient reaction temperature of −78 °C. The results are presented in Table 1. With use of 2.4 equiv of *sec*-butyllithium/(−)-sparteine in Et_2O at −78 °C for 5 h followed by warming to room temperature, cyclooctene oxide **5** gave bicyclic alcohol (−)-**6** in 84% yield and with 83:17 er (entry 1), virtually identical with that reported by Hodgson et al. (81% yield, 85:15 er[5]) under comparable conditions. When the reactions were carried out with diamines **1** and **2a**−**c** (entries 2−5), bicyclic alcohol (+)-**6** was the major product (opposite enantioselectivity to (−)-sparteine) and enantioselectivity comparable to that obtained with (−)-sparteine (entry 1) was observed with diamines **1** (81:19 er) and **2a** (82:18 er) (entries 2 and 3), i.e., ligands that have the least sterically demanding *N*-alkyl substituents. In contrast, as the steric size of the *N*-alkyl group increased, the enantioselectivity was compromised (entries 4−5): diamine **2c** with the most sterically hindered *N*-alkyl group (*N*-$CH_2{}^t$Bu) gave bicyclic alcohol (+)-**6** in 53% yield and with 66:34 er (entry 5). From this, we conclude that sterically undemanding *N*-alkyl groups (e.g. *N*-Me in **1** and *N*-Et in **2a**) in (−)-cytisine-derived diamines or conformationally constrained bispidines such as (−)-sparteine are optimal for high enantioselectivity in the α-lithiation rearrangement of cyclooctene oxide **5**.

Next, the palladium(II)/diamine catalyzed oxidative kinetic resolution of 1-indanol was used to evaluate the enantioselectivity with the different diamines. The use of palladium(II)/(−)-sparteine/oxygen as reagents for the kinetic resolution of secondary alcohols (by oxidation to the corresponding ketones) was independently reported by the groups of Sigman[6] and Stolz[7] in 2001. Since then, extensive efforts from both groups have resulted in additional mechanistic insight[17] (e.g., the role of excess (−)-sparteine) and the development of new reagent systems[18] (e.g., the use of carbonate bases, *tert*-butyl alcohol, as solvent or additive). In particular, these efforts culminated in Bagdanoff and Stolz's report of an optimized room-temperature system that utilizes palladium(II)/(−)-sparteine/cesium carbonate in chloroform and air.[19] Surprisingly, despite all of the developments to reaction conditions and significant efforts in addressing substrate scope, there has been only one example of ligand variation ((−)-α-isosparteine[17d]) since those in the original disclosures[6,7] (where (−)-sparteine was identified as the optimum chiral ligand).

We limited the initial study described here to the conditions originally reported by Ferraira and Stolz[7] and selected the resolution of 1-indanol *rac*-**7** (actually one of the worst substrates) as representative. Thus, 1-indanol *rac*-**7** was subjected to reaction with palladium(II)/diamine/oxygen in toluene at 60 °C for 54 h and the selectivity factor (*s*) was calculated by using the percent conversion (*C*) to ketone **8** and the percent ee of the unreacted 1-indanol **7**.[20] The results obtained with the different diamines are shown in Table 2. With (−)-sparteine, indanol (*R*)-**7** was obtained as the major

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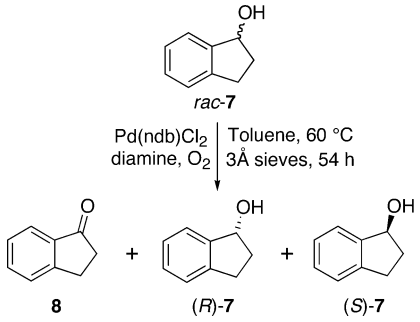
TABLE 2. Evaluation of Diamines in the Oxidative Kinetic Resolution of 1-Indanol



entry	diamine[a]	major product	*C* (%)[b]	er of **7** (%)[c]	*s*[d]
1	(−)-sparteine	(*R*)-**7**	67	96:4	8.0 (8.3)
2	**1**	(*S*)-**7**	41	28:72	6.8
3	**2a**	(*S*)-**7**	68	9:91	5.3
4	**2b**	(*S*)-**7**	64	21:79	3.4
5	**2c**	−	0		

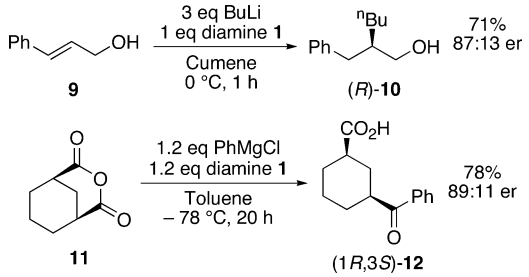
[a] Reaction conditions: 20 mol % of diamine, 5 mol % of $Pd(nbd)Cl_2$, toluene, O_2, 3 Å molecular sieves, 60 °C, 54 h. [b] *C* = % conversion to ketone **8**, determined from the ^1H NMR spectrum of the crude product. [c] Enantiomer of **7** determined by chiral HPLC (Daicel Chiralpak OJ-R) of the crude product. [d] *s* = selectivity factor, calculated from the % conversion (*C*) and the % ee of **7**[20] (the value in parentheses is the literature selectivity factor under essentially the same reaction conditions[7]).

product with *s* = 8.0 (entry 1) and this was satisfyingly comparable to the literature value (*s* = 8.3).[7] With diamines **1** and **2a**,**b**, the kinetic resolution proceeded in the opposite sense and indanol (*S*)-**7** was the major product, but with reduced selectivity factors (entries 2−4). The least sterically hindered diamine **1** (*N*-Me) gave the most selective kinetic resolution (*s* = 6.8; entry 2) and this is the largest selectivity factor reported for a reaction that proceeds with the opposite sense of induction compared to (−)-sparteine. In contrast, increasing the steric size of the *N*-alkyl group in diamines **2a**−**c** had a detrimental effect on the selectivity factor. Indeed, with the most sterically hindered diamine **2c**, there was no conversion into ketone **8** (entry 5). Similarly poor selectivity and low reactivity were noted by Stolz when (−)-sparteine was replaced with (−)-α-isosparteine and were rationalized by an experimentally derived model.[17d] This process is clearly very sensitive to seemingly small changes in diamine structure and it appears that (−)-sparteine is an optimal ligand for this process.

The results presented thus far indicate that the originally introduced diamine **1** (*N*-Me substituent) is the best (+)-sparteine mimic, a conclusion that Kann et al. independently reached using a *N*-^{i}Pr-substituted analogue of diamine **1** in phosphine−borane lithiations.[4] Thus, we went on to evaluate the scope and limitations of diamine **1** in five other reactions. Since three out of four of our originally reported "test reactions" were in fact asymmetric deprotonations,[1] it was particularly important to show that diamine **1** could induce similar

(20) The selectivity factor (*s*) is a measure of the relative rate of reaction of the two enantiomers ($k_{rel(fast/slow)}$) and can be calculated from the following equation: $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where *C* is the % conversion and ee is the % enantiomeric excess. See: Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, pp 249−330.

SCHEME 2. Evaluation of Diamine 1 in Carbolithiation and Desymmetrization of a *meso* Anhydride



but opposite enantioselectivity to (−)-sparteine in a mechanistically diverse set of reactions. Two examples are shown in Scheme 2. Normant, Marek, and co-workers have demonstrated that highly enantioselective carbolithiation of cinnamyl derivateives (e.g. **9** → **10**) can be achieved using alkyllithiums in the presence of (−)-sparteine.[8] In our hands, carbolithiation of (*E*)-cinnamyl alcohol **9** using *n*-butyllithium/diamine **1** in cumene at 0 °C for 1 h gave alcohol (*R*)-**10** in 71% yield with 87:13 er. This is essentially opposite to the enantioselectivity obtained by Normant with (−)-sparteine (82% yield, 91.5:8.5 er in favor of (*S*)-**10**).[8] It should be noted in passing that Normant has also described a complementary route to alcohol (*R*)-**10** (85:15 er) via carbolithiation of (*Z*)-cinnamyl alcohol using (−)-sparteine.[8] More recently, Shintani and Fu reported the combination of Grignard reagents and (−)-sparteine as a way of desymmetrizing *meso* anhydrides to the corresponding keto acids (e.g. **11** → **12**).[9] Indeed, this was the first highly selective example of asymmetric synthesis with Grignard reagents and (−)-sparteine. Following Fu's protocol, reaction of phenylmagnesium chloride/diamine **1** with *meso* anhydride **11** in toluene at −78 °C for 20 h generated a 78% yield of keto acid (1*R*,3*S*)-**12** with 89:11 er (Fu reported a 77% yield of (1*S*,3*R*)-**12** with 91:9 er using (−)-sparteine[9]). These results clearly indicate that diamine **1** is a good surrogate for (+)-sparteine in these two reactions.

For completeness, we felt it important to demonstrate that diamine **1** was able to match (−)-sparteine in reactions where thermodynamic equilibration at some stage in the reaction profile was the driving force for the observed enantioselectivity.[21] Three very different examples were selected and the results are presented in Scheme 3. Following detailed mechanistic work, Beak and co-workers demonstrated that the lithiation−electrophilic trapping of *N*-pivaloyl-*o*-ethylaniline **13** (e.g. **13** → **14**) proceeded via a dynamic thermodynamic resolution of the intermediate lithiated species.[10,21] With Beak's protocol, *N*-pivaloyl-*o*-ethylaniline **13** was treated with 2.4 equiv of *s*-butyllithium in Et_2O at −25 °C for 2 h to generate the dianion. Subsequently, diamine **1** (2.9 equiv) was added and the organolithium species were allowed to equilibrate over 45 min. The predominant organolithium at −25 °C was then "trapped" by rapid cooling to −78 °C (a temperature where it is presumed to be

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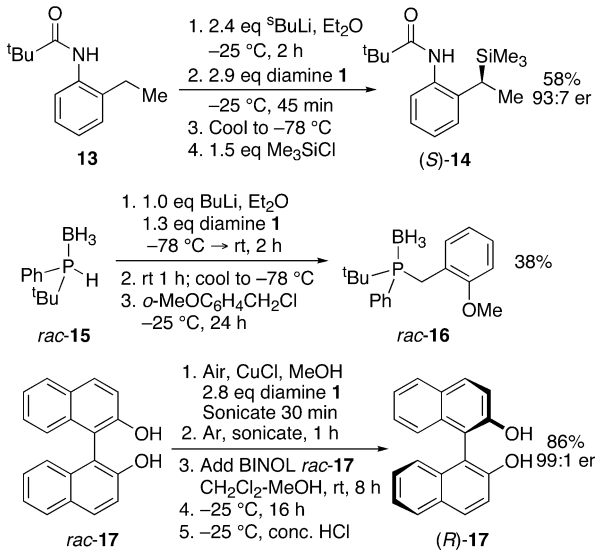
SCHEME 3. Evaluation of Diamine 1 in Dynamic Thermodynamic Resolutions.



configurationally stable). Electrophilic quenching at −78 °C followed by workup then gave a 58% yield of silyl adduct (*S*)-**14** (93:7 er). This should be compared to the 72% yield of (*R*)-**14** (95:5 er) obtained by Basu and Beak using (−)-sparteine.[10a] It is worth noting in passing that Beak has also reported two routes (involving either a transmetalation protocol or a sacrificial electrophile) to silyl adduct (*S*)-**14** using (−)-sparteine but neither proceed with very high enantioselectivity.

In contrast to the success observed with the asymmetric substitution of *N*-pivaloyl-*o*-ethylaniline **13**, the attempted dynamic thermodynamic resolution of lithiated *tert*-butylphenylphosphine−borane *rac*-**15** returned only racemic **16**. As reported by Wolfe and Livinghouse,[11] lithiation of *rac*-**15** with *n*-butyllithium/diamine **1** followed by equilibration at room temperature for 1 h and then trapping with 2-(chloromethyl)anisole at −78 °C gave a 38% yield of phosphine−borane *rac*-**16** (Scheme 3). Crucial to the success of the Livinghouse procedure is the formation of a "voluminous precipitate" during the 1 h at room temperature, a process that presumably drives the dynamic resolution under these conditions.[11] Using diamine **1**, we did not observe a precipitate with the solution remaining homogeneous throughout. For comparison, we repeated the reaction with (−)-sparteine: a precipitate did indeed form and the enantioselectivity (96:4 er) was essentially the same as that reported by Livinghouse.[11]

As a final example, we were attracted to the recent work of Wulff et al. on the use of copper(II) and (−)-sparteine to resolve racemic BINOL **17**. Following Kocovsky and co-worker's original report,[22] Wulff optimized a procedure for the efficient resolution of BINOL *rac*-**17** using (−)-sparteine and in situ-generated copper(II).[12] Mechanistically, it is presumed that the resolution proceeds via dynamic thermodynamic resolution of the BINOL−copper(II)−sparteine complex. In our hands, Wulff's protocol gave a good yield and excellent er using diamine **1** (Scheme 3). Thus, copper(I) chloride was sonicated in MeOH/air for 30 min before degassing with argon/sonication for 1 h. Complexation with BINOL *rac*-**17** (in CH_2Cl_2) followed by equilibration for 8 h at room temperature and then "trapping" at −25 °C for 16 h before low temperature (−25 °C) quench and workup afforded an 86% yield of BINOL (*R*)-**17** with 99:1 er. Using (−)-sparteine, Wulff reported a 96% yield of BINOL (*S*)-**17** with 96:4 er.[12]

In summary, three new (+)-sparteine-like diamines were prepared and evaluated in two different reactions. From this, together with Kann's recent report using a *N*-^{i}Pr-substituted analogue of **1** and other results from our laboratory,[23] we conclude that diamine **1** is the most useful (+)-sparteine surrogate to date. Increasing the steric size of the *N*-alkyl substituent from *N*-Me (as in diamine **1**) has an adverse effect on the enantioselectivity of the α-lithiation rearrangement of cyclooctene oxide and the palladium(II)/diamine catalyzed oxidative kinetic resolution of 1-indanol. The epoxide rearrangement reaction was somewhat more tolerant and both diamines **1** (*N*-Me) and **2a** (*N*-Et) gave good enantioselectivity. In contrast, the oxidative kinetic resolution of 1-indanol was very sensitive to the steric hindrance of the diamine ligand: diamine **1** (*N*-Me) gave the highest selectivity factor ($s = 6.8$) with the opposite sense to (−)-sparteine whereas diamine **2c** (*N*-$CH_2{}^t$Bu) did not oxidize any 1-indanol to the corresponding ketone. Significantly, we have also demonstrated the usefulness of diamine **1** in a wide range of asymmetric transformations that utilize different metals (lithium, palladium, magnesium, and copper) and proceed via diverse mechanistic pathways. Further optimization of the ligand and/or reaction conditions will be required to obtain satisfactory results in Livinghouse's dynamic thermodynamic resolution of *tert*-butylphenylphosphine−borane **15**. Nonetheless, in six out of the seven processes presented here (and two others[4,23]), diamine **1** is the best way of accessing the opposite enantiomers of the products obtained from the (−)-sparteine-mediated reactions.

Acknowledgment. This work was supported by the BBSRC (M.J.D.) and the EPSRC (M.J.M.).

Supporting Information Available: Full experimental procedures and characterization data, derivatization procedures for determining er of **6**, **10**, and **12**, characterization data for lactams **4a**−**c**, and $^1H/^{13}C$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) We have also found that diamine **1** is optimal for the asymmetric lithiation-trapping of *N*-Boc pyrrolidine. These results will be reported elsewhere, together with a detailed computational study.