Conjugate Additions of Organocuprates to Cycloalkenone Complexes of the Chiral Rhenium Lewis Acid $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$. Enantioselective Syntheses of 3-Substituted Cycloalkanones†

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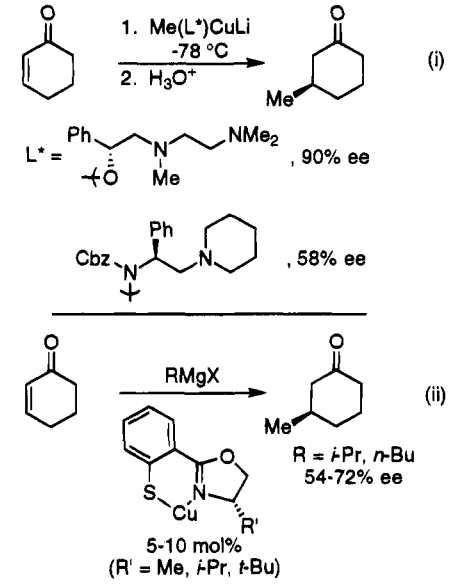
Reactions of organocuprates R_2CuLi and cycloalkenone complexes (+)-(*R*)-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^1\text{-}O{=}\overline{CCH{=}CHCH_2(CH_2)_n}\,)]^+$ BF_4^- (n = 2, 1) are conducted in THF or CH_2Cl_2 between −15 °C and −116 °C. Workups with aqueous HI give the corresponding 3-substituted cycloalkanones and iodide complex $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)$ (I). Under optimized conditions, 3-substituted cyclohexanones are obtained in 39–83% yields and 64–85% ee (R = Me, *R*; *n*-Bu, *R*; *t*-Bu, *S*; Ph, *S* or *R*), and 3-substituted cyclopentanones are obtained in 50–73% yields and 79–93% ee (*R* = Me, *R*; Ph, *S*). Evidence for intermediate enolate complexes is presented, protocols for recycling the chiral rhenium auxiliary are described, and possible mechanisms of 1,4-asymmetric induction are discussed.

Conjugate additions of nucleophiles to α,β-unsaturated carbonyl compounds are widely used in synthesis and commonly generate new carbon stereocenters. Thus, there has been intense interest in the development of enantioselective versions.[1,2] Particular attention has been focused upon organocopper reagents, to which chiral ligands are easily appended. Scheme 1 shows some representative protocols that employ stoichiometric (eq i)[3,4] or catalytic (eq ii)[5] amounts of chiral copper species. However, general solutions to this synthetic problem have proved elusive.

Surprisingly, there have not to our knowledge been prior attempts to effect enantioselective conjugate additions of organocopper reagents via initial binding of carbonyl compounds to chiral Lewis acids. We have previously prepared a variety of complexes of carbonyl compounds and the chiral rhenium Lewis acid $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ (**I**), including α,β-unsaturated derivatives.[6–9] Simple aldehyde and ketone adducts undergo highly diastereoselective 1,2 additions of nucleophiles.[6]

Scheme 1. Representative Enantioselective Conjugate Additions to Cyclohexenone



The resulting alkoxide complexes are easily converted to alcohols or derivatives of high enantiomeric purities, and the rhenium fragment may be recycled without loss of configuration. All isolated yields are very good, and spectroscopic yields are essentially quantitative. Hence, we sought to extend these studies to conjugate additions.

In this paper, we report a detailed investigation of reactions of organocopper reagents with the σ cyclohexenone and cyclopentenone complexes (+)-(*R*)-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^1\text{-}O{=}\overline{CCH{=}CHCH_2CH_2CH_2}\,)]^+$ BF_4^- ((+)-(*R*)-**1**) and (+)-(*R*)-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(\eta^1\text{-}O{=}\overline{CCH{=}CHCH_2CH_2}\,)]^+$ BF_4^- ((+)-(*R*)-**2**).[10] Workups give 3-substituted cycloalkanones, which by careful op-

† Dedicated to the memory of Bryant E. Rossiter (deceased February 5, 1995), a pioneer in enantioselective organocuprate addition reactions and cherished Utah neighbor.

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(10) The *R/S* nomenclature follows conventions described earlier.[6] Fortuitously, for the 3-substituted cycloalkanones in this study, compounds of identical relative configurations also have identical *R/S* and (+)/(−) attributes.

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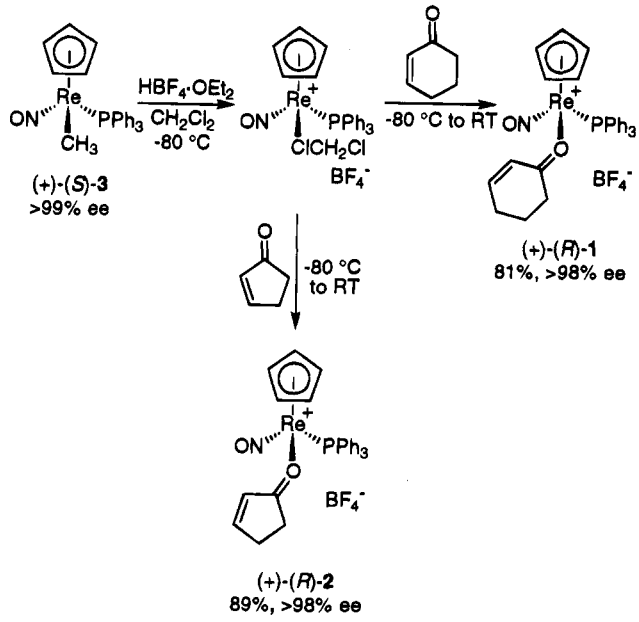
Scheme 2. Syntheses of Cycloalkenone Complexes 1 and 2



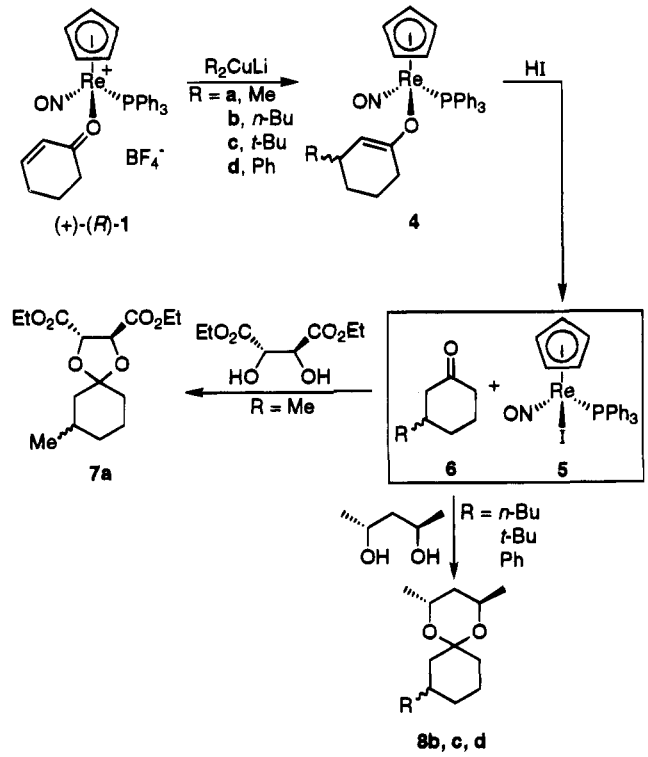
timization of solvent and temperature can be obtained in high yields and enantiomeric purities.

Results

1. Substrates and Exploratory Reactions. A sample of the optically active methyl complex (+)-(*S*)-(η^5-C_5H_5)Re(NO)(PPh_3)(CH_3) ((+)-(*S*)-**3**)[11] that was >99% ee (chiral HPLC)[12] was converted to the air-stable cyclohexenone and cyclopentenone complexes (+)-(*R*)-**1** and (+)-(*R*)-**2** by procedures analogous to those used for the racemates (Scheme 2).[9,13] The absolute configurations, which correspond to retention at rhenium, were assigned by analogy to related reactions of (+)-(*S*)-**3** and the commonly observed correlation with the sign of the optical rotation.[14,15] Both (+)-(*R*)-**1** and (+)-(*R*)-**2** were >98% ee, as assayed by ^{1}H NMR in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$ (3 equiv, CD_2Cl_2; C_5H_5 resonances) and gave correct microanalyses.

In initial screening reactions, CH_2Cl_2 solutions of cyclohexenone complex (+)-(*R*)-**1** and different methyl nucleophiles (2 equiv) were combined at −80 °C, as illustrated for Me_2CuLi in Scheme 3. These were presumed to generate varying amounts of the enolate complex (η^5-C_5H_5)Re(NO)(PPh_3)(O-C=CHCH(CH_3)CH_2-CH_2CH_2) (**4a**). After 0.5 h, the reactions were quenched with aqueous HI, giving the iodide complex (η^5-C_5H_5)Re(NO)(PPh_3)(I) (**5**)[16] and 3-methylcyclohexanone (**6a**). Yields of **6a** were assayed by GC relative to an internal standard. Following an analytical procedure utilized by

Scheme 3. Additions of Organocuprates to Cyclohexenone Complex 1



Rossiter,[17] **6a** was then treated with (−)-(2*S*,3*S*)-diethyl tartrate (diethyl D-tartrate; >99% ee, 1.5−2.0 equiv) to form the corresponding ketal **7a** (Scheme 3). The diastereomeric purity of **7a** was assayed by GC and was assumed to be identical to the enantiomeric purity of precursor **6a**.

Screening reactions conducted with Me_2CuLi/ether, Me_2CuLi/THF,[18] Me_2CuLi·SMe_2/THF,[19] and $Me_2Cu(CN)Li_2$/THF[20] gave 3-methylcyclohexanone (**6a**) in 34−53% yields and 85−71% ee. Reactions that utilized $MeCu$·SMe_2/THF,[21] Me_3ZnLi/THF,[22] MeMgBr/ether, and MeLi/ether gave **6a** in only 4−20% yields.[23] Hence, efforts were focused on organocuprate addition reactions.

A brief *sotto voce* on these protocols is merited. First, enolate complexes such as **4** have been independently generated.[24] However, they are extremely labile and have not to date proved isolable in analytically pure form. Second, subsequent additions of Brønsted acids (HX) should first give cationic 3-substituted cycloalkanone complexes. The free cycloalkanone would then be generated in a slower substitution step involving the counteranion (X^-). The selection of HI for exploratory work was arbitrary. Finally, convenient procedures have been developed that recycle iodide complex **5** and related species to methyl complex **3** with retention of configuration.[16,25]

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(23) Additional details may be found in Wang, Y., Ph.D. Thesis, Ch. 4, University of Utah, 1994.
(24) Peng, T. S. Unpublished data, University of Utah. The ^{31}P NMR chemical shift of enolate complex **4** with R = H is 19.1−19.7 ppm, depending upon solvent and temperature.

Table 1. Conjugate Additions of Organocuprates to Cyclohexenone Complex (+)-(*R*)-1[a]

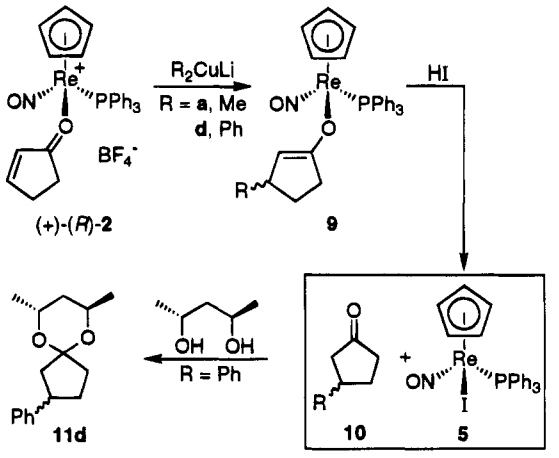
entry	solvent	organocuprate/ solvent	*T* (°C)	yield[b]	%ee[a]	configuration[a]
1	CH_2Cl_2	Me_2CuLi/THF	−61	33	69	*R*
2*	CH_2Cl_2	Me_2CuLi/THF	−80	41	83	*R*
3	CH_2Cl_2	Me_2CuLi/THF	−98	59	76	*R*
4	CH_2Cl_2	Me_2CuLi/THF	−116	42	56	*R*
5*	CH_2Cl_2	Me_2CuLi/ether	−80	39	85	*R*
6	THF	Me_2CuLi/THF	−98	56	78	*R*
7	CH_2Cl_2	*n*-Bu_2CuLi/THF	−61	33	48	*R*
8	CH_2Cl_2	*n*-Bu_2CuLi/THF	−80	48	52	*R*
9	CH_2Cl_2	*n*-Bu_2CuLi/THF	−98	43	53	*R*
10	CH_2Cl_2	*n*-Bu_2CuLi/ether	−80	56	48	*R*
11	THF	*n*-Bu_2CuLi/ether	−15	40	74	*R*
12*	THF	*n*-Bu_2CuLi/ether	−29	64	74	*R*
13	THF	*n*-Bu_2CuLi/ether	−45	61	73	*R*
14	THF	*n*-Bu_2CuLi/ether	−61	51	66	*R*
15	THF	*n*-Bu_2CuLi/ether	−80	60	64	*R*
16	THF	*n*-Bu_2CuLi/ether	−98	66	16	*R*
17	THF	*n*-Bu_2CuLi/THF	−80	52	34	*R*
18	CH_2Cl_2	*t*-Bu_2CuLi/THF	−15	48	70	*S*
19	CH_2Cl_2	*t*-Bu_2CuLi/THF	−29	59	66	*S*
20	CH_2Cl_2	*t*-Bu_2CuLi/THF	−45	66	58	*S*
21	CH_2Cl_2	*t*-Bu_2CuLi/THF	−61	65	37	*S*
22	CH_2Cl_2	*t*-Bu_2CuLi/THF	−80	65	12	*S*
23	THF	*t*-Bu_2CuLi/THF	−61	75	6	*S*
24	THF	*t*-Bu_2CuLi/THF	−80	58	19	*S*
25*	THF	*t*-Bu_2CuLi/THF	−98	53	77	*S*
26	THF	*t*-Bu_2CuLi/THF	−116	47	75	*S*
27	CH_2Cl_2	Ph_2CuLi/THF	−80	76	26	*S*
28	CH_2Cl_2	Ph_2CuLi/THF	−98	76	11	*S*
29	CH_2Cl_2	Ph_2CuLi/ether	−80	82	52	*R*
30	THF	Ph_2CuLi/THF	−80	93	21	*R*
31	THF	Ph_2CuLi/ether	−61	82	52	*R*
32*	THF	Ph_2CuLi/ether	−80	83	64	*R*
33	THF	Ph_2CuLi/ether	−98	46	22	*S*

[a] For conditions and analytical methods, see text and Scheme 3. Optimum runs are designated with a "*". [b] GC yields of 3-substituted cyclohexanones **6**.

2. Additions of Organocuprates to (+)-(*R*)-1. The cyclohexenone complex (+)-(*R*)-**1** was treated with organocuprates (2 equiv) under a variety of conditions, as outlined in Scheme 3 and summarized in Table 1. After 0.5 h at the indicated temperature, reactions were worked up and analyzed as above. However, the enantiomeric purities of 3-*n*-butyl, 3-*tert*-butyl, and 3-phenylcyclohexanone (**6b–d**) were assayed by variants of Rossiter's procedure using ketals of (−)-(2*R*,4*R*)-pentanediol (**8b–d**).[17,26] Absolute configurations of **6a,c,d** were assigned by GC comparisons of the ketals with those generated from authentic scalemic samples.[27] Absolute configurations of **6b** were assigned from ^{13}C NMR spectra of the previously characterized (−)-(2*R*,3*R*)-butanediol ketal.[3a]

The data in Table 1 show that solvent and temperature can dramatically affect the chemical and optical yields of 3-substituted cyclohexanones. Optimal conditions varied for each organocuprate and are marked with a "*". In the case of Me_2CuLi, (*R*)-3-methylcyclohexanone ((*R*)-**6a**) was produced. The best enantioselectivity was achieved in CH_2Cl_2 at −80 °C, utilizing reagent that had been prepared either in THF or ether (entries 2, 5; 83–85% ee). The chemical yield (39–41%) improved to 59% at −98 °C (entry 3; 76% ee), but enantioselectivity dropped significantly at −116 °C or −61 °C. Comparable results were obtained in THF solvent at −98 °C (entries 6 vs 3).

Scheme 4. Additions of Organocuprates to Cyclopentenone Complex 2



In the case of *n*-Bu_2CuLi, (*R*)-3-*n*-butylcyclohexanone ((*R*)-**6b**) was produced. The best enantioselectivity was found in THF at −29 °C, utilizing reagent prepared in ether (entry 12; 74% ee). The chemical yield dropped from 64% to 61–40% at −15 °C and −45 °C, but enantioselectivities were essentially identical. At −98 °C, the enantioselectivity sharply decreased (entry 16; 16% ee). When the reagent was prepared in THF, the enantioselectivity was lower (entry 17 vs 15). When CH_2Cl_2 was used as solvent, no special trend was apparent (entries 8 vs 17, 10 vs 15), and ether and THF were equally effective for reagent preparation (entries 8 and 10 vs 15).

With *t*-Bu_2CuLi, (*S*)-3-*tert*-butylcyclohexanone was produced ((*S*)-**6c**). Importantly, the configuration of this product is *opposite* to those obtained above. The enantioselectivity was best in THF at −98 °C (entry 25; 77% ee). The chemical yields improved from 53% to 58–75% at higher temperatures, but enantioselectivities dropped precipitously. In contrast, in CH_2Cl_2 solvent the enantioselectivity maximized at −15 °C (entry 18; 70% ee) and regularly dropped with decreased temperature. Since *t*-Bu_2CuLi is insoluble in ether, only THF solutions of the reagent were employed.

Finally, Ph_2CuLi gave (*R*)-3-phenylcyclohexanone ((*R*)-**6d**) of the best enantiomeric purity when prepared in ether and reacted in THF at −80 °C (entry 32; 64% ee). The enantioselectivity dropped at higher or lower temperatures or under analogous conditions in CH_2Cl_2 (entry 29; 52% ee). In most cases, chemical yields were high (82–83%). Curiously, when Ph_2CuLi was prepared in THF and reacted in CH_2Cl_2, the *opposite* enantiomer, (*S*)-**6d**, was obtained, albeit in modest enantiomeric purities (entries 27, 28; 26–11% ee). One other similar reversal occurred (entry 33).

3. Additions of Organocuprates to (+)-(*R*)-2. Reactions of Me_2CuLi and Ph_2CuLi with cyclopentenone complex (+)-(*R*)-**2** were investigated under a variety of conditions, as outlined in Scheme 4 and summarized in Table 2. The enantiomeric purity of 3-methylcyclopentanone (**10a**) was assayed by chiral GC.[31] That of

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(26) The diastereomeric ketals derived from (−)-(2*R*,4*R*)-pentanediol gave better GC separations than those derived from (−)-(2*S*,3*S*)-diethyl tartrate.

(27) Authentic (*R*)-**6a** and (*R*)-**10a** were obtained from Aldrich, and samples enriched in (*S*)-**6c**,[28] (*R*)-**6d**,[29] and (*S*)-**10d**[29] were prepared by literature methods. The last constituted a new synthesis, so the sign of the optical rotation was checked versus that in the literature.[30]

(28) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040.

Table 2. Conjugate Additions of Organocuprates to Cyclopentenone Complex (+)-(*R*)-2[a]

entry	solvent	organocuprate/ solvent	*T* (°C)	yield[b]	% ee[a]	configuration[a]
34	CH_2Cl_2	Me_2CuLi/ether	−45	<1	–	–
35	CH_2Cl_2	Me_2CuLi/ether	−61	6	65	*R*
36	CH_2Cl_2	Me_2CuLi/ether	−80	9	85	*R*
37	CH_2Cl_2	Me_2CuLi/ether	−98	10	75	*R*
38	CH_2Cl_2	Me_2CuLi/THF	−45	6	67	*R*
39	CH_2Cl_2	Me_2CuLi/THF	−61	7	74	*R*
40	CH_2Cl_2	Me_2CuLi/THF	−80	8	73	*R*
41	CH_2Cl_2	Me_2CuLi/THF	−98	10	76	*R*
42	THF	Me_2CuLi/THF	−61	86	41	*R*
43	THF	Me_2CuLi/THF	−80	72	56	*R*
44	THF	Me_2CuLi/THF	−98	40	37	*R*
45*	THF	Me_2CuLi/ether	−29	73	79	*R*
46	THF	Me_2CuLi/ether	−45	81	71	*R*
47	THF	Me_2CuLi/ether	−61	89	64	*R*
48	THF	Me_2CuLi/ether	−80	83	22	*R*
49	THF	Me_2CuLi/ether	−98	18	15	*R*
50	CH_2Cl_2	Ph_2CuLi/THF	−61	17	59	*S*
51	CH_2Cl_2	Ph_2CuLi/THF	−80	20	92	*S*
52*	CH_2Cl_2	Ph_2CuLi/THF	−98	50	93	*S*
53	CH_2Cl_2	Ph_2CuLi/THF	−116	47	76	*S*
54	CH_2Cl_2	Ph_2CuLi/ether	−80	22	87	*S*
55	CH_2Cl_2	Ph_2CuLi/ether	−98	41	92	*S*
56	THF	Ph_2CuLi/THF	−45	62	21	*S*
57	THF	Ph_2CuLi/THF	−61	75	55	*S*
58	THF	Ph_2CuLi/THF	−80	48	45	*S*
59	THF	Ph_2CuLi/ether	−80	75	17	*S*
60	THF	Ph_2CuLi/ether	−98	14	98	*S*

[a] For conditions and analytical methods, see text and Scheme 4. Optimum runs are designated with a "*". [b] GC yields of 3-substituted cyclopentanones **10**.

3-phenylcyclopentanone (**10d**) was assayed via the ketal derived from (−)-(2*R*,4*R*)-pentanediol, **11d**. Absolute configurations were assigned by GC comparisons with commercial (*R*)-**10a** or the ketal derived from independently prepared (*S*)-**10d**.[27]

In the case of Me_2CuLi, (*R*)-3-methylcyclopentanone ((*R*)-**10a**) was produced. When reactions were conducted in CH_2Cl_2 at various temperatures using reagent prepared either in ether or THF, chemical yields were poor (entries 34−41), although enantioselectivities were as high as 85% ee (−80 °C; entry 36). In all cases, free cyclopentenone was detected by GC. When reactions were conducted in THF, chemical yields were generally 72−89%. The best enantioselectivity was achieved at −29 °C, utilizing reagent generated in ether (entry 45; 79% ee). As temperatures were lowered to −98 °C, enantioselectivities decreased monotonically to 15% ee (entries 46−49). When Me_2CuLi was generated in THF, the enantioselectivities were lower at −61 °C, but somewhat higher at −80 °C and −98 °C (entries 42−44).

With Ph_2CuLi, (*S*)-3-phenylcyclopentanone ((*S*)-**10d**) was produced under all conditions investigated. The configuration of this product is opposite to that obtained above. High enantioselectivity was realized in CH_2Cl_2 at −98 °C, utilizing reagent generated in THF (entry 52; 93% ee), although the chemical yield was only fair (50%). Similar results were obtained with Ph_2CuLi generated in ether (entry 55). When analogous reactions were conducted in THF, enantioselectivities were usually lower. However, the enantioselectivity was very high at −98 °C, utilizing reagent generated in ether (entry 60; 98% ee), although the chemical yield was poor (14%).

4. Other Data. In order to help optimize or clarify aspects of the preceding reactions, other preparative and spectroscopic experiments were conducted. We first wondered whether longer reaction times might be beneficial when product yields were low but enantioselectivities were high. Thus, entries 25, 36, and 60 of Tables 1 and 2 were repeated with 4 h reaction times. Only in the last case did the yield increase significantly (27%). Curiously, the enantioselectivity sharply decreased (26% ee). One of several possible rationales would involve a slower organocuprate addition to *free* cycloalkenone that had been displaced from the rhenium fragment **I** under the reaction conditions.

In pursuit of this point, cyclohexenone complex (+)-(*R*)-**1** and Me_2CuLi (in THF) were analogously reacted at −80 °C in CH_2Cl_2 in an NMR tube. After 7 min, a ^{31}P NMR spectrum showed that (+)-(*R*)-**1** (18.3 ppm) had been consumed. Four new resonances appeared (27.0, 18.8, 17.6, 16.5 ppm; 17:45:16:22). When the probe was warmed to 0 °C (26.2, 18.4, 17.5 ppm; 27:43:30) or room temperature (26.0, 18.4, 17.7 ppm; 35:39:26), only three resonances were detected. The 26−27 ppm resonance was assigned to methyl complex **3** on the basis of spiking and a diagnostic ReC ^{13}C NMR signal (−37.5 ppm, d, J_{CP} = 6.8 Hz)[11] obtained in a separate experiment involving racemic **1**. The chemical shifts of the other resonances were plausible for enolate complex **4a**.[24] Hence, the displacement of cyclohexenone appears to be competitive with 1,4-addition. After 1 day at room temperature, the iodide complex **5** was detected (14.2 ppm, 22%)—presumably originating from the CuI used to generate Me_2CuLi.

The yields of **5** were measured only in some of the entries in Tables 1 and 2. They were not optimized, and ranged from 93 to 52%. In our experience with this type of transformation, >90% yields can be routinely achieved. Pure **5** is configurationally stable,[16] but earlier studies have shown that racemization can occur in the presence of some reagents.[6a] Indeed, recovered **5** always showed at least partial racemization (entry 4: 76% ee, chiral HPLC).[12] However, other types of Brønsted acids should give configurationally more robust derivatives.[6a-c]

Toward this end, $HBF_4{\cdot}OEt_2$ was briefly investigated as an alternative to HI. This Brønsted acid has a nonnucleophilic counteranion, so reactions with enolate complexes **4** or **9** should give cationic 3-substituted cycloalkanone complexes, such as **12** in Scheme 5 (bottom). Furthermore, cyclohex*en*one displaces cyclohex*an*one from the rhenium fragment **I**, as shown in Scheme 5 (top).[9] This reflects a higher thermodynamic binding constant and suggests a particularly attractive strategy for simultaneously liberating the organic addition product and recycling the rhenium auxiliary.

Thus, racemic **1** and Ph_2CuLi (2 equiv; in THF) were combined in an NMR tube as described for Me_2CuLi above. A ^{31}P NMR spectrum (−80 °C) showed a major signal at 18.9 ppm (68%), plausible for enolate complex **4d**.[24] Then $HBF_4{\cdot}OEt_2$ was added (7 equiv), and a ^{31}P NMR spectrum (−80 °C) showed a major signal at 19.1 ppm (95%), plausible for a 3-phenylcyclohexanone complex of **I**.[6,7] Cyclohexenone was added (5 equiv), and the sample was warmed to room temperature. After 15 h, a new resonance at 18.7 ppm dominated (90%), which IR and ^1H NMR spectra confirmed was cyclohexenone complex **1**. Workup of an analogous preparative reaction of (+)-(*R*)-**1** and Ph_2CuLi gave recovered (+)-(*R*)-**1** of 78% purity in 73% yield and 91% ee. However, the chemical yield and enantiomeric purity of the resulting 3-phenyl-

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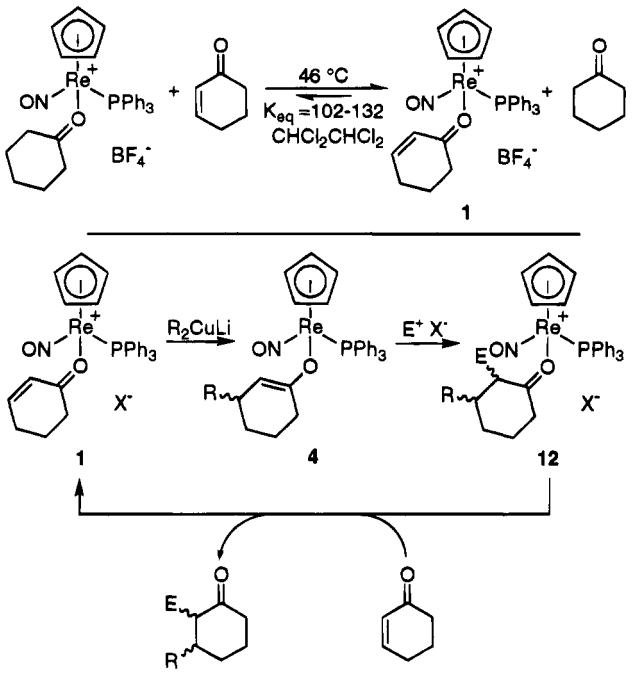
(30) Paquette, L. A.; Gilday, J. P.; Ra, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6858.
(31) 30 m Chiraldex APH column (Astec Inc., Whippany, NJ).

Scheme 5. Binding Equilibrium and Possible Recycling Protocols



cyclohexanone (*S*)-**6d** (39%, 5% ee) was somewhat lower than that of the corresponding reaction in Table 1 (entry 27).

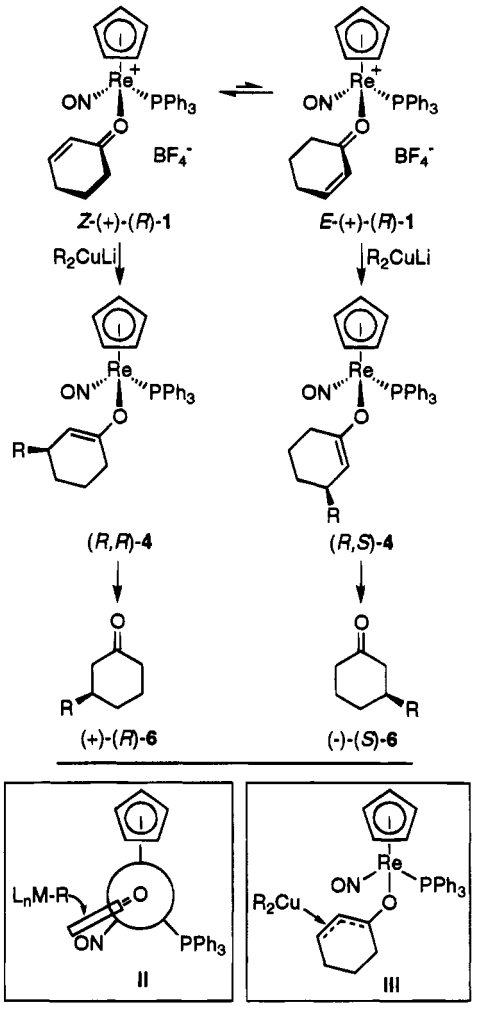
Finally, no improvements occurred when reactions were conducted in the presence of $(CH_3)_3SiCl$. This additive often gives enhanced yields and enantioselectivities in conjugate additions of achiral or chiral organocuprates.[23,29,32]

Discussion

1. Mechanism of Enantioselection. The preceding data show that the rhenium Lewis acid **I** can be an effective chiral auxiliary for enantioselective conjugate additions of organocuprates to cyclohexenone and cyclopentenone. However, numerous variables affect the product yields, enantiomeric purities, and configurations. Thus, possible transition state models and origins of enantioselection are considered first. In this context, some adducts of **I** and α,β-unsaturated carbonyl compounds (e.g., crotonaldehyde) exist as rapidly equilibrating mixtures of σ and π O=C isomers.[9] Importantly, rate data show that the σ isomers are much more reactive toward nucleophiles.[6d]

When unsymmetrical ketones form σ adducts with Lewis acids, *Z*/*E* O=C geometric isomers are possible. In attempts to detect *Z*/*E* isomers of **1**, ^{31}P and ^{13}C NMR spectra were recorded in CD_2Cl_2 at −100 °C.[9] However, no decoalescence was observed. The *Z*/*E* O=C substituents in acetone and 3-pentanone complexes of **I** exchange with barriers of only 6–7 kcal/mol.[6b,7] Thus, we assume that the *Z*/*E* isomers of **1** are in rapid equilibrium. Two crystal structures of cyclopentadienyl iron σ-cyclohexenone complexes have been executed.[33] Both show *Z* isomers in the solid state, with the slightly smaller =CH

Scheme 6. Analysis of Stereochemistry of Organocuprate Addition to Cyclohexenone Complex (+)-(*R*)-1



group *cis* to the metal and the CH_2 group *trans*. We therefore presume that the *Z*/*E* equilibrium ratio for **1** in solution is greater than unity (Scheme 6).

Cycloalkenone complexes **1** and **2** would be expected to adopt Re–O conformations similar to those of other ketone complexes of **I**,[6b] as illustrated in **II** (Scheme 6). It has been shown that in a variety of types of reactions, nucleophiles or electrophiles preferentially attack ligands bound to **I** from a direction *anti* to the bulky PPh_3 ligand.[6b–d,34] Thus, organocuprates should approach **1** and **2** as sketched in **II**. Furthermore, there is strong evidence that organocuprate additions involve reversibly-formed *d*-π* complexes.[35] These undergo rate determining collapse to enolates, setting the configuration of any new carbon stereocenter. One possible formulation for a *d*-π* adduct derived from **1** is given in **III** (Scheme 6).

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However, it is in our opinion conceivable, in view of the many unique features of substrates **1** and **2**, that the initial organocuprate attack might be rate determining.

The consequences of this model are analyzed in Scheme 6, which uses (+)-(*R*)-**1** for illustration. Organocuprate attack upon the *Z* O=C isomer from a direction *anti* to the PPh_3 ligand would ultimately give the *RR* Re/C diastereomer of enolate complex **4**, and then 3-substituted cyclohexanones (*R*)-**6**.[9] Analogous attack upon the *E* isomer would give the *RS* diastereomer of **4** and then (*S*)-**6**. In view of the ease of *Z*/*E* isomerization noted above, the Curtin–Hammett limit likely applies. Thus, the *R*/*S* ratios would be controlled by the relative energies of the transition states of the rate determining steps—either those connecting *d*-π^* complexes such as **III** and enolate complexes **4**, or the initial organocuprate attack.

The organocuprates Me_2CuLi and *n*-Bu_2CuLi have smaller alkyl groups, and give cycloalkanones (*R*)-**6a,b** and (*R*)-**10a**, consistent with attack upon the *Z* O=C isomers of (+)-(*R*)-**1** and (+)-(*R*)-**2** from directions *anti* to the PPh_3 ligand. In contrast *t*-Bu_2CuLi, which has bulky alkyl groups, gives (*S*)-**6c**, consistent with analogous attack upon the *E* O=C isomer of (+)-(*R*)-**1**. This would allow a greater separation of the bulkier organocuprate and the rhenium fragment. However, depending upon temperature and solvent, Ph_2CuLi gives either (*R*)-**6d** or (*S*)-**6d**.

There are numerous possible explanations for such effects, as well as the decreased enantioselectivities sometimes found at lower temperatures in Tables 1 and 2. In particular, organocuprates can exist in different aggregation states, and such equilibria are sensitive functions of temperature and solvent.[35] Thus, the effective bulk of the organocuprate (e.g., larger at low temperature), as well as the kinetically dominant species, can vary greatly. The transition states responsible for enantioselection are in turn altered—even to the point where the dominant enantiomer generated is reversed, as observed with **6d**. Similar phenomena have been noted in conjugate additions of some chiral organocopper reagents.[4b,29]

2. Merits of Methodology. The methyl complex (+)-(*S*)-**3** that originates the above chemistry (Scheme 2) can be prepared in five steps and 42% overall yield (including resolution) from commercially available $Re_2(CO)_{10}$.[11,34d] The enantiomeric excesses of the resulting 3-substituted cycloalkanones are, under optimized conditions, good to excellent. Those obtained for (*R*)-**6a** (entry 5, 85% ee), (*R*)-**6b** (entry 12, 74% ee), (*R*)-**6d** (entry 32, 64% ee), and (*R*)-**10a** (entry 45, 79% ee) are somewhat lower than the best previously reported in the literature (90%,[3a] 81%,[4a] 97%,[17] >98% ee[37]). To our knowledge, that obtained for (*S*)-**6d** (entry 25, 77% ee) is the highest to date (69% ee).[28] That obtained for (*S*)-**10d** (entry 52, 93% ee) is comparable with the best previously reported (92% ee).[38]

However, these optimized enantiomeric excesses were achieved empirically and with much effort. In retrospect, some guiding trends can be identified, as illustrated graphically for solvent effects upon reactions of (+)-(*R*)-**2** in Figure 1. Nonetheless, our methodology cannot presently be extended or generalized with a high degree of predictability. Furthermore, chemical yields are sometimes only fair. Similar situations are encountered with conjugate additions of most chiral organocopper reagents. Hence, some possibilities for future refinements are analyzed below.

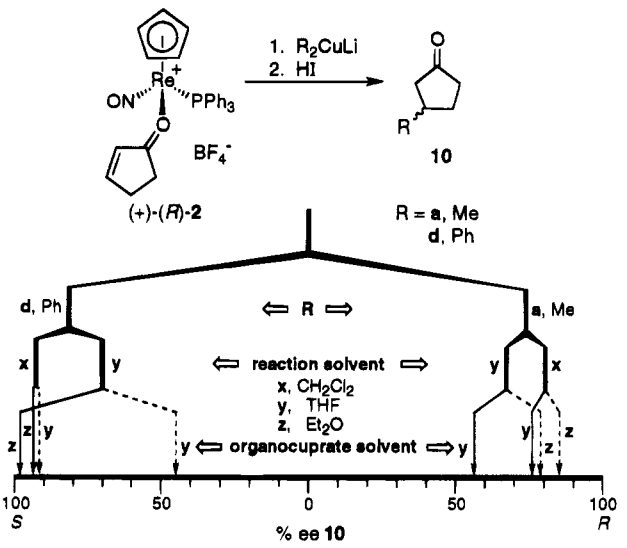

Figure 1. Additions of organocuprates to cyclopentenone complex (+)-(*R*)-**2**: graphical representation of the effect of the R-groups and the solvent upon the enantiomeric excesses of the resulting 3-substituted cyclopentanones (data are from the optimum examples in Table 2 in each solvent).

First, one strategy for improving chemical yields would be to assay for the displacement of cycloalkenone ligands under the reaction conditions. This problem is intrinsic to all approaches to enantioselective conjugate additions involving prior substrate binding to chiral Lewis acids. It is probable that such side reactions can be minimized by an appropriate solvent choice. Furthermore, enantioselectivities may also be enhanced, as any additions to free cycloalkenones would give racemic products.

Second, reactions of the intermediate enolate complexes **4** or **9** with alkylating agents[39] should give cationic ketone complexes, as depicted with **12** in Scheme 5 (bottom). This introduces a new stereocenter and illustrates a powerful attribute of auxiliary-based approaches to enantioselective syntheses—the potential to control configurations in a *sequence* of new stereocenters. Furthermore, when **12** is generated from an alkylating agent that would give a weakly nucleophilic counteranion (e.g., ROTf), it should be long-lived and amenable to the recycling protocol shown at the bottom of Scheme 5.

Third, O=C adducts of most α,β-unsaturated carbonyl compounds and **I** undergo linkage isomerization to thermodynamically more stable C=C adducts at 25–95 °C.[9] Interestingly, **1** and **2** are the only compounds known to date that do not isomerize completely. Regardless, the styrene complex of **I** undergoes regiospecific, diastereospecific, and enantiospecific addition of Me_2CuLi to give the β-branched alkyl complex (η^5-C_5H_5)Re(NO)(PPh_3)($CH_2CH(CH_3)Ph$) in quantitative yield.[40] Thus, it might also be possible to effect enantioselective conjugate additions to α,β unsaturated carbonyl compounds

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via their C=C adducts with **I** or other transition metal Lewis acids.

In conclusion, we have established the feasibility of a new approach to enantioselective conjugate additions of organocuprates—one in which a chiral Lewis acid first binds and activates the substrate. Our protocol utilizes the easily accessed rhenium fragment **I** and compares well with the best methodologies currently available. Although some problematic issues remain, rational approaches to their solution can be formulated, and several attractive extensions are readily envisioned. We believe that chiral transition metal auxiliaries have a rich potential for enantioselective conjugate addition reactions, and further examples and refinements will be reported in due course.

Experimental Section

General Data.[23] All reactions were carried out under dry N_2 atmospheres. NMR spectra were recorded on 300 MHz spectrometers. Chemicals were obtained as described previously,[9] with the following additions: anhydrous $MgSO_4$ and K_2CO_3 (Mallinckrodt), HI (47% aqueous, Fisher), alumina (80–200 mesh, Fisher), CuI and HOTs (Aldrich), (−)-(2*S*,3*S*)-diethyl tartrate, (−)-(2*R*,4*R*)-pentanediol, and (−)-(2*R*,3*R*)-butanediol (all Aldrich, ≥99% ee), used as received; RLi (Aldrich), standardized before use.[41]

(+)-(*R*)-[(η^5-C_5H_5)Re(NO)(PPh$_3$)(η^1-O=CCH=CHCH$_2$CH$_2$CH$_2$)]$^+$ BF$_4^-$ ((+)-(*R*)-1). Complex (+)-(*S*)-(η^5-C_5H_5)Re(NO)(PPh$_3$)(CH$_3$) ((+)-(*S*)-**3**,[11] 0.205 g, 0.367 mmol), CH_2Cl_2 (5 mL), HBF_4·OEt_2 (42 μL, 0.39 mmol), and cyclohexenone (200 μL, 2.01 mmol) were combined in a procedure identical with that used for the racemate.[9] An identical workup gave (+)-(*R*)-**1** as a red powder (0.216 g, 0.298 mmol, 81%), mp 178–185 °C dec, $[\alpha]_{589}^{25}$ 413 ± 7° (*c* 0.51 mg/mL, CH_2Cl_2).[42] Anal. Calcd for $C_{29}H_{28}BF_4NO_2PRe$: C, 47.97; H, 3.88. Found: C, 47.84; H, 3.90.[13]

(+)-(*R*)-[(η^5-C_5H_5)Re(NO)(PPh$_3$)(η^1-O=CCH=CHCH$_2$CH$_2$)]$^+$ BF$_4^-$ ((+)-(*R*)-2). Complex (+)-(*S*)-**3** (1.05 g, 1.88 mmol), CH_2Cl_2 (8 mL), HBF_4·OEt_2 (215 μL, 1.99 mmol), and cyclopentenone (800 μL, 9.55 mmol) were combined in a procedure identical with that used for the racemate.[9] An identical workup gave (+)-(*R*)-**2** as a red powder (1.19 g, 1.67 mmol, 89%), mp 168–176 °C dec, $[\alpha]_{589}^{25}$ 448 ± 6° (*c* 0.45 mg/mL, CH_2Cl_2).[42] Anal. Calcd for $C_{28}H_{26}BF_4NO_2PRe$: C, 47.20; H, 3.68. Found: C, 47.06; H, 3.72.[13]

Conjugate Additions. In all cases, 0.093–0.140 g of (+)-(*R*)-**1** or (+)-(*R*)-**2** and 2 equiv of R_2CuLi[43] were used. The chemical yields of 3-substituted cycloalkanones were determined on a 25 m × 0.2 mm × 0.5 μm HP-5 fused silica capillary GC column, referenced to the following internal standards: **10a**, decane; **6a–c**, dodecane; **6d** and **10d**, tetradecane (see Schemes 2–3). Ratios of the corresponding diastereomeric ketals were assayed on a 25 m × 0.2 mm × 0.5 μm HP carbowax capillary GC column. Retention times (min, flow rate 35 mL/min): **7a** (200 °C) 7.61/7.78, from (*S*)/(*R*)-**6a**; **8b** (130 °C) 5.27/5.59, from (*R*)/(*S*)-**6b**; **8c** (90 °C) 16.43/16.82, from (*S*)/(*R*)-**6c**; **8d** (200 °C) 5.39/5.62, from (*S*)/(*R*)-**6d**; **11d** (200 °C) 4.36/4.70, from (*S*)/(*R*)-**10d**.[27] The enantiomeric purity of **10a** was assayed directly.[31] All data are averages of two injections.

The following was typical. A Schlenk flask was charged with (+)-(*R*)-**1** (0.136 g, 0.187 mmol), CH_2Cl_2 (10 mL), and a stir bar and cooled to −98 °C (methanol/N_2). After 10 min, Me_2CuLi (ca. 2 equiv in THF)[43] and dodecane (14.0 μL) were added with stirring. After 30 min, HI (47% aqueous; 170 μL, 0.937 mmol) was added. The cold bath was allowed to slowly warm to room temperature. After 4 h, some white solid formed. The mixture was filtered through solid K_2CO_3 in a coarse frit sintered glass funnel.[44] The filtrate was concentrated to ca. 1 mL and added to pentane (50 mL). A pink solid formed. The supernatant was removed by pipet and filtered through an alumina column (0.6 × 7 cm). GC analysis (100–150 °C, 5 °C/min) showed **6a** (59%). The pink solid was dried to give (η^5-C_5H_5)Re(NO)(PPh$_3$)(I) (**5**;[16] 0.066 g, 0.097 mmol, 52%).

The solution of **6a** was concentrated to ca. 0.5 mL in a round bottom flask. Then (−)-(2*S*,3*S*)-diethyl tartrate (0.039 g, 0.19 mmol), benzene (2 mL), HOTs (ca. 0.006 g, 0.03 mmol), and solid $MgSO_4$ were added.[17,45] The mixture was refluxed (24 h) and filtered through an alumina column that was rinsed with ether (2 mL). GC analysis of the eluate (200 °C) showed ketals **7a** in 76% de, with that from (*R*)-**6a** dominant.

Acknowledgment. We thank the NIH for support of this research, Dr. T. Bartik for Figure 1, and Professor B. Rossiter and his research group (BYU) for experimental assistance.

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(42) Dewey, M. A.; Gladysz, J. A. *Organometallics* **1993**, *12*, 2390.

(43) The following was typical.[18] A round bottom flask was charged with CuI (0.072 g, 0.38 mmol), THF or ether (1 mL), and a stir bar and cooled to 0 °C. Then MeLi (1.4 M in ether, 540 μL, 0.76 mmol) was added with stirring. After 30 min, the resulting colorless solution was added to (+)-(*R*)-**1** or (+)-(*R*)-**2**.

(44) Reactions conducted in THF remained homogeneous through this stage. The filtrate was concentrated to ca. 0.5 mL, and CH_2Cl_2 (1 mL) was added. A yellow precipitate formed. The mixture was filtered through a pipet plugged with glass fiber, and the filtrate was added to pentane to give **5** as a pink solid. The remaining workup details were the same.

(45) This procedure is adapted from van Leusen, D.; Rouwette, P. H. F. M.; van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159.