mixture was suction filtered over celite, and the filtrate was concentrated. The residual solid was then stirred under 0.005 torr with gradual warming to 90 °C (oil bath) to remove MeHgCl. The residue in the flask was then dissolved in 50 mL of hexanes and suction filtered through Celite. Rotary evaporation of the filtrate gave 1.25 g (63%) of the product as a white crystalline solid, mp 64–6 °C, $[\alpha]^{25}_D$ +53.52° (c 2.78, $CHCl_3$). Recrystallization from hexanes afforded the analytical sample, mp 71–2 °C. ^1H NMR ($CDCl_3$): 1.02 (s, 3, Me), 1.04 (d, 1, J = 9.1 Hz), 1.25 (s, 3, $^2J(^{119}SnCH)$ = 65.9 Hz, $SnMeCl_2$), 1.27 (s, 3, Me), 1.46 (s, 9, $C(Me)_3$), 2.10 (br m, 1), 245 (m, 4), 2.93 (dd, 1, J = 19.0, 10.2 Hz), 3.33 (dd, 1, J = 9.3, 2.3 Hz, $HCCO_2Bu$, $^3J(^{119}SnCCH)$ = 163.5 Hz). IR (KBr): 1672, 1367, 1157, 776, 542, 527, 313 cm^{-1}.

Anal. Calcd for $C_{15}H_{26}SnO_2Cl_2$: C, 42.10; H, 6.12. Found: C, 42.16; H, 6.10.

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Asymmetric Induction with Amidocuprates

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Optically active amines such as (*R*)- or (*S*)-α-methylbenzylamine and (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane can be lithiated with an alkyllithium and added to an organocopper(I) compound, prepared from a lithium reagent and CuI, to give a chiral organocuprate. The 3-phenylcyclohexanone obtained from such a phenyl cuprate and 2-cyclohexenone has up to 50% ee. Running the reaction in the presence of chlorotrimethylsilane improved the results in some cases. The counterion in the Cu(I) precursor, the cation (Li^+ or Mg^{2+}), the solvent, and the temperature also have important effects.

Organocopper reagents are among the most useful of C–C bond forming reagents, and a chiral organocopper reagent that would give high levels of asymmetric induction would be an especially valuable addition to existing methodology for the synthesis of optically active products. Pioneering work toward this goal has been done by a number of groups. Kretchmer[1] used the alkaloid (–)-sparteine as a complexing agent with organocopper(I) compounds of the type $RCuMgX_2$ in the conjugate addition reaction of α,β-unsaturated ketones and obtained products of low optical purity (<10%). Low optical purity (≤27%) was also characteristic of the products of organocopper conjugate additions run in the presence of the chiral cosolvents (*R*,*R*)- or (*S*,*S*)-1,4-(dimethylamino)-2,3-dimethoxybutane by Langer and Seebach.[2]

As far as heterocuprates[3] R(Het)CuLi are concerned, Crabbé and co-workers[4] investigated the alcoholates of (–)-*N*-methylephedrine and 1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose as chiral auxiliary ligands (Het), and they likewise observed very low optical purities from reactions with α-enones. The best results with such a heterocuprate coordinated by oxygen (*O*-heterocuprate for abbreviation[5]) are due to Huché et al.,[6] who obtained a 34% ee for the methylated product from chalcone. Crabbé et al.[7] also studied *N*-heterocuprates; again the optical yields were low (<5%).

The Swedish school of Gustafsson, Ullenius, Nilsson, and co-workers have studied mixed cuprates RR*CuLi, where R* = (–)-2-[1-(dimethylamino)ethyl]phenyl[8] or *o*-[cyclohexyl(dimethylamino)methyl]phenyl,[9] and their results for the conjugate addition reactions of α,β-unsaturated ketones and esters were also disappointing (<5% ee). They also prepared *S*-heterocuprates[5] from the thiols (+)-neomenthylthiol and (+)-α-cyclohexylbenzenemethanethiol and observed ee's of 15% and 0%, respectively, for the addition of butyl to 2-cyclohexenone.[10]

In certain situations, much higher optical yields have been recorded. Imamoto and Mukaiyama[11] obtained 61–68% optical yields in the conjugate addition of MeMgBr to chalcone in the presence of CuBr and (*S*)-*N*-methylprolinol (reactant ratio 8.8:1.0:4.0:5.6). Leyendecker and co-workers reinvestigated this reaction and obtained an 88% ee under more dilute conditions.[12] The (4*S*)-*tert*-butylthio-(*S*)-prolinol derivatives have also been introduced by this group,[13] who observed as high as 94% ee in the methylation of chalcone using Me_2CuLi and one such chiral auxiliary.

In addition to these approaches based on attaching the chiral auxiliary to the cuprate, several research groups have attached it to the substrate; e.g., Posner's group has studied optically pure α-carbonyl-α,β-ethylenic sulfoxides,[14] and Oppolzer's has focused on (–)-*trans*-8-phenylmenthyl enoates.[15] The ee's in these well-engineered systems are usually very good; in some cases >99% enantiomeric purity has been observed.

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(5) In a similar fashion *N*-heterocuprate and *S*-heterocuprate refer to organocuprates RCu(L)Li, in which L is a ligand coordinated to Cu at a N or S atom of the ligand, respectively. Such nomenclature is needed because a term such as "thiocuprate" might refer to $Cu(SPh)_2Li$.
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(15) Oppolzer, W.; Löher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2808.

0022-3263/86/1951-4953$01.50/0

Finally, there have been several cases in which the group transferred in the conjugate addition is chiral.[16-18] Although these additions are not as generally applicable as some of those discussed above, they can be effective in special cases and are included here for completeness.

Our interest in asymmetric induction using *N*-heterocuprates derives from our previous work on thermally stable, yet reactive *N*-heterocuprates and *P*-heterocuprates.[19,20] Since many optically active primary and secondary amines of known absolute configuration are readily available, we decided to examine the amidocuprates prepared from them in order to assay the products of their conjugate addition reactions for enantiomeric enrichment. Our goal is the development of a useful chiral auxiliary that would be attached to the reagent rather than the substrate in order to minimize the substrate's complexity[21]

Results

Reactions were run on a 1.0-mmol scale at a concentration of 0.1 M. Cyclohex-2-en-1-one was the substrate for all the reactions reported here, and the ratio of cuprate to substrate was 1.0. The *N*-lithio amides, from which the amidocuprates were prepared, were made from the corresponding amines and MeLi or BuLi; any excess of alkyllithium was easily detected by monitoring the reaction mixtures for 3-methylcyclohexanone or 3-butylcyclohexanone.

Phenylamidocuprates were used throughout and were prepared in one of two ways. Either 1 equiv of PhLi was added to the Cu(I) amide prepared from the *N*-lithio derivative of an optically active amine and a Cu(I) salt such as CuI ("method A")[22] or the Li amide was added to a suspension of PhCu prepared from PhLi and the Cu(I) salt ("method B"). Unless noted otherwise, the cuprates were prepared at −50 °C to 0 °C and then cooled to −78 °C, at which temperature the reactions with enone were started. Reaction mixtures were quenched with aqueous NH_4Cl after 1 h at −78 °C. Typically, six to nine reactions were run simultaneously. The chemical yields of all products were determined by GLC calibrated with authentic products by using the internal standard method. Optical yields of 3-phenylcyclohexanone were determined by HPLC with a Daicel OP+ Chiralpak column.

Of the two procedures for preparing the cuprates, method B proved to be superior. For example, when the amine was ephedrine, ee's as high as 50% were obtained with method B in ether. The corresponding optical yield using method A was 10%. When (*S*)-α-1-naphthylethylamine was studied in THF, the cuprate prepared by method A gave no ee, whereas the cuprate prepared by method B gave a 10% ee. Accordingly, method B was adopted for most experiments.

Table I shows that, of the four Cu(I) salts studied as precursors for organocuprates, CuI appears to be the best one overall and CuCN appears to be the worst. In two of the three cases studied, *N*-heterocuprates prepared from CuCN gave no significant ee. In some cases CuBr and Cu(I) trifluoromethanesulfonate (Cu(I) triflate, CuOTf) were as good as CuI, but this was not generally the case. Therefore, CuI was used in conjunction with method B for experiments screening various optically active amines.

Table I. Effect of Counterion[a]

entry	amine	solvent	Cu(I) salt	*R*/*S* ratio	yield, %
1	(−)-ephedrine	ether	CuI	75:25	94
2			CuBr[b]	60:40	91
3			CuOTf[c]	70:30	48
4			CuCN	60:40	72
5		THF	CuI	75:25	34
6			CuBr[b]	55:45	46
7			CuOTf[c]	75:25	39
8			CuCN	50:50	38
9	(*R*)-(+)-α-1-	ether	CuI	70:30	62
10	naphthylethyl-		CuBr[b]	70:30	47
11	amine		CuOTf[c]	60:40	34
12			CuCN	50:50	35

[a] Cuprates prepared by method B. [b] Dimethyl sulfide complex (Aldrich) was used. [c] Benzene complex (Strem) was used.

The screening experiments are summarized in Table II. Of the more than 40 amines examined, only a few gave a good chemical yield (>50%) and a significant optical yield (>10%). The best ones were (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (entry 23: 62%, 50% ee), (*R*)- or (*S*)-α-methylbenzylamine (entries 7 and 8: ~70%, 30% ee), (*R*)- or (*S*)-α-(1-naphthyl)ethylamine (entries 4 and 5: ~70%, 30% ee), and (−)-α-2-naphthylethylamine (entry 6: 50%, 40% ee). The use of some other amines resulted in comparable ee's but poorer chemical yields: (*S*,*S*)-(−)-*N*,*N*′-bis(α-methylbenzyl)sulfamide (entry 12: 24%, 50% ee), (*S*)-(−)-*N*-benzyl-α-methylbenzylamine (entry 9: 23%, 40% ee), and (*R*)-(−)-coniine (entry 34: 31%, 30% ee). On the other hand, other amines gave very good chemical yields, but lower ee's, for example, (*S*)-(−)-1-amino-2-methylbutane (entry 27: 88%, 10% ee), and (*R*)-(+)-bornylamine (entry 31: 86%, 20% ee). One further conclusion from Table II is the superiority of the alkoxyamine over the corresponding hydroxyamine; compare entries 14–15, 22–23, and 24–25. In the cases of the hydroxyamines, enough alkyllithium was added to deprotonate both O and N.

Once the better amines were identified, other experimental variables were examined in an attempt to further improve the results. To this end PhMgBr was substituted for PhLi in the preparation of the cuprates; however, as can be seen in Table III, this substitution generally gave poorer results.

The effect of added salts (1.0 equiv) is summarized in Table IV. The addition of LiCN to the cuprate prepared from CuI had no effect on the ee; however, this may be a consequence of the insolubility of LiCN. In contrast, addition of LiI to the cuprate prepared from CuCN markedly improved the ee. The *R*/*S* ratio for the experiment in which LiI was added to the cuprate prepared from CuCN is much closer to the value for the cuprate prepared from CuI than it is to the value for the cuprate prepared from CuCN. There does not appear to be a common ion effect on the ee, which was independent of the addition of LiI or $LiBPh_4$ to the cuprate prepared from CuI.

Table V summarizes the effects of varying the solvent. Generally speaking, ether and THF, the traditional solvents for organocuprates, gave the best results. Of these two, the chemical yields were better in ether. For ligands capable of chelation, THF gave the best optical yields. The solvents which coordinate Cu(I) most strongly (dimethyl ether, dimethyl sulfide, and dioxane) yielded virtually no ee. In the case of simple amines such as (*S*)-α-methylbenzylamine, there is a reversal of the *R*/*S* ratio upon

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Table II. Effect of Ligand[a]

entry	amine or other auxiliary	R/S ratio	yield, %
1	(−)-ephedrine [(1*R*,2*S*)-2-(methylamino)-1-phenyl-1-propanol]	60:40	65
2	(−)-pseudoephedrine [(1*S*,2*R*)-2-(methylamino)-1-phenyl-1-propanol]	50:50	73
3	(+)-norephedrine [(1*S*,2*R*)-2-amino-1-phenyl-1-propanol]	50:50	44
4	(*R*)-(+)-α-1-naphthylethylamine	65:35	72
5	(*S*)-(−)-α-1-naphthylethylamine	35:65	74
6	(−)-α-2-naphthylethylamine	30:70	50
7	(*R*)-(+)-α-methylbenzylamine	65:35	72
8	(*S*)-(−)-α-methylbenzylamine	35:65	69
9	(*S*)-(−)-*N*-benzyl-α-methylbenzylamine	70:30	23
10	(*S,S*)-(−)-bis(α-methylbenzyl)amine	60:40	32
11	(*R,R*)-(+)-*N*-(2-methoxy-α-methylbenzyl)-*N*-(α-methylbenzyl)amine	70:30	34
12	(*S,S*)-(−)-*N,N'*-bis(α-methylbenzyl)-sulfamide	75:25	24
13	D-(−)-*erythro*-α,β-diphenyl-β-hydroxyethylamine	55:45	14
14	L-prolinol [(*S*)-2-(hydroxymethyl)pyrrolidine]	45:55	52
15	(*S*)-(+)-2-(methoxymethyl)pyrrolidine	60:40	36
16	L-α-phenylglycinol [(*S*)-(+)-2-amino-2-phenylethanol]	55:45	38
17	L-phenylalaninol [(*S*)-(−)-2-amino-3-phenylpropanol]	55:45	37
18	L-cysteine ethyl ester	55:45	12
19	*N*-acetyl-L-cysteine	55:45	49
20	D-cycloserine	55:45	72
21	(1*R*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol	55:45	53
22	(1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol	60:40	51
23	(4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane	75:25	62
24	(4*S*,5*S*)-(−)-4-(hydroxymethyl)-2-methyl-5-phenyl-2-oxazoline	55:45	36
25	(4*S*,5*S*)-(−)-4-(methoxymethyl)-2-methyl-5-phenyl-2-oxazoline	60:40[b]	53[b]
26	(*S*)-(−)-2-aminoheptane	50:50	74
27	(*S*)-(−)-1-amino-2-methylbutane	45:55	88
28	(*R,R*)-(−)-diaminocyclohexane	55:45	66
29	(*S*)-(+)-tetrahydrofurfurylamine	45:55	47
30	(−)-menthylamine [(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexylamine]	45:55	48
31	(*R*)-(+)-bornylamine	40:60	86
32	(*R*)-(−)-isobornylamine	45:55	69
33	(+)-3-(aminomethyl)pinane	50:50	42
34	(*R*)-(−)-coniine [(*R*)-2-propylpiperidine]	65:35	31
35	(−)-emetine (MI 3523[c])	70:30	6
36	(−)-ajmalicine (MI 181[c])	55:45[b]	47[b]
37	(+)-calycanthine (MI 1702[c])	50:50	33
38	(*S*)-(−)-anabasine [(*S*)-2-(3-pyridyl)piperidine]	45:55	32
39	(+)-tomatidine (MI 9375[c])	50:50	27
40	(−)-solasodine (MI 8554[c])	55:45	34
41	(+)-yohimbine (MI 9913[c])	40:60	6
42	(−)-reserpine (MI 8042[c])	45:55	59
43	(−)-reserpiline (MI 8041[c])	45:55	8
44	(−)-corynanthine (MI 2525[c])	50:50	33
45	(2*R*,3*R*)-(−)-butanediol	50:50	53
46	(*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol	55:45	31
47	(*R*)-(+)-1,1'-bi-2-naphthol	60:40	15
48	2'-deoxyguanosine	60:40	14
49	(*S,S*)-2,3-bis(diphenylphosphino)-butane	50:50	16

[a] Cuprates prepared in ether by method B. Results are for samples taken after 1 h at −78 °C unless otherwise noted. [b] Sampled after 0.5 h at 0 °C. [c] *Merck Index*, 10th ed.; Merck & Co.: Rahway, NJ, 1983.

switching from ether to THF. This is not the case for chelating amines such as ephedrine or *N*-acetyl-L-cysteine.

The temperature dependence of the optical yield was investigated by using the cuprate prepared from (*S*)-(−)-α-1-naphthylethylamine. The data in Table VI show that there is a monotonic decrease in optical yield with increasing temperature. The chemical yield was not affected significantly by the changes in temperature in this case. In other cases the chemical yields were improved by warming the reaction mixtures to 0 °C. For example, the chemical yield of 3-phenylcyclohexanone was improved from 72% to 95% for the cuprate prepared from D-cycloserine, from 36% to 79% for (4*S*,5*S*)-(−)-4-(hydroxymethyl)-2-methyl-5-phenyl-2-oxazoline, from 3% to 53%

Table III. Effect of Cation[a]

entry	amine	solvent	reagent	R/S ratio	yield, %
1	(−)-ephedrine	ether	PhLi	60:40	65
2			PhMgBr	45:55	41
3		THF	PhLi	75:25	39
4			PhMgBr	25:75	7
5	(*S*)-(−)-α-1-naphthylethylamine	ether	PhLi	35:65	74
6			PhMgBr	50:50	2
7		THF	PhLi	55:45	6
8			PhMgBr	55:45	11
9	(4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane	ether	PhLi	75:25	62
10			PhMgBr	55:45	29
11		THF	PhLi	50:50	26
12			PhMgBr	55:45	10

[a] Cuprates prepared by method B.

Table IV. Effect of Added Salts[a]

entry	amine	Cu(I) salt	added salt	R/S ratio	yield, %
1	(*R*)-(+)-α-1-naphthylethylamine	CuI	none	70:30	62
2		CuI	LiCN	70:30	54
3		CuCN	none	50:50	35
4		CuCN	LiI	65:35	52
5		CuI	LiI	70:30	46
6		CuI	$LiBPh_4$	70:30	41

[a] Cuprates prepared in ether by method B.

Table V. Effect of Solvent[a]

entry	amine	solvent	R/S ratio	yield, %
1	(−)-ephedrine	ether	60:40	65
2		THF	75:25	39
3		DME	65:35	30
4		$(i\text{-Pr})_2O$	60:40	45
5		Me_2O	50:50	39
6		dioxane	50:50	12
7		Me_2S	50:50	98
8	(4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane	ether	75:25	62
9		THF	50:50	26
10		hexane	35:65	51
11		Me_2S	55:45	53
12		Et_2S	50:50	56
13	(*S*)-(−)-α-methylbenzylamine	ether	35:65	69
14		THF	65:35	12
15	(*S*)-(−)-α-1-naphthylethylamine	ether	35:65	74
16		THF	55:45	6
17	*N*-acetyl-L-cysteine	ether	55:45	49
18		THF	80:20	22

[a] Cuprates prepared by method B.

Table VI. Effect of Temperature[a]

entry	amine	temp, °C	R/S ratio	yield, %
1	(*S*)-(−)-α-1-naphthylethylamine	−78	35:65	74
2	(*S*)-(−)-α-1-naphthylethylamine	0	40:60	78
3	(*S*)-(−)-α-1-naphthylethylamine	25	45:55	79

[a] Cuprates prepared in ether by method B.

Table VII. Reproducibility of Results[a]

entry	amine	solvent	R/S ratio H-P[b]	R/S ratio Waters[c]	R/S ratio C&W[d]	yield, %
1	(R)-(+)-α-1-naphthylethylamine	ether	67:33	62:38	67:33	65
2			70:30	80:20	72:28	62
3			67:33	90:10	68:32	72
4	(S)-(−)-α-1-naphthylethylamine	ether	37:63	46:54	36:64	74
5			36:64	33:67	36:64	57
6			33:67	28:72	35:65	57
7	(−)-ephedrine	ether	74:26	85:15	74:26	94
8			—	60:40	60:40	99
9			59:41	—	60:40	65
10		THF	73:27	74:26	70:30	37
11			73:27	74:26	71:29	39
12			74:26	74:26	73:27	34

[a] Cuprates prepared by method B. [b] Hewlett-Packard 3390A integrator. [c] Waters Associates 730 data module. [d] Cutting and weighing Waters 730 trace.

for (4S,5S)-(−)-4-(methoxymethyl)-2-methyl-5-phenyl-2-oxazoline, from 42% to 68% for (+)-3-(aminomethyl)pinane, from 31% to 53% for (R)-(−)-coniine, and from 1% to 47% for (−)-ajmalicine. There were many other instances in which allowing the reaction mixtures to warm to 0 °C improved the chemical yields; only the most dramatic ones (>20% improvement) are cited above. For two of the amines in Table II (entries 25 and 36), the chemical yields after 1 h at −78 °C were too poor (3% and 1%, respectively) for optical yields to be measured, and the optical yields cited were measured after an additional 0.5 h at 0 °C.

The results of running the conjugate addition reactions of the best amidocuprates in the presence of chlorotrimethylsilane[23] were not better than 50% ee, which was obtained with (4S,5S)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane in THF (vs. 0% ee without chlorotrimethylsilane).

Table VII addresses the question of the precision of our results. The several entries for each amine are the results of experiments performed on different days. The % R (or % S) values vary between ±1% and ±5% based upon integration with a Hewlett-Packard 3390A or by cutting and weighing, except for (−)-ephedrine in ether, where one value differs by 14–15% from the other two. (The variation for the Waters 730 was as much as 28%.) Consequently, the R/S ratios are quoted to the nearest 5% (ee's to the nearest 10%). Most of the values reported in Tables I–VI represent the average of at least two integrations agreeing to within 5% and have been rounded to the nearest 5%.

Several of the ligands listed in Table II are diamines (e.g. entries 12, 20, 28, and 37); the data in Table II refer to the cuprate prepared from the monolithiated material. In those cases where the two NH groups are close enough for interaction to occur, the dianions were also prepared by using 2 equiv of BuLi and then added to PhCu. In the case of (S,S)-(−)-N,N′-bis(α-methylbenzyl)sulfamide, the optical yield was the same, but the chemical yield was decreased to 9%. With D-cycloserine the chemical and optical yields were unchanged. In contrast, with R,R-(−)-diaminocyclohexane both chemical and optical yields were improved: 72%, 20% ee vs. 66%, 10% ee for the cuprate prepared from the monoanion.

Finally, the reaction with (4S,5S)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane was scaled up from 1 mmol to ca. 80 mmol. Unfortunately, the chemical yield decreased from 62% to 55% (after 1 h at −78 °C) and the optical yield decreased from 50% to ~25% ee.

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Discussion

Studies of asymmetric induction in the 1,4-addition of organocuprates to α-enones tend to be empirical in nature because of two unfortunate facts. First, the structures of organocopper reagents in solution are not known with any detail,[24] and second, the mechanism of their conjugate addition reactions is not yet fully understood. The difficulty with such an empirical approach is due to the large number of variables that are known to influence organocuprate reactions: the nature of the cuprate (alkyl vs. aryl, Li vs. Mg counterion, Cu(I) salt used in its preparation) and the exact details of its preparation (temperature, time, order of addition), the reaction solvent, reaction temperature and time, the presence of additional species (e.g., halides or phosphines), and the structural features of the substrate. Ideally, one would investigate each of these variables with all the others held constant and map out the entire "yield space" to determine the optimal conditions. This approach is rarely practical due to the large number of combinations of variables. Therefore, it is necessary to adopt a search strategy that will find the optimal conditions more quickly by identifying the most important variables for investigation and setting the rest according to similar cases in the literature. (The assumptions used to set the secondary variables can be checked later, or course).

As far as the cuprate is concerned, we decided to focus on N-heterocuprates, which we developed in our studies on the thermal stabilities of organocopper reagents.[19] Fortunately, a great variety of optically pure amines is commercially available, which greatly facilitated the study of the effects of structural changes in the chiral auxiliary. There is one previous report[7] of attempted asymmetric induction using N-heterocuprates; unfortunately, they were prepared using the order of addition we term method A (see Results section), which we have determined to be inferior to method B. Several groups[11,12] have added L-prolinol to $Me_2CuMgBr$, but this procedure must give the O-heterocuprate, since organocopper reagents are not basic enough to deprotonate an amine.

Phenyl was chosen as the transferable group because the phenyl-containing products are easier to resolve by HPLC with chiral supports than the corresponding alkyl ones. Most of the studies that have been done in this area used the optical rotations of the purified products to measure optical yields. With HPLC we obviated the purification step (which requires the reactions to be run on a relatively

(24) An X-ray crystal structure has been done on "lithium diphenylcuprate, see: Hope, H.; Oram, D.; Power, P. P. *J. Am. Chem. Soc.* **1984**, *106*, 1149.

large scale), and we were able to optimize conditions much more efficiently. Typically, six to nine small-scale (1-mmol) reactions were run simultaneously one day, and the HPLC results were obtained for them on the next. One large-scale (80-mmol) reaction was run and the product purified in about the same time (see Experimental Section).

Most of the previous studies (see the introduction) have used either 2-cyclohexenone or chalcone as the substrate. We chose to use one of these in order to make comparisons with the literature results possible and settled on 2-cyclohexenone, since the results secured with this substrate should be more generally applicable.

Having chosen the phenylamidocuprates for study, we proceeded to optimize what we guessed would be the most important variable other than amine structure, namely, the Cu(I) salt from which the cuprate was prepared. On the basis of literature precedent, we chose −78 °C for the reaction temperature, since it seems to be a general phenomenon that ee is inversely proportional to temperature. (We confirmed this effect in our system later on.) The initial study of the Cu(I) precursors used (−)-ephedrine in ether and was repeated in THF. On the basis of the results (Table I, entries 1–8), CuI—the classical cuprate precursor—was chosen. Yields of conjugate addition reactions run in ether are generally better than the corresponding yields in THF, and this proved to be the case in our systems as well. Next, the method of preparation was studied, as described in the Results section. By use of method B to prepare the cuprates from CuI in ether, the effect of amine structure was determined in the most extensive part of the project.

The best amines for use as chiral auxiliaries turned out to be (*R*)- or (*S*)-α-methylbenzylamine, (*R*)- or (*S*)-α-1-naphthylethylamine, and (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane. We were fortunate in our choice of ephedrine for our early studies, since it turned out to be one of the better ligands; however, it gave less reproducible results than the three listed above (see Results section dealing with Table VII). For this reason we reinvestigated the Cu(I) precursors with a simple amine (Table I, entries 9–12) to make sure that our initial choice was not a special case.

Using one of the best amines, we investigated the effect of temperature (Table VI) to confirm our original choice of −78 °C, and we completed our optimization by studying the effects of the cation (Table III), added salts (Table IV), and solvent (Table V). As far as we have been able to determine, the amines listed in the previous paragraph are best used in conjunction with a lithium reagent and CuI in ether to prepare the cuprate (by method B), which is then allowed to react with substrate at −78 °C. Considering optical yield, chemical yield, and the cost of the amine, we prefer (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane as our chiral auxiliary of choice and used it for the large-scale work.

While the optical yields we have obtained may not be high enough for the synthesis of biologically active substances, they are useful for other kinds of investigations. For example, we have been able to revise the value for the maximum rotation of 3-phenylcyclohexanone. The value quoted in the *Dictionary of Organic Compounds* is $[\alpha]^{25}_D$ +14.35°, determined at a concentration of 9.674 g per 100 mL of chloroform.[25] Curiously, the value quoted[26] for 3-methylcyclohexanone is also $[\alpha]^{25}_D$ +14.35°, also determined at 9.674 g/100 mL of chloroform. Apparently, both values were taken from the same footnote of Kretchmer's Table II,[1] which actually referred to the latter compound only. Our large-scale reaction gave material with a rotation α^{26}_D = +1.555° (neat), which HPLC showed to have 26% ee (63:37 *R*/*S* ratio). Based upon these data, we conclude that optically pure 3-phenylcyclohexanone should have $\alpha_D \approx 6°$ and not ~14° as reported.[25] Unfortunately, the value of +14.35° has been used to calculate optical purity by other workers.[27]

Some of our results also have ramifications as far as the structures of heterocuprates are concerned. Lipshutz and co-workers have advocated CuCN as the precursor of "higher order" organocuprates, meaning the CN is involved in the cuprate cluster.[28] From the dependence of optical yield upon which Cu(I) salt is used to prepare the cuprate and which common ions are added (see Tables I and IV), it may be concluded that all of our organocuprates are "higher order". The improvement in ee upon the addition of CuI to the cuprate prepared from CuCN establishes that iodide is at least as involved in the cuprate as cyanide.

It is interesting to note that the use of CuCN gave the lowest optical yields in each case; in fact, in two of the three cases the ee is zero. In contrast the Cu(I) halides and Cu(I) triflate generally gave significantly higher optical yields. This raises the interesting possibility that the structure of the cyanocuprate is fundamentally different from those of the other cuprates in some way that is more subtle than the terms "higher order" or "lower order" convey. While triflate is usually considered a "noncoordinating" anion, even triflate appears to be involved in the cuprate cluster, as the optical yields with triflate present are more similar to those observed with the halocuprates than those with the cyanocuprates.

Corey and Boaz[23] have shown that the presence of chlorotrimethylsilane can have a dramatic effect on the conjugate addition reaction of organocuprates to α,β-unsaturated ketones as far as both rate and stereochemistry are concerned. They attribute the effect of Me_3SiCl to the trapping of a Cu–enone complex. The effect of Me_3SiCl on the *R*/*S* ratio indicates that this complex formation is indeed reversible in the case of phenylamidocuprates and 2-cyclohexenone, as the *R* and *S* enantiomers are the result of cuprate addition to opposite faces of the π-system.

Finally, some generalizations about the relationship between the absolute stereochemistry of the product and that of the chiral auxiliary can be made. For simple amines such as α-methylbenzylamine which have one stereogenic center and no chelating groups, the absolute stereochemistry is conserved when the asymmetric C is adjacent to the N. For example, the phenylamidocuprate prepared from (*R*)-α-methylbenzylamine yields an excess of (*R*)-3-phenylcyclohexanone over the *S* enantiomer when treated with 2-cyclohexenone in ether. Other simple amines which give the same result are α-1-naphthylethylamine, coniine (2-propylpiperidine), and emetine. Emetine has other functional groups (e.g., methoxyl and aryl); however, they are not in a position to form a chelate involving the amino group. Furthermore the other stereocenters are too remote from the N to be influential (vide infra). Therefore, under our definition it approximates a simple amine.

If the amino group is not directly attached to the stereocenter, the ee in the product is lower and the absolute stereochemistry is not as predictable. For example, (*S*)-1-amino-2-methylbutane gives (*S*)-3-phenylcyclo-

(25) *Dictionary of Organic Compounds*; Buckingham, J., Ed.; Chapman and Hall: New York, 1982; Vol. 5; p 4614.
(26) Reference 25; Vol. 4, pp 3802–3803.
(27) Posner, G. H.; Frye, L. L. *Isr. J. Chem.* 1984, *24*, 88.
(28) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* 1984, *40*, 5005.

hexanone (10% ee), whereas (−)-reserpine, which has an *R* stereocenter two bonds away from NH, gives the *S* enantiomer (10% ee). If there is a stereocenter adjacent to N and one two bonds away, the situation is again not straightforward. Thus, (−)-menthylamine, which has an *R* stereocenter adjacent to N and an *S* stereocenter two bonds away, gives *S* product but so does (−)-isobornylamine, which has *R* stereocenters one bond and two bonds away, and (+)-bornylamine, which has an *S* stereocenter next to N and an *R* stereocenter two bonds removed.

The presence of other coordinating functional groups close enough to participate with the N in chelation generally gives the opposite result as simple amines, i.e., reversal of absolute stereochemistry. Examples include (−)-ephedrine, (*S*)-2-(methoxymethyl)pyrrolidine, (*S*)-α-phenylglycinol, (*S*)-phenylalaninol, (1*R*,2*S*)- and (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol, (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane, and (4*S*,5*S*)-4-(hydroxymethyl)- and (4*S*,5*S*)-4-(methoxymethyl)-2-methyl-5-phenyl-2-oxazoline, which all give *R* product. While reversal of absolute stereochemistry appears to be the rule, there are exceptions: (*S*)-prolinol gives rise to *S* product and (*R*,*R*)-diaminocyclohexane gives rise to *R* product in excess.

Whereas (*S*)-α-methylbenzylamine gives *S* product in ether according to the rule for simple amines, (*S*)-*N*-benzyl-α-methylbenzylamine, (*S*,*S*)-bis(α-methylbenzyl)-amine, and (*S*,*S*)-*N*,*N*′-bis(α-methylbenzyl)sulfamide give *R* product, suggesting chelation may be important in these cases. In the first two cases, a benzene ring would be the second coordinating group. This is not without precedent, e.g., Cu(I) triflate is commercially available as a benzene complex, and Posner has suggested such coordination as a controlling factor in the stereochemical outcome of some enolate reactions.[29] The last case may involve chelation by an S=O group.

Our stereochemical results[30] for phenyl addition are the opposite of those observed by Dieter[31] for alkyl (e.g., Me or Bu) addition (with the same amide, of course), which suggests that there are significant structural differences between the phenyl and alkyl cuprates. Vapor pressure depression studies have established that Me_2CuLi is dimeric in ether solution.[32] The solution structure of Ph_2CuLi has not been determined, but an X-ray crystal structure shows that it is a trimer in the solid state.[24] The reversal of stereochemistry upon changing from ether to THF in the case of simple amines indicates that the structures of the heterocuprates in these two solvents must have significant differences.

In summary, several amines can be used as chiral auxiliaries for *N*-heterocuprates which give useful levels of asymmetric induction. Using such reactions as probes of organocuprate structure, we have been able to establish that the counterions from the Cu(I) salts used as precursors remain in the cuprate clusters and affect their reactivity. Furthermore, the structures of the heterocuprates prepared from simple amines appear to be different in ether and THF.

Experimental Section

General Procedure. A 1.00-mmol quantity of optically active amine dissolved in 4 mL of ether, which had been freshly distilled from Na/benzophenone, was treated with 0.80 mL of 1.25 M MeLi (low halide) or 0.70 mL of 1.44 M BuLi (1.01 mmol) in hexane at −78 °C, and the solution was then allowed to warm to 25 °C over a period of 0.5 h. It was cooled to 0 °C and added via syringe to a suspension of PhCu, which was prepared by adding 0.55 mL of 1.81 M PhLi (0.996 mmol) to 190.5 ± 0.5 mg (0.998–1.003 mmol) of CuI suspended in 4 mL of ether at 0 °C. After being stirred at 0 °C for 15 min, the dark homogeneous-looking solution was cooled to −78 °C in a dry ice/2-propanol bath, and 2 mL of ether containing 96–97 mg (0.999–1.01 of 2-cyclohexenone and 50 μL (weighed to the nearest 0.1 mg) of decane, an internal standard, was added. The substrate solution was cooled briefly with dry ice before injection. After 1.0 h at −78 °C, a 3-mL sample of the reaction mixture was removed with a dry ice-cooled 10-mL Becton-Dickinson disposable syringe fitted with a 6 in 18 G needle (sealed to the syringe with a tight winding of Teflon tape) and injected into 2 mL of deoxygenated 3 M aqueous NH_4Cl. (The dry ice and syringe were held with a large insulated glove.) The reaction mixture was then placed in an ice bath and stirred at 0 °C for 0.5 h, after which time it was quenched by adding 3 mL of 3 M NH_4Cl. The yield of 3-phenylcyclohexanone in each sample was determined by GLC on a 50-m nonpolar glass capillary column heated from 40 to 250 °C at the rate of 10 °C/min. Typical retention times were as follows: 2-cyclohexenone, 11 min; decane, 13 min; 3-phenylcyclohexanone, 22 min. Optical yields of the 3-phenylcyclohexanone were determined by HPLC on a Daicel Chiralpak OP+ column. With 0.5% 2-propanol in isooctane at a flowrate of 0.5 mL/min, the retention times were ~28 min for the (+)-isomer and ~30 min for the (−)-isomer. The signs of the rotations were determined by plumbing the HPLC effluent through a standard 3-mm-bore 10-mm-long polarimeter cell.

Large-Scale Reaction. To 16.54 g (79.8 mmol) of (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (Fluka) dissolved in 150 mL of freshly distilled (Na/benzophenone) ether cooled to 0 °C was added 58.0 mL of 1.44 M BuLi (83.5 mmol, 0.18 M residual base, Aldrich). The clear brown solution was allowed to warm to 25 °C for 30 min and then cooled to −50 °C. This Li amide solution was transferred via canula to an ether suspension of PhCu, which had been prepared by adding 54.5 mL of 1.465 M ethereal PhLi[33] (79.8 mmol, 0.28 M residual base) to an ether suspension of 15.2 g of CuI (79.8 mmol, Alfa) cooled to −50 °C. The resulting suspension was stirred at −50 °C for 30 min and then at 0 °C for 15 min to obtain a dark brown solution, which was cooled to −78 °C. To this phenylamidocuprate solution was added a cold (−78 °C) solution of 7.67 g (79.8 mmol) of 2-cyclohexenone in 25 mL of ether.

Aliquots of 1.00 mL were removed after 1 and 17 h and injected into vials containing 1 mL of 3 M NH_4Cl and 50 μL (weighed to the nearest milligram) of decane, an internal standard for GLC. GLC analysis revealed that the respective yields were 55% and 47%; therefore, the reaction mixture was quenched with 300 mL of 1 M HCl. The organic phase was separated and washed with three 100-mL portions of 3 M NH_4Cl. The combined aqueous layers were extracted with 100 mL of ether. The combined organic layers were dried over anhydrous Na_2SO_4, and the

(29) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

(30) If the original assignment of absolute configuration (see ref 1) were incorrect, then our stereochemical results would be the same as Dieter's (ref 31). The CD spectrum of our (+)-enantiomer shows a strong positive Cotton effect at 270 nm, confirming the original assignment (*R*).

(31) Dieter, R. K. submitted for publication in *J. Am. Chem. Soc.*

(32) Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 4098.

(33) Schlosser, M.; Ladenberger, V. *J. Organomet. Chem.* **1967**, *8*, 193.

ether was removed at reduced pressure on a rotary evaporator to obtain 12.7 g of tan oil.

The oil was purified by silica gel chromatography using a Waters Prep 500 HPLC and eluting with 20% ethyl acetate/hexane. Distillation of the major HPLC fractions (the third and fourth 400 mL volumes of eluant) at 0.1 torr afforded 1.75 g (92–100 °C, 97% pure by GLC), 2.04 g (100–102 °C, 99% pure), and 1.08 g (100–103 °C, 97% pure) cuts of purity ≥97% (4.9 g total, 35%). HPLC on a Daicel Chiralpak OP+ column eluted with 0.5% 2-propanol/isooctane indicated a 63:37 R/S ratio. The optical rotation of the neat 3-phenylcyclohexanone measured in a 10.00-cm cell was α^{26}_D +1.555°.

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Imidyl Radicals. The Chemistries of 1,8-Naphthalenedicarboximidyl and Phthalimidyl Radicals

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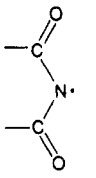
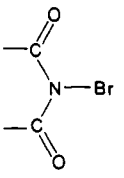
The chemistries of 1,8-naphthalenedicarboximidyl (N•) and phthalimidyl (P•) radicals are described: Hydrogen abstractions from alkanes and additions to olefins and benzene proceed in high yield. The low cost of phthalimide, coupled with the absence of a parasitic ring-opening reaction for P•, makes N-bromophthalimide an economical reagent for low-selectivity brominations. The chemistry of N• resembles that of other imidyl radicals (succinimidyl, glutarimidyl) with respect to selectivities. Conversely, P• is somewhat of a maverick among imidyl radicals, being slightly more selective in its reactions, but still 10^2–10^4 less selective than Br•.

Reactions of imidyl radicals (A) remained unrecognized until the importance of two factors became apparent: (1) the necessity to use solvents in which the solubility of the imidyl radical precursor, N-halo imide (B), was sufficiently



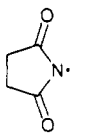
A



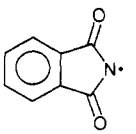
B

high and (2) the necessity to eliminate competitive chain reactions based on halogen atom (X•), accomplished by including alkenes to selectively scavenge X• and X_2. Consequently, the chemistries of succinimidyl and glutarimidyl radicals became accessible.[1,2]

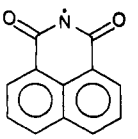
Earlier papers describe the chemistries of succinimidyl[1,2] and, to a lesser extent, phthalimidyl radicals.[2] In this paper, we describe both the chemistry of the 1,8-naphthalenedicarboximidyl radical and additional phthalimidyl chemistry. The behavior of these structurally related radicals is compared. N-Bromophthalimide



succinimidyl (S•)



phthalimidyl (P•)



1,8-naphthalenedicarboximidyl (N•)

proves to be a low-cost, useful reagent for both Br substitutions and for additions to alkenes and arenes.

Results

In order to observe imidyl chemistry, the following precautions were followed: Reactions were carried out in systems containing alkenes to limit competing bromine atom chain reactions. Dioxygen, an inhibitor of free radical chain reactions, was rigorously excluded. Any HBr which might be produced in these reactions is efficiently scavenged by the N-bromo compounds yielding Br_2,[3] which is subsequently removed by addition to the alkene scavenger.

$$HBr + N{-}Br \rightarrow NH + Br_2$$

A. Reactions of the 1,8-Naphthalenedicarboximidyl Radical (N•). Both 1,8-naphthalenedicarboximide (NH) and N-bromo-1,8-naphthalenedicarboximide (NBr) are readily synthesized from 1,8-naphthalenedicarboxylic acid. A saturated solution of NBr in methylene chloride, a suitable solvent for these reactions, is 0.024 M.

1. Addition of N• to Unsaturated Compounds. As with other N-bromo imides,[2,4] the photoinitiated addition of NBr to an alkene produces the corresponding NBr/alkene adduct in good yield (Table I). The observation of the naphthalenedicarboximidyl moiety in the products provides evidence for the presence of N• as the chain carrier. These results are explicable by a chain sequence which involves as a key step, addition of N• to the olefin (Scheme I). Since less than 7% of the initial bromine appears as the *vic*-dibromide of the alkene scavenger, chain lengths greater than 20 are indicated.

(1) Skell, P. S.; Day, J. C. *Acc. Chem. Res.* **1978**, *11*, 381–387.
(2) Lüning, U.; Skell, P. S. *Tetrahedron* **1985**, *41*, 4289–4302 and references therein.
(3) Shea, K. J.; Lewis, D. C.; Skell, P. S. *J. Am. Chem. Soc.* **1973**, *95*, 7768–7776.
(4) Lüning, U.; McBain, D. S.; Skell, P. S. *J. Org. Chem.* **1986**, *51*, 2077.

0022-3263/86/1951-4959$01.50/0