Asymmetric Conjugate Addition

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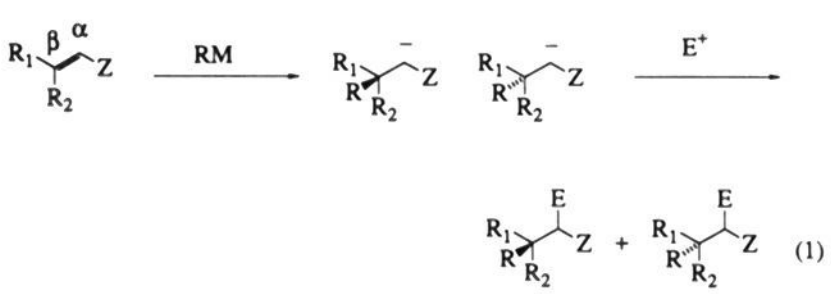
I. Introduction

Conjugate addition of organometallic reagents to α,β-unsaturated organic substrates is an important and well-known method of assembling structurally complex organic molecules.[1] In these reactions, the organic portion of an organometallic reagent adds to the β-carbon of an electron-deficient alkene, giving first a stabilized carbanion and then, after protonation or some other form of quenching, the β-substituted product (eq 1). Substrates used in this reaction are usually α,β-unsaturated ketones, aldehydes, esters, amides, sulfoxides, or nitro compounds. Reactions involving organometallic reagents are generally run under anhydrous, oxygen-free conditions. Often referred to as 1,4-addition, these reactions use a variety of organo-



(1)

Z = COR, CHO, COOR, $CONR_2$, CN, SOR, SO_2R, etc.

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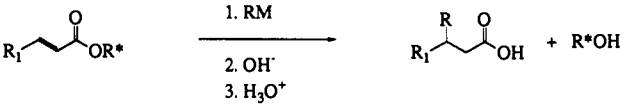
Table 1. Diastereoselective Conjugate Addition of Organometallics to Scalemic α,β-Unsaturated Esters

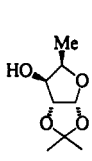


entry	R_1	R*OH[a]	RM	T, °C	% yield	% ee	R/S	ref
1	Me	1	PhMgBr/cat. CuCl	−15	61	58	*R*	8
2		4		−8	64	10	*R*	9
3		2		−15	50	68	*R*	8
4		3			58	74	*R*	
5	Ph	1	*n*-BuMgCl/CuCl		56	17	(−)	
6		4			61	27	(−)	
7		2			40	22	(−)	
8		3			58	17	(−)	
9	Me	5	$PhCu{\cdot}BF_3$	−70	76	>99	*R*	12
10			n-$BuCu{\cdot}BF_3$		75	>99	*R*	
11	Me (*Z* isomer)		$PhCu{\cdot}BF_3$		36	24	*S*	
12	Me (*Z* isomer)		n-$BuCu{\cdot}BF_3$		76	70	*R*	
13	*n*-Bu		$MeCu{\cdot}BF_3$		28	78	*R*	
14			$MeCuP(n\text{-}Bu)_3{\cdot}BF_3$		96	87	*R*	13
15		7			82	94	*R*	
16			$LiCu(CN)Me{\cdot}BF_3$		80	82	*R*	
17	Et		$MeCuP(n\text{-}Bu)_3{\cdot}BF_3$		85	92	*R*	
18			$LiCu(CN)Me{\cdot}BF_3$		76	80	*R*	
19	*n*-octyl	6	$MeCuP(n\text{-}Bu)_3{\cdot}BF_3$		90	98	*S*	
20	Me	7	$(CH_3)_2C{=}CH(CH_2)_2CuP(n\text{-}Bu)_3{\cdot}BF_3$		81	98	*S*	
21	$(CH_3)_2C{=}CH(CH_2)_2$	6	$MeCuP(n\text{-}Bu)_3{\cdot}BF_3$		90	92	*S*	
22	Me	7	$(CH_2{=}CH)CuP(n\text{-}Bu)_3{\cdot}BF_3$		85	94	*R*	15
23			$(CH_2{=}CCH_3)CuP(n\text{-}Bu)_3{\cdot}BF_3$		86	99	*R*	
24	$CH_2{=}CH(CH_2)_2$				89	98	*R*	
25	Me	8	n-$PrCuP(n\text{-}Bu)_3{\cdot}BF_3$		98	95	*S*	18
26			n-$BuCuP(n\text{-}Bu)_3{\cdot}BF_3$		89	97	*S*	
27			$(CH_2{=}CH)CuP(n\text{-}Bu)_3{\cdot}BF_3$		80	98	*R*	
28			$(CH_3CH{=}CH)CuP(n\text{-}Bu)_3{\cdot}BF_3$		84	94	*R*	
29	*n*-Pr		$MeCuP(n\text{-}Bu)_3{\cdot}BF_3$		89	94	*R*	
30	*n*-Bu				93	97	*R*	
31	Me	9	$(n\text{-}Bu)_2CuLi$	−25	90	0	(−)	20
32		10			81	50	*S*	
33		11			77	60	*S*	
34		12			73	33	*S*	
35				−78	71	45	*S*	
36		13		−25	75	87	*S*	
37				−78	74	95	*S*	
38			n-BuCu/TMSI	−60	93	98	*S*	21
39		14	CCl_3Li	−110	85	24	*R*	22
40			CCl_3MgCl		99	97	*S*	
41	Me		$EtCu{\cdot}BF_3$	−80	90	99	*R*	23
42		15			84	99	*S*	
43		14	i-$PrCu{\cdot}BF_3$		90	99	*R*	
44		15			97	96	*S*	
45	Et	14	$MeCu{\cdot}BF_3$		86	98	*S*	
46		15			88	99	*R*	
47		14	i-$PrCu{\cdot}BF_3$		96	99	*S*	
48		15			94	99	*R*	
49	*i*-Pr	14	$MeCu{\cdot}BF_3$		92	99	*R*	
50		15			93	99	*S*	
51		14	$EtCu{\cdot}BF_3$		76	99	*R*	
52			$Cu{\cdot}BF_3$		81	97	*R*	
53		15			98	99	*S*	
54	Me	14	$(CH_2{=}CH)Cu{\cdot}BF_3$		94	99	*S*	
55		15			81	99	*R*	
56		14	$PhCu{\cdot}BF_3$		97	99	*S*	
57		15			94	99	*R*	
58			$p\text{-}(CH_3)C_6H_4Li$		85	99	*R*	
59		16	Ph_2CuLi	−50	66	88	*R*	24a
60	Ph		Me_2CuLi	−30	71	84	*S*	
61	Et		Ph_2CuLi		63	72	*R*	
62	Me		$(n\text{-}Bu)_2CuLi$		91	72	*S*	
63	Ph				79	82	*S*	
64			n-$BuCu{\cdot}BF_3$	−78	33	25	*S*	
65	Ph		n-BuMgBr		15	38	*S*	
66			n-BuLi		20	68	*R*	
67	Et		PhLi		31	82	*S*	
68	Me	17	Ph_2CuLi	−30	60	28	*R*	24b
69		18			88	84	*S*	
70		19		0	87	36	*S*	

Table 1. (Continued)

entry	R_1	R*OH[a]	RM	T, °C	% yield	% ee	R/S	ref
71		**20**		−30	55	34	*R*	
72		**21**		0	23	20	*R*	
73		**16**	PhMgBr·CuI	−78	46	56	*R*	
74		**18**			52	86	*S*	
75			$(H_2C{=}CH)MgBr{\cdot}CuI$		42	88	*S*	
76			EtMgBr·CuI		51	78	*R*	
77		**19**	PhMgBr·CuI		45	2	(−)	
78		**20**			50	4	(−)	
79		**21**			45	6	(−)	
80	$(CH_2)_3Cl$	**16**	Ph_2CuLi	0	50	76	1*R*,2*R*	24a
81			n-Bu_2CuLi		51	80	1*R*,2*S*	
82			Me_2CuLi		57	76	1*R*,2*S*	
83	$(CH_2)_4I$		Ph_2CuLi		61	78	1*R*,2*R*	
84	Ph	**5**	$(PhMe_2Si)_2CuLi_2CN$	−78	82	20	*R*	25
85		**7**			74	8	*R*	
86		**8**			77	88	*R*	
87	Me				74	10	*S*	
88	*i*-Pr				74	56	*R*	
89	$PhMe_2Si$		PhMgBr/CuCN		71	74	*R*	
90			$MeMgI/Cu(OAc)_2$	−15	76	54	*S*	

[a] R*OH =



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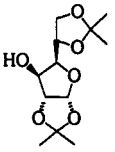

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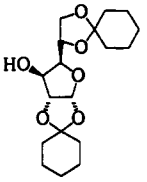

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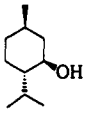

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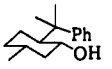

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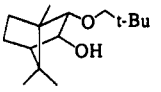

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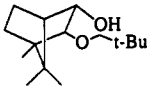

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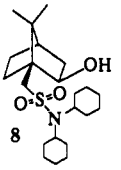

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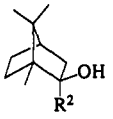
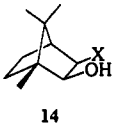


R^2 = H, Methyl, Phenyl, Benzyl, 1-Naphthyl

9 10 11 12 13



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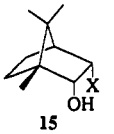

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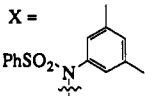

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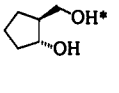

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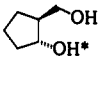

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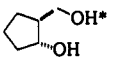

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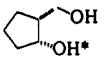

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* hydroxyl group incorporated into the ester group

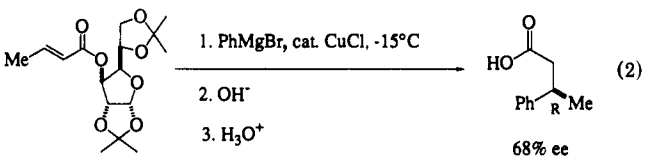
metallic reagents, the most common of which are organolithiums,[2] Grignards,[2] and cuprates.[3] The primary advantage of these reactions is that they allow the direct introduction of nonstabilized organic moieties into an organic structure with high chemo- and regioselectivity starting from substrates which are generally readily available.

An important characteristic of these reactions is that they transform an sp^2 carbon into an sp^3 carbon through addition of the R moiety to the β-position. Where $R_1 \neq R_2$, this transformation can, in principle, occur enantioselectively.[4] Enantioselective conjugate addition (referred to hereafter as ECA) can be achieved in two ways: (1) by reaction of an achiral reagent with a scalemic substrate,[5] or (2) by reaction of a chiral reagent with a prochiral substrate. In cases where the starting substrate is chiral, the reaction can occur diastereoselectively. Diastereoselective conjugate addition (referred to hereafter as DCA) can lead to the synthesis of enantiomers if the original source of chirality is removed. Thus in cases where an achiral reagent reacts with a substrate in which Z is chiral, an unequal mixture of diastereomers will usually be produced by relative asymmetric induction. Modification of Z to eliminate its stereogenic elements will produce an enantiomeric rather than diastereomeric mixture of isomers. Alternatively, one may react a prochiral substrate with a chiral reagent which induces ECA of an achiral moiety to the substrate. In this paper, we review synthetic methods which have been developed and reported for enantioselective carbon–carbon bond formation via conjugate addition of organometallic reagents to unsaturated organic substrates using either of the two strategies mentioned above. We will not review diastereo- or enantioselective conjugate addition involving stabilized carbon nucleophiles or non-carbon nucleophiles.[4] We will also not review reactions involving conjugate addition to racemic substrates or reactions in which the objective is not to obtain enantiomerically pure products. The review is divided into three sections. The first section reviews synthetic methods developed for DCA to scalemic substances giving diastereomerically enriched products which are subsequently transformed to enantiomers. The second and third sections review chiral reagents developed to react enantioselectively with prochiral substrates.

II. Diastereoselective Conjugate Addition to Scalemic Substrates

A. α,β-Unsaturated Esters

One of the first methods developed for asymmetric conjugate addition involves the reaction of organocopper reagents with enantiomerically enriched α,β-unsaturated esters (Table 1). These esters, derived from scalemic alcohols and α,β-unsaturated carboxylic acids, react to give diastereomeric products which upon hydrolysis yield enantiomers. In principle, this provides a simple and economical method of obtaining enantiomerically enriched products, especially if the alcohol used is readily available and recovered without racemization. It has been known for some time that copper(I) salts catalyze the conjugate addition of Grignard reagents to α,β-unsaturated ketones[6] and esters.[7] In 1966, Kawana and Emoto reported the copper(I)-catalyzed addition of phenylmagnesium bromide to the 1,2:5,6-di-*O*-isopropylidene-α-D-glucose ester of crotonic acid, **22** (eq 2).[8,9] This reaction, followed by hydrolysis, gives (*R*)-(−)-3-phenylbutanoic acid (**23**) in 70% ee. Difficulties in reproducing these results have been reported.[10] Reactions with similar substrates give product with ee's ranging from 10 to 74% (entries 1–8).



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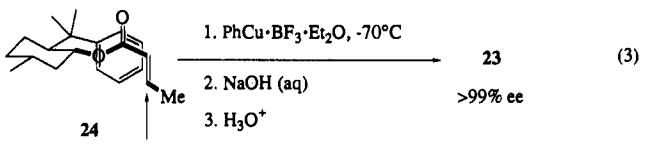
Yamamoto and Maruyama described the use of $RCuBF_3{\cdot}Et_2O$ for conjugate addition of R to α,β-unsaturated carbonyl compounds.[11] Oppolzer and Löher used this method for DCA to (−)-8-phenylmenthol derived enoates (entries 9–13).[12] For example, reaction of $PhCu{\cdot}BF_3$ with (−)-8-phenylmenthyl crotonate (**24**) gives, after hydrolysis, (*R*)-**23** in 76% yield and >99% ee (eq 3). Mediocre results were obtained with *Z* isomers



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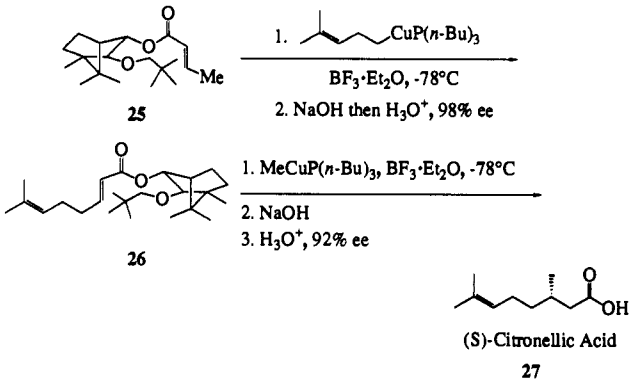
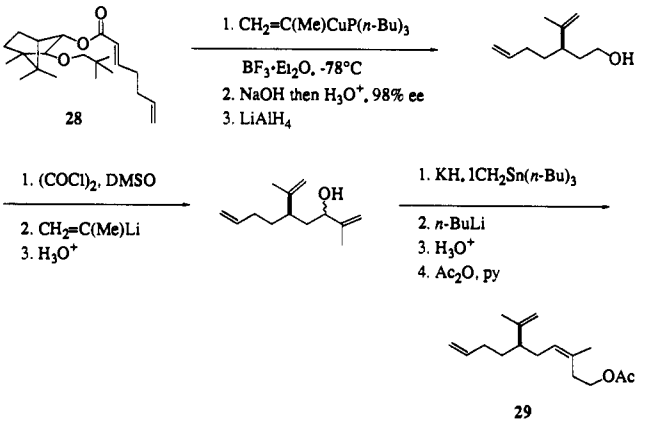
or with tri- and tetrasubstituted enoates. The high diastereoselectivity is believed to occur as a result of the ester assuming a conformation in which the carbonyl group, the ether oxygen, and the alkoxy C–H bond are coplanar and the carbonyl group and alkene are antiplanar. The phenyl group blocks one face of the alkene directing conjugate addition to the opposite face. $MeCu{\cdot}BF_3$ reacts with significantly poorer diastereoselectivity. Subsequently, Oppolzer et al. demonstrated that other chiral enoates, in which the substrate is made using camphor-derived alcohols, **6** and **7**, could be used as well in this reaction with varying degrees of diastereoselectivity (entries 15–24).[13,14] Improved results were obtained by adding $P(n\text{-}Bu)_3$ to stabilize the organocopper reagent. These chiral auxiliaries and the improved method were used in the synthesis of (*S*)-citronellic acid (**27**) from **25** and **26**

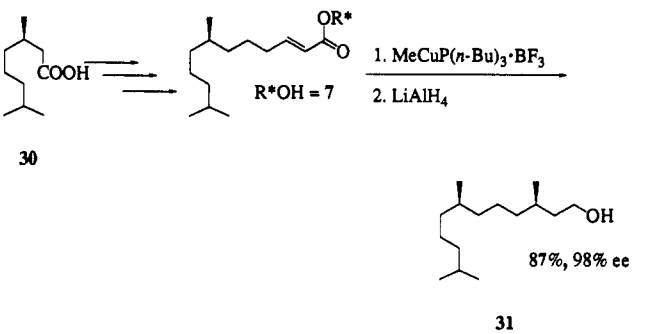
Scheme 1. Synthesis of Citronellic Acid via Diastereoselective Conjugate Addition to Scalemic Enoates



Scheme 2. Synthesis of California Red Scale Pheromone via Diastereoselective Conjugate Addition to Scalemic Enoates

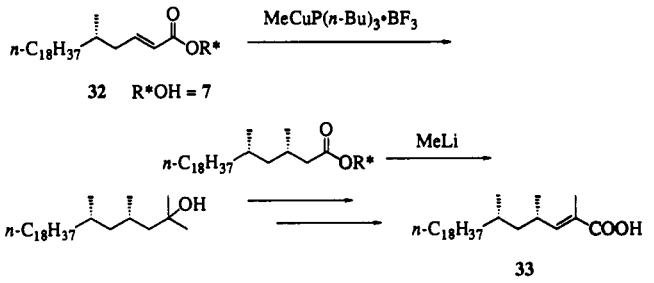


Scheme 3. Synthesis of Vitamin E Side Chain via Diastereoselective Conjugate Addition to Scalemic Enoates

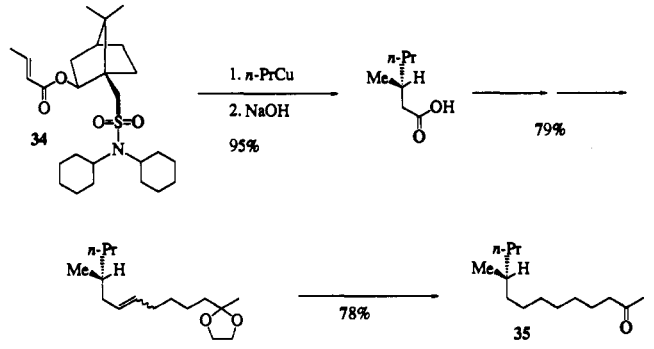


(Scheme 1)[13] and California red scale pheromone **29** from **28** (Scheme 2).[15] More than one chiral center can be established with this method. For example, the vitamin E side chain **31** was synthesized using this technology starting from (*R*)-citronellic acid. The new stereogenic center was established with 98% enantioselectivity (Scheme 3).[16] Similarly, mycolipenic acid (**33**) was also synthesized (Scheme 4).[17] Camphorsulfonamide esters, derived from alcohol **8**, have also been used (entries 25–30)[18] and are more efficient than the esters derived from alcohols **6** and **7**. Chiral auxiliary **8** is readily obtained in two steps from camphor-10-sulfonyl chloride making this protocol highly useful. This method was used to synthesize southern corn rootworm pheromone **35** (Scheme 5)[18] and norpectinatone (**36**, Scheme 6).[19]

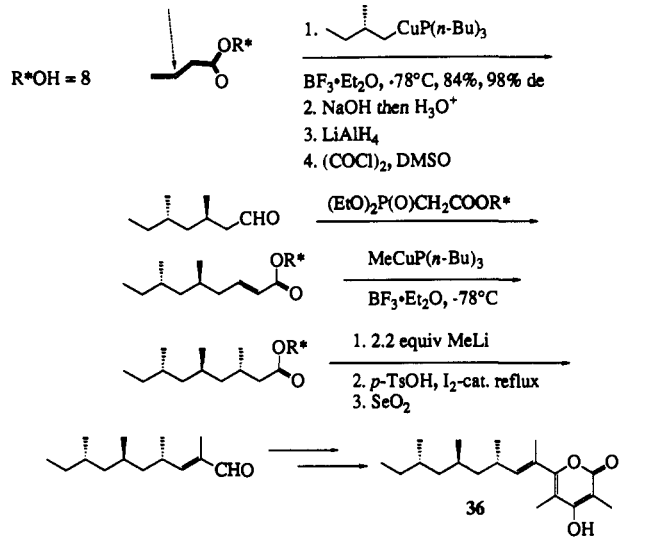
Scheme 4. Synthesis of Mycolipenic Acid via Diastereoselective Conjugate Addition to Scalemic Enoates



Scheme 5. Synthesis of Southern Corn Rootworm Pheromone via Diastereoselective Conjugate Addition to Scalemic Enoates



Scheme 6. Synthesis of Norpectinatone via Diastereoselective Conjugate Addition to Scalemic Enoates



Somfai, Tanner, and Olsson have performed similar experiments using chiral enoates derived from alcohols **9**–**13** (entries 31–37).[20] The chiral auxiliary is available in one step from camphor. In this case $(n\text{-Bu})_2CuLi$ was used as the reagent for conjugate addition. High yields and diastereoselectivites were attained with this reagent albeit in a limited number of cases. Bergdahl, Nilsson, and Olsson recently reported that TMSI/*n*-BuCu reacts with chiral ester **13** (entry 38) in high chemical yield and with high diastereoselectivity.[21]

Helmchen and Wegner also reported highly diastereoselective conjugate addition of organometallics to enoates derived from alcohols **14** and **15** (entries 39–58). Their initial report concerned the DCA of trichloromethyl magnesium chloride to the scalemic crotonate **37** derived from **14** (eq 4).[22] They were able to optimize this reaction so as to obtain 3(*S*)-(trichloromethyl)-butanoic acid (**38**) in 90% yield and 100% ee.

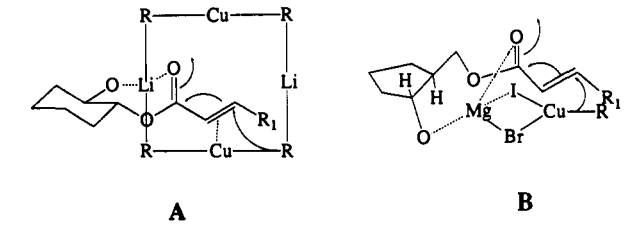
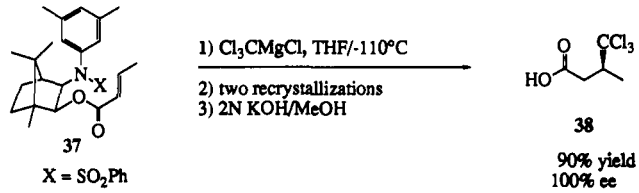
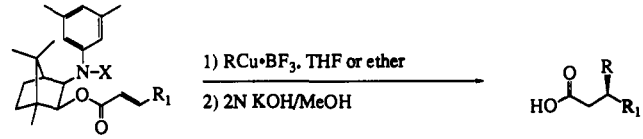


Figure 1.

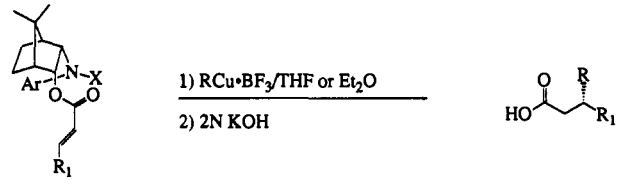


(4)

They expanded their study in order to see how well these types of esters perform in conjugate addition with nonhalogenated substituents.[23] Reaction of esters formed either from alcohol **14** or **15** and an alkyl or aryl copper reagent with BF_3 gave high diastereoselectivities in the conjugate addition. The two esters react to give products of opposite configuration allowing one access to both enantiomers of a desired product (eqs 5 and 6). Best results are obtained when the organocopper reagent formed using an alkyl lithium reagent is used in ether and when the organocopper reagent formed using a Grignard reagent is used in THF.



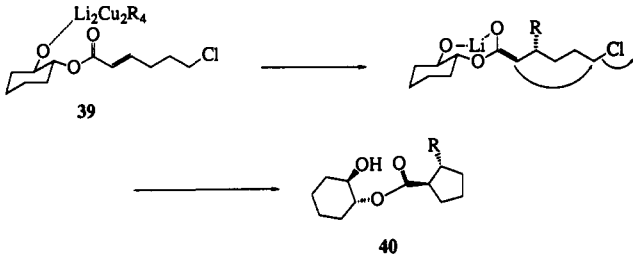
(5)



(6)

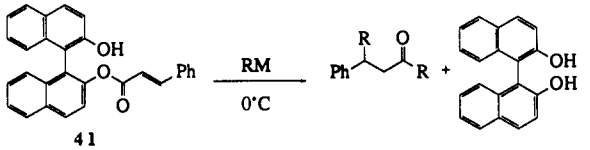
Recently, Fang, Suemune, and Sakai have reported the reaction of several organometallic reagents with chiral esters derived from α,β-unsaturated carboxylic acids and chiral diols **16**–**21** to give DCA with diastereoselectivities as high as 88% (entries 59–83).[24] The highest diastereoselectivities were attained using cuprates and chiral diol **16** or Grignards with catalytic CuI and chiral diol **18**. The absolute configurations of the products obtained for these two cases were rationalized by assuming the transition states shown in Figure 1. In both cases, an alcohol oxygen and an ester carbonyl oxygen coordinate with lithium or magnesium to produce an intermediate complex. In this complex, one face of the olefin is more readily available to the copper portion of the reagent than is the other face.

Scheme 7. Diastereoselective Conjugate Addition to Scalemic Enoates Followed by Internal Enolate Alkylation



39 40

Table 2. Diastereoselective Conjugate Addition to Scalemic Binaphthyl Esters



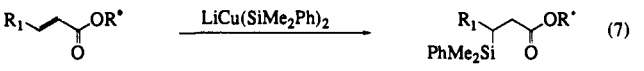
41

entry	RM[a]	solvent	% yield	% ee	R/S
1	Me_2CuLi	ether–toluene	84	87	R
2		ether	73	82	R
3		toluene	77	74	R
4		ether–THF–toluene	72	63	R
5		ether–DME	26	11	R
6		THF	21	36	S[b]
7		ether–THF	62	63	R
8	Et_2CuLi	ether–toluene	39	14	–
9	i-Pr_2CuLi		37	32	–
10	n-Bu_2CuLi		71	58	–
11	MeMgBr/ 5% CuI	ether–THF	73	48	S
12		ether–DME	31	49	S
13	EtMgBr/ 5% CuI	ether–THF	38	20	–[b]

[a] 10 equiv of reagent were used. [b] (R)-Binaphthol was used to form the ester.

By performing these reactions with substrates halogenated at the terminal carbon, such as **39**, cyclized products were obtained as a result of DCA followed by internal alkylation of the intermediate enolate to give **40** (Scheme 7).

Fleming and Kindon used chiral alcohols **5**, **7**, and **8** to form scalemic α,β-unsaturated esters which were then reacted with phenyldimethylsilyl cuprate reagents to give products with varying degrees of diastereomeric purity (eq 7).[25] They also reacted scalemic α,β-unsaturated amides and an oxazolidine to give similar products.



(7)

Fuji et al. were able to obtain enantiomerically enriched ketones of up to 87% ee by reacting the scalemic 1,1′-binaphthol monoester of cinnamic acid **41** with a large excess of lithium cuprates or with Grignard reagents and a copper(I) catalyst (Table 2).[26] In this system, conjugate addition is followed by reaction with the ester group to give the β-substituted ketone. Interestingly, the two reagents gave products of opposite configuration. They rationalize the stereoselectivity observed by assuming a lithium chelate of the binaphthol oxygen followed by addition of the cuprate (Figure 2). They also suggest that the ortho hydrogen blocks

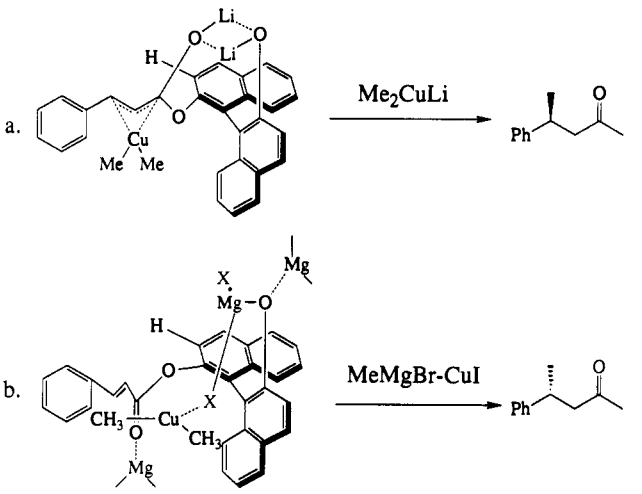
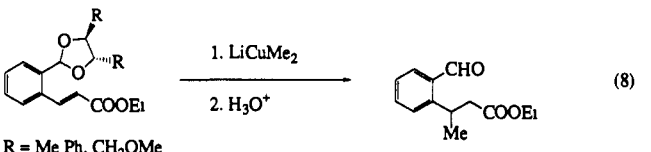


Figure 2.

the back side of the enoate system. An alternative complex is suggested to form with Grignard reagents which leads to the ketone of opposite configuration.

Another approach to DCA is to use scalemic esters in which the stereogenic elements are located in some part of the enoate other than the ester group. Alexakis et al. reported high diastereoselectivity when cinnamates bearing a scalemic oxazolidine or imidazolidine ring undergo DCA with achiral organocuprate reagents to give conjugate addition product (Table 3).[27] Their first attempts with analogous cyclic chiral acetals **42** yielded **43** with low de's (eq 8). Diastereoselectivity improves dramatically when one or two of the oxygens in the ring are replaced with nitrogen. Hydrolysis of the chiral rings yields the corresponding enantiomerically enriched aldehyde esters. Best results are obtained with a substrate containing an imidazolidine ring prepared from (R,R)-(−)-1,2-bis(methylamino)cyclohexane (entries 8–11).



(8)

R = Me Ph, CH_2OMe

42 43

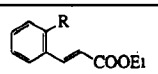
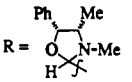
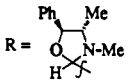
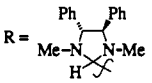
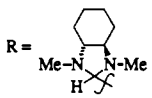
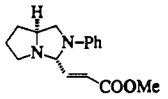
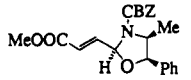
Asami and Mukaiyama have used a similar approach with scalemic vinyl aminals (Table 3, entries 12–16).[28] They suggest that complexation of the Grignard with the bridge-head nitrogen directs the reaction (Figure 3).

Scolastico and co-workers have examined the reaction of cuprates with α,β-unsaturated aldehydes, ketones, and esters in which a norephedrine derived oxazolidine is substituted at the 4-position (Table 3, entries 17–21).[29] The starting materials are formed by reacting an α,β-unsaturated aldehyde with norephedrine followed by benzyl chloroformate. A 95:5 mixture of diastereomeric oxazolidines is formed. With aldehydes and ketones, yields are improved by adding TMSCl.

B. α,β-Unsaturated Amides

Mukaiyama and Iwasawa were able to obtain β,β-disubstituted carboxylic acids in good overall yield and

Table 3. Diastereoselective Conjugate Addition of Cuprate Reagents to α,β-Unsaturated Esters Substituted with Scalemic Acetals, Aminals, and Oxazolidines

entry	substrate	cuprate	% yield	% ee	R/S	ref
1		$LiCuMe_2$	51	55	R	27
						
2		$LiCu(n\text{-}Bu)_2$	68	62	R	
3		$LiCuPh_2$	73	98	S	
4		$LiCu(CH{=}CHCH_2CH_3)_2$	73	82	S	
5		$LiCuMe_2$	43	93	S	
6		$LiCu(n\text{-}Bu)_2$	65	70	S	
7		$LiCuMe_2$	57	78	R	
8			85	94	S	
9		$LiCu(n\text{-}Bu)_2$	90	95	S	
10		$LiCuPh_2$	84	96	R	
11		$LiCu(CH{=}CHCH_2CH_3)_2$	80	90	R	
12		EtMgBr, CuI	73	93	R	28
13		n-PrMgBr, CuI	75	89	R	
14		n-BuMgBr, CuI	83	93	R	
15		$n\text{-}C_5H_{11}MgBr$, CuI	65	92	R	
16		$PhCH_2MgBr$, CuI	38	35	R	
17		$LiCuMe_2$	70	90	S	29
18		$LiCuMe_2$/TMSCl	72	90	S	
19		$LiCu(n\text{-}Bu)_2$	70	90	S	
20		$LiCu(CH{=}CH_2)_2$	75	90	R	
21		$LiCu(CH_2CH{=}CH_2)_2$	54	78	S	

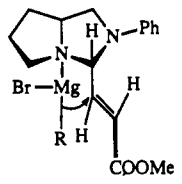
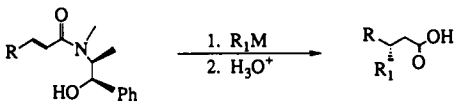


Figure 3.

high enantioselectivity by reaction of Grignard reagents with α,β-unsaturated amides derived from L-ephedrine (Table 4).[30] Initial deprotonation of the alcohol by the Grignard reagent forms an intermediate chelating magnesium complex (Figure 4). This complex is believed to help direct the approach of the subsequent Grignard to the relatively unencumbered side of the complex. Enantioselectivities as high as 99% are obtained in the final product. This method was used in the synthesis of (−)-malyngolide (**45**) from **44** (Scheme 8).[31]

Mukaiyama et al. carried out similar transformations by forming scalemic oxazepines and reacting them with Grignard reagents in the presence of nickel catalysts (Table 5).[32] Conjugate addition occurs to the sterically unencumbered face of the olefin (Figure 5). This method was used in the synthesis of indolmycin[33] (Scheme 9).

Table 4. Diastereoselective Conjugate Addition to α,β-Unsaturated Amides of Ephedrine



entry	R	R_1M	solvent	% yield	% ee	config
1	Me	n-BuMgBr	ether	53	85	S
2		PhMgBr		55	95	R
3		EtMgBr		58	98	S
4		$n\text{-}C_6H_{13}MgBr$		63	91	S
5	Ph	n-BuMgBr		63	99	S
6	Et			44	79	S
7	n-Bu	PhMgBr		54	99	R
8				61	99	R
9	Ph	EtMgBr		47	98	S
10	Et	PhMgBr		62	93	R
11	Me	n-BuMgBr	Me_2O	52	19	S
12			THF	66	22	S
13			toluene	57	48	S
14		n-BuLi	ether	58	28	S
15		n-BuMgCl		73	72	S
16		n-BuMgI		71	34	S

Several studies by Soai and co-workers have also focused on DCA of organolithium and organomagnesium reagents to scalemic α,β-unsaturated amides. One study involves DCA of Grignard reagents to scalemic α,β-unsaturated amido alcohols derived from crotonoic

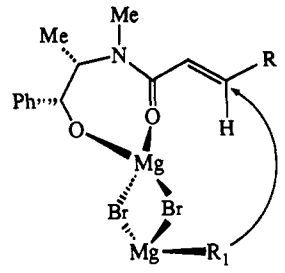


Figure 4.

Scheme 8. Enantioselective Synthesis of (−)-Malyngolide

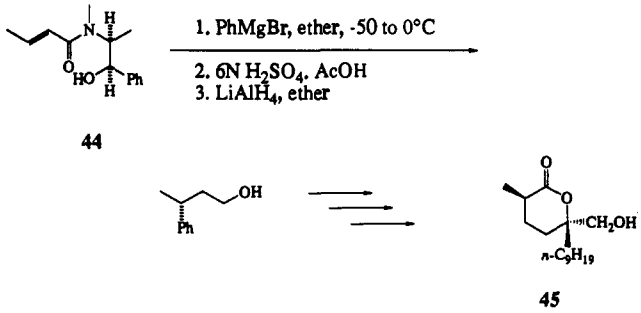
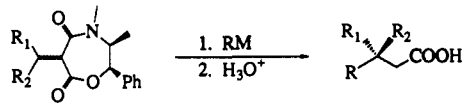


Table 5. Diastereomeric Conjugate Addition to Scalemic Alkylidene Oxazapinediones



entry	R_1	R_2	RM	% yield	% ee	R/S
1	H	Ph	*n*-BuMgBr	85	88	*R*
2			*n*-BuMgBr/$NiCl_2$	92	99	*R*
3			*n*-BuMgBr/$ZnCl_2$	76	85	*R*
4			*n*-BuMgBr/$FeCl_3$	70	60	*R*
5			$PhCH_2MgCl$	75	9	*R*
6			$PhCH_2MgCl$	78	7	*R*
7			$PhCH_2MgCl/ZnCl_2$	85	15	*R*
8			$PhCH_2MgCl/FeCl_3$	62	18	*R*
9			$PhCH_2MgCl$	68	73	*R*
10			$PhCH_2MgCl/NiCl_2$	76	75	*R*
11			$PhCH_2MgCl$/CuI	64	71	*R*
12			EtMgBr	94	99	*R*
13	Ph	H	MeMgBr	85	92	*S*
14			EtMgBr	94	>99	*S*
15			*n*-BuMgBr	92	93	*S*
16	Me		*i*-PrMgBr	55	82	*R*
17			*n*-BuMgBr	82	89	*S*
18			PhMgBr	88	89	*R*
19	Et		*n*-BuMgBr	78	62	*S*
20			PhMgBr	84	99	*R*
21	*i*-Pr		MeMgBr	73	93	*S*
22	*n*-Bu		EtMgBr	77	58	*R*
23	H	Ph	$(n\text{-Bu})_2CuLi$	76	>99	*S*
24	Ph	H		64	99	*S*
25	Me			70	90	*S*
26			Ph_2CuLi	79	66	*R*
27	Et		$(n\text{-Bu})_2CuLi$	73	56	*S*
28			Ph_2CuLi	66	65	*R*
29	*n*-Bu			66	67	*R*

and cinnamic acids and derivatives of proline (Table 6).[34,35] Conjugate addition followed by hydrolysis of the 1,4-adducts yields enantiomerically enriched 3-substituted carboxylic acids with ee's ≤100% and recovery of the chiral auxiliary. Best results were obtained using toluene as the solvent and alkyl magnesium bromides as the organometallic reagents. The addition of a tertiary amine, especially DBU, improves

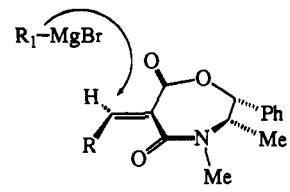


Figure 5.

Scheme 9. Enantioselective Synthesis of Indolmycin via Diastereoselective Conjugate Addition

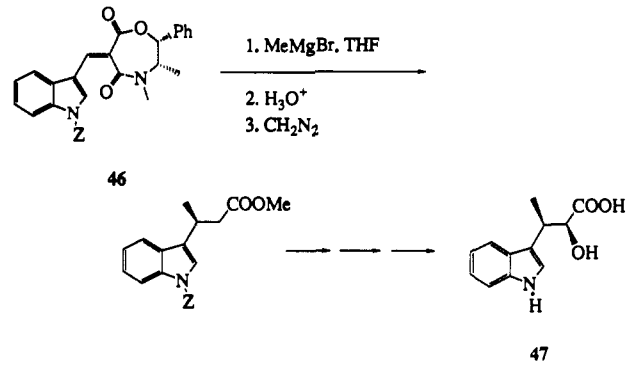
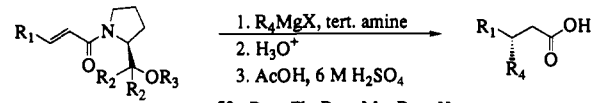


Table 6. Diastereoselective Conjugate Addition of Grignard Reagents to α,β-Unsaturated Amides Derived from (*S*)-2-(1-Hydroxy-1-methylethyl)pyrrolidine



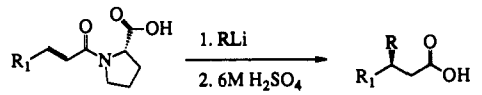
50 : R_1 = Ph, R_2 = Me, R_3 = H
51 : R_1 = Me R_2 = Me, R_3 = H
52 : R_1 = Ph, R_2 = H, R_3 = H
53 : R_1 = Ph, R_2 = H, R_3 = Me

entry	substrate	R_4	tertiary amine	solvent	% yield	% ee	ref
1	**50**	*n*-Bu	DBU	toluene	49	100	34
2					45	96	
3			Et_3N		23	75	
4		Et	DBU		51	88	
5	**53**	*n*-Bu			45	60	
6		Et			21	53	
7		Ph			47	67	
8	**50**	*n*-Bu	-	THF	33	16	35
9			-	toluene	52	37	
10			DBU		81	88	
11				THF	39	89	
12				ether	62	69	
13				THF	27	50	
14			TMEDA		30	67	
15			(−)-sparteine		25	69	
16			DBU	toluene	60	74	
17		Et			66	82	
18		Me			22	64	
19	**51**	*n*-Bu			29	84	
20	**50**			THF	21	23	
21	**52**		-	toluene	73	14	
22			DBU		23	4	
23	**53**				13	50	
24		Et			27	69	
25		*n*-hexyl			23	68	
26					33	55	
27			TMEDA		22	66	

the diastereoselectivity. Stereoselectivity virtually disappears when the hydroxyl group is converted to a methyl ether. This procedure was used to prepare (*S*)-citronellol in 63% ee.

In a similar study, Soai and Ookawa investigated the addition of organolithium reagents to *N*-cinnamoyl- and

Table 7. Conjugate Addition of Organolithium Reagents to *N*-Cinnamoyl- and *N*-Crotonoylproline



entry	R_1	reagent	additive	equiv of additive[a]	% yield	% ee	*R*/*S*
1	Ph	*n*-BuLi	-	-	24	21	*S*
2			hexamethylene-tetramine	4.5	30	3	*R*
3			Me_3N		48	48	*R*
4			Et_3N		36	49	*R*
5			TMEDA		29	51	*R*
6			(-)-sparteine		41	57	*R*
7			*N*,*N*-dimethyl-aniline		24	24	*S*
8			proton sponge		40	24	*R*
9			*t*-BuOK		35	6	*S*
10			12-crown·4		44	8	*S*
11			DBU	0.5	43	37	*R*
12				1.0	55	60	*R*
13				4.5	48	55	*R*
14				9.0	51	50	*R*
15				1.0 (B)	34	29	*S*
16				1.0 (C)	35	57	*R*
17			TMEDA	4.5 (B)	43	39	*S*
18				4.5 (C)	25	38	*S*
19			sparteine	4.5 (B)	26	16	*S*
20		MeLi	DBU	1.0 (A)	36	11	*S*
21				1.0 (B)	10	14	*R*
22	Me			1.0 (A)	60	37	*R*
23				1.0 (B)	47	10	*S*
24		PhLi		1.0 (A)	29	14	*S*
25				1.0 (B)	33	8	*R*

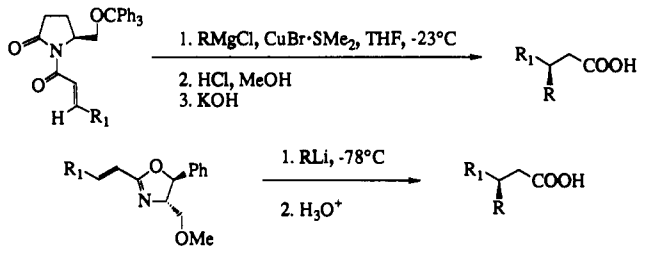
[a] Order of addition: (A) amide, additive, *n*-BuLi; (B) amide, *n*-BuLi, additive; and (C) amide, mixture of *n*-BuLi and additive.

N-crotonoylproline (Table 7).[36] They discovered again that both synthetic yields and diastereoselectivities increase with the addition of tertiary amines. They also reported that the order of addition of reagents determines the configuration of the predominant isomer. Addition of the amine to the reaction mixture containing the substrate followed by the organolithium reagent produces the *R* isomer in diastereoselectivities of ≤60% (entries 20, 22, and 24). Addition of the lithium reagent before the amine or addition of a mixture of the amine and the lithium reagent yields the *S* isomer with lower diastereoselectivities (entries 21, 23, and 25). Acidic hydrolysis subsequently yields 3-substituted carboxylic acids with enantiomeric excesses of up to 60%. Tomioka, Suenaga, and Koga reported a study in which a scalemic γ-butyrolactam is used as a chiral auxiliary to form 3-substituted carboxylic acids (Table 8).[37] Conjugate addition occurs to the α face to give the scalemic product.

C. *N*-Enoyl Sultams

Similar to their work with chiral enoates, Oppolzer et al. have reported the DCA of organocopper and Grignard reagents to *N*-enoyl sultams readily derived from (+)- and (-)-camphor-10-sulfonyl chloride (Table 9).[38,39] The primary advantages of working with sultams are that the starting material and product are conveniently purified by recrystallization, the stereochemistry of the product is readily discerned and the sultam group is easily removed under mild conditions. The first application of this methodology was the DCA of phosphine-stabilized alkenyl- and alkylcopper reagents to

Table 8. Diastereoselective Conjugate Addition to Scalemic Imides



entry	R_1	RMgCl	% yield	% ee
1	Me	*p*-Tol	85	89
2		Ph	89	94
3		cyclohexyl	88	77
4		*n*-Bu	91	92
5		Et	75	80
6		vinyl	82	88
7	*n*-Bu	Ph	77	96
8		cyclohexyl	76	97
9		Et	88	81
10		vinyl	90	85

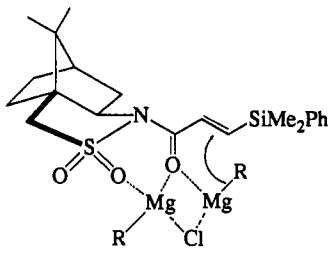


Figure 6.

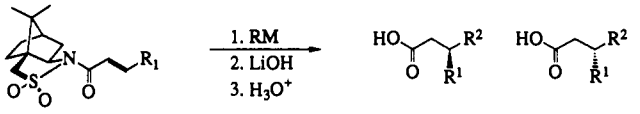
N-[α-(silyl)enoyl] sultams with up to 96% de (entries 1–10). The reaction also works well with silylcopper reagents (entry 11). Subsequent removal of the sultam group yields the enantiomerically enriched carboxylic acid. The steric course of the reaction is believed to occur by formation of the complex shown in Figure 6 followed by addition of the organic group to the face of the olefin shown. Addition of lithium cuprate reagents to these substrates also occurs readily with good diastereoselectivity.

Oppolzer et al. have also described the DCA of methyl, vinyl, and aryl organometallic reagents to (*E*)-*N*-enoyl sultams, followed by asymmetric protonation or alkylation of the enolate which gives a product with two new stereogenic centers (Table 10).[40,41] This method has been used in the synthesis of β-necrodol (**49**) from **47** (Scheme 10).[42]

D. 2-Cycloalkenones

One of the first effective protocols for the synthesis of enantiomerically enriched 3-substituted cyclic ketones was that developed by Posner and co-workers.[43] According to this method, 2-*p*-(tolylsulfinyl)-2-cycloalkenones, readily synthesized in two steps from 2-bromocycloalkenones, are treated with one of several organometallic reagents which react to give conjugate addition (Table 11). Cuprates react sluggishly. Reaction of (*S*)-2-(*p*-tolylsulfinyl)-2-cyclopentenone with R_2Mg, in the absence of other salts, gives the *S* product in high de. A reversal in selectivity was observed when $ZnBr_2$ was added to the sulfinyl ketone followed by addition of Grignard reagents. Reaction with $(i\text{-}PrO)_3TiCl$/RLi gave high de's. Improvements in de's

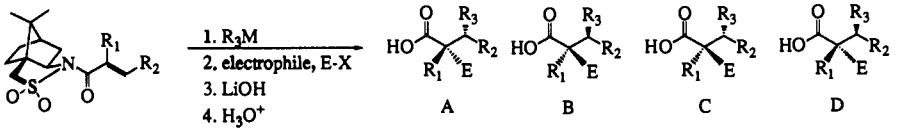
Table 9. Diastereoselective Conjugate Addition to *N*-Enoyl Sultams



entry	R_1	RM	Lewis acid	% de	% de[a]	% yield[a]	ref
1	$SiPhMe_2$	CH_2=CHCu·P(*n*-Bu)$_3$	BF_3·OEt_2	44	94	60	38
2			$EtAlCl_2$	90	96	57	
3		(*Z*)-CH_3CH=CHCu·P(*n*-Bu)$_3$		96	98	65	
4		(*E*)-CH_3CH=CHCu·P(*n*-Bu)$_3$		96	96	67	
5		MeCu·P(*n*-Bu)$_3$		86	93	61	
6		EtCu·P(*n*-Bu)$_3$		86	92	62	
7		*n*-PrCu·P(*n*-Bu)$_3$		88	96	57	
8		*i*-PrCu·P(*n*-Bu)$_3$		86	94	64	
9		*n*-BuCu·P(*n*-Bu)$_3$		92	97	61	
10		PhCu·P(*n*-Bu)$_3$		94	100	86	
11	Ph	$SiPhMe_2$Cu·P(*n*-Bu)$_3$		80	97	43	
12	Me	EtMgCl	–	89		80	39
13		*n*-PrMgCl	–	85		90	
14		*i*-PrMgCl	–	72		92	
15		*n*-BuMgCl	–	86		78	
16		*n*-C_6H_{13}MgCl	–	84		73	
17		*n*-C_8H_{17}MgCl	–	82		81	
18	Et	*n*-BuMgCl	–	89		89	

[a] After recrystallization of the product sultam.

Table 10. Diastereoselective Conjugate Addition to *N*-Enoyl Sultams and Subsequent Treatment of the Enolate with an Electrophile



entry	R_3M	R_1	R_2	E–X	A/B/C/D[a]	% yield[b]	% purity[c]	config	ref
1	*n*-BuMgCl	H	Me	Me–I	87:0:5:9	48	98	2*R*,3*R*	39
2			Et		88:0:3:9	36	98	2*R*,3*R*	
3	EtMgCl	Me	Me	H–OH	99:0:1:0	81	100	2*R*,3*R*	
4	BuMgCl			H–$NH_3^+Cl^-$	98:0:1:1	66	100	2*R*,3*R*	
5	PhMgCl				97:0:2:1	48	99	2*R*,3*S*	
6	*n*-BuMgCl		Et		97:0:3:0	78	100	2*R*,3*R*	
7	EtMgCl		Bu		97:0:1:2	60	100	2*R*,3*S*	
8	*n*-BuMgCl/CuCl		Me		0:2:86:12	67	98	2*S*,3*S*	40
9	*n*-BuMgCl/CuCN		Me		0:2:84:14	–	–	2*S*,3*S*	
10	EtMgCl/CuCl		Me		0:2:85:12	66	99	2*S*,3*S*	
11	*n*-BuMgCl/CuCl		Et		0:0:92:8	71	100	2*S*,3*S*	
12	EtMgCl/CuCl		Bu		0:0:97:3	63	99	2*S*,3*R*	
13	*n*-BuMgCl/CuCl		(*t*-Bu)Me_2SiOCH_2		0:0:97:3	56	99	2*S*,3*S*	
14	*n*-BuMgCl		(*t*-Bu)Me_2SiOCH_2			83	100	2*R*,3*R*	
15	MeMgCl/CuCl		*n*-Bu		8:11:69:13	–	–	2*S*,3*R*	
16	PhMgCl/CuCl		Me		3:3:72:22	–	–	2*S*,3*R*	
17	Me_2CuLi		Et		15:85:0:0			2*S*,3*R*	41
18					9:91:0:0			2*S*,3*R*	
19			*n*-Bu		5:89:3:4			2*S*,3*S*	
20			Ph		6:90:(4)			2*S*,3*R*	
21	Ph_2CuLi		Me		11:83:0:6			2*S*,3*S*	
22	$(CH_2$=$CH)_2CuLi$				12:86:0:1				

[a] Ratio of the diastereomeric products before purification. [b] Yield of the major diastereomer after purification. [c] Purity of the major diastereomer after purification.

were obtained by switching from the *p*-tolylsulfinyl to *p*-anisylsulfinyl ketones.[44] Posner and Frye also synthesized 3-substituted cyclohexanones (65–96% enantiomeric purity) from (*S*)-2-(*p*-tolylsulfinyl)-2-cyclohexenone and various organometallic reagents.[45]

Normally the 2-(arylsulfinyl)-2-cycloalkenones exist in a conformation in which the sulfinyl sulfur–oxygen bond dipole and the carbonyl carbon–oxygen bond dipole are anti to one another. Reaction of diorganomagnesium compounds with these substrates in the absence of metal salts and in THF results in highly stereoselective conjugate addition as shown (Figure 7). Addition of metal salts such as $ZnBr_2$ results in a reversal of the diastereoselectivity because of chelation with the sulfinyl and ketone oxygens which results in blocking the backside of the enone system. Furthermore, Posner and co-workers found that one generally obtains higher ee's if 2,5-dimethyltetrahydrofuran (DMTHF) is used as the solvent instead of THF. The diminished complexing ability of DMTHF to the metal ion allows more effective metal ion chelation by the bidentate β-keto sulfoxide, which in turn results in

Scheme 10. Enantioselective Synthesis of β-Necrodol

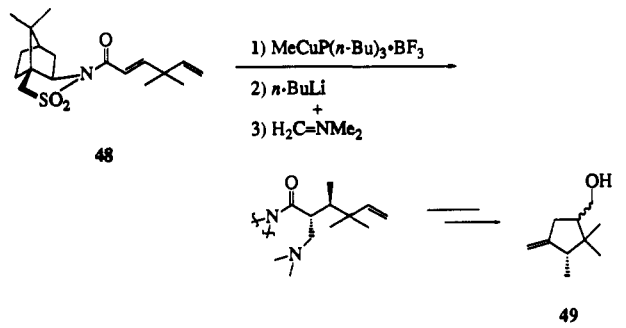
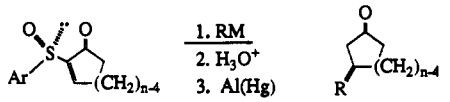
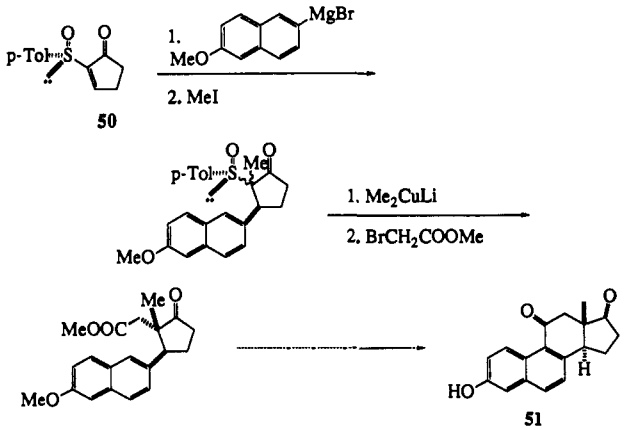


Table 11. Diastereoselective Conjugate Addition of Organometallics to (*S*)-2-(Arylsulfinyl)-2-cycloalkenones



entry	*n*	Ar	RM	solvent	% yield	% ee	*R*/*S*
1	5	*p*-Tol	Me_2Mg	THF	60	97	*S*
2			Et_2Mg		81	81	*S*
3			Ph_2Mg		72	97	*S*
4	6		Me_2Mg		50	79	*S*
5	5		MeMgCl		91	>98	*R*
6			$ZnBr_2$/EtMgCl		84	80	*R*
7			(*i*-OPr)$_3$TiEt		67	>98	*R*
8			$ZnBr_2$/*t*-BuMgCl		98	86	*R*
9			$ZnBr_2$/CH_2=CHMgBr		75	99	*R*
10			$ZnBr_2$/PhMgCl		70	92	*R*
11			6-MeONaphthMgBr		90	>98	*R*
12			$ZnBr_2$/TolMgBr			58	*R*
13		*p*-An				69	*R*
14		*p*-Tol		DMTHF	74	86	*R*
15			$ZnBr_2$/Me_3CCH_2MgCl	THF		17	*R*
16				DMTHF	81	77	*R*
17	6		$ZnBr_2$/CH_2=CHMgBr		74	65	*R*
18			(*i*-PrO)$_3$TiCl/MeLi	THF		87	*R*
19				DMTHF	83	96	*R*
20			(*i*-PrO)$_3$TiCl/PhLi	THF		43	*R*
21				DMTHF	58	93	*R*
22			(*i*-PrO)$_3$TiCl/EtMgBr	THF	65	90	*R*

Scheme 11. Synthesis of Equinelin via Diastereoselective Conjugate Addition



higher selectivities. Posner and Frye obtained the best results using RTi(O-*i*-Pr)$_3$ in DMTHF or $ZnBr_2$/RMgX in DMTHF.

Using this methodology, Posner and co-workers were able to stereoselectively synthesize several interesting chiral substrates including equilenin (**51**; Scheme 11), (−)-podorhizon (**53**; eq 9), and (+)-A factor (**54**), a potent

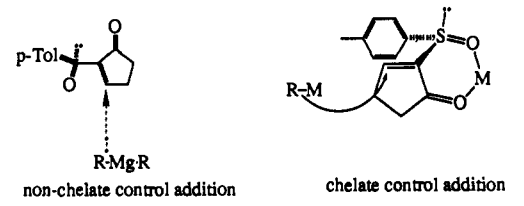
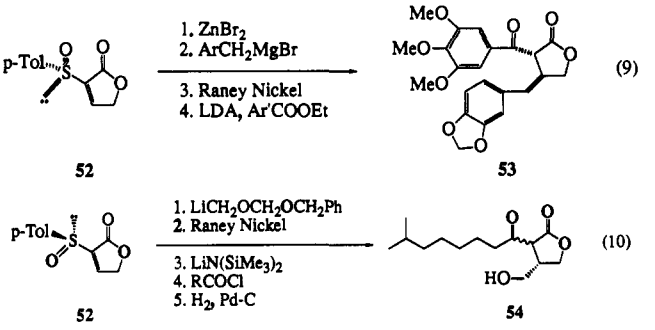
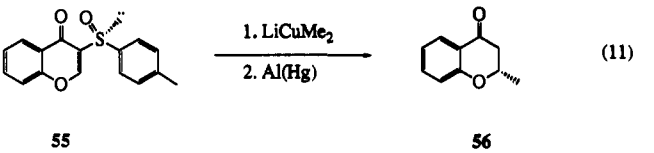


Figure 7.

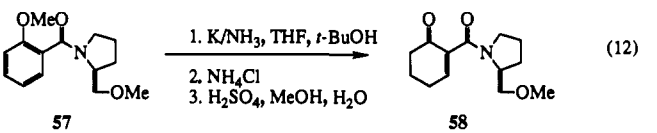
autoregulating factor essential for streptomycin production (eq 10).



Saengchantava and Wallace used this approach to synthesize enantiomerically enriched 2-substituted chroman-4-ones (eq 11).[46] DCA of lithium dimethyl cuprate to (*S*)-3-(*p*-tolylsulfinyl)chromone (**55**) gave, after chromatographic purification and removal of the sulfoxide group with aluminum amalgam, (*S*)-2-methychroman-4-one (**56**) in 88% ee.

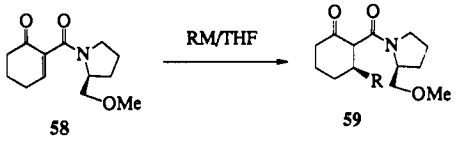


Schultz and Harrington recently reported a procedure for the synthesis of enantiomerically enriched 3-substituted cyclohexanones via DCA to scalemic 2-(aminocarbonyl)-2-cyclohexenone **58**.[47] Substrate **58** is readily obtained by Birch reduction of amide **57**, followed by acid-catalyzed hydrolysis and olefin migration (eq 12). DCA with various organometallic reagents gave products **59** with diastereoselectivities ranging from 0 to 94% (Table 12). Treatment of the product with hydroxyl amine results in removal of the chiral auxiliary to give the (*S*)-3-methyl cyclohexanone.



Smith, Dunlap, and Sulikowski reported the conjugate addition of Gilman's reagent to 5(*R*)-methoxy-2-cyclopentenone followed by hydrolysis and removal of the methoxy group with samarium iodide to give scalemic 3-methylcyclopentanone (eq 13).[48] Though not developed as a method to obtain enantiomerically enriched products, such is possible, if one has access to scalemic 5-methoxy-2-cyclopentenone. Other cuprates were found to react with this and other racemic cyclopentenones with moderate to high diastereoselectivities.

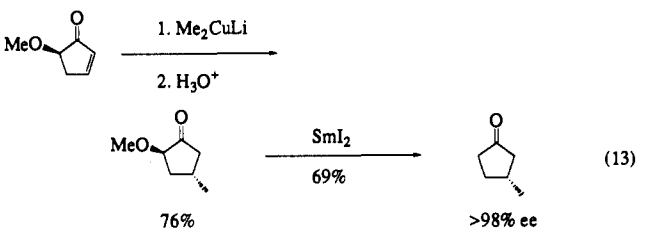
Table 12. Diastereoselective Conjugate Addition to 2-(Aminocarbonyl)-2-Cyclohexenone 55



58 59

entry	RM	RM, equiv	$ZnBr_2$, equiv	TMSCl, equiv	% yield	% de
1	MeMgCl	1.5			8	0
2		3.6	1.0	5.0	80	67
3	MeLi	4.0	1.2		89	60
4	EtMgBr	3.6	1.2		54	94
5	*n*-PrMgCl	3.6	1.2		57	94
6	CH_2=$CHCH_2MgBr$	3.6	1.2		19	95
7		1.2	*a*	5.0	36	>94
8	CH_2=CHMgBr	3.6	1.2		73	>94
9	PhMgBr	1.5	0		37	0
10		2.0	*b*	5.0	99	67
11		3.6	1.2		49	94

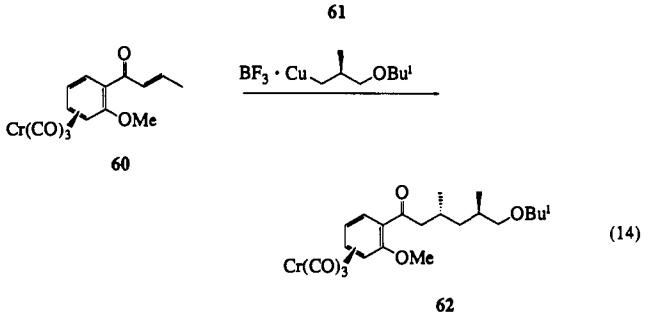
[a] 10% $CuBr_2$. [b] 1.0 equiv CuBr.



(13)

Jung and Lew recently reported DCA of several cuprate reagents to scalemic enone ketals with low to moderate diastereoselectivity (Table 13).[49]

Vemura and co-workers have explored the conjugate addition of organocopper reagents with scalemic (*o*-methoxyphenyl 1-propenyl ketone)chromium complex.[50] Reaction of the (*R*)-chromium complex **60** with ((*S*)-2-methyl-3-*tert*-butoxypropyl)copper–boron trifluoride (**61**) gives exclusively conjugate addition with 99:1 selectivity, yielding **62** (eq 14). Reaction of the same organocopper reagent with the *S* enantiomer of the chromium complex gives the product in a ratio of 66:34. Thus, the first reaction represents a matched case and the latter a mismatched case in this reaction manifesting double diastereoselectivity. This protocol is somewhat limited because of the need to resolve the chromium complex.

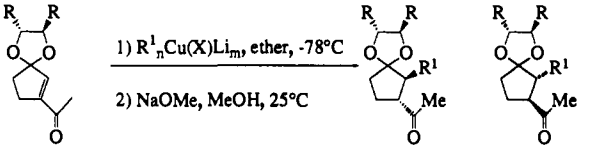


(14)

E. Vinyl Acetals, Oxazolidines, and Imidazolidines

Another approach to stereoselective conjugate addition is to react an organometallic reagent with α,β-unsaturated aldehydes masked as acetals, oxazolidines, or imidazolidines derived from scalemic diols, amino alcohols, or diamines, respectively. Alexakis et al. reported the DCA of achiral organocopper reagents to chiral α,β-unsaturated acetals (Table 14, entries 1–15).[51] They first prepared a cyclic chiral acetal from the aldehyde and a chiral diol usually having a C_2 axis of symmetry. Aryl-, alkenyl-, or vinylcopper with $BF_3 \cdot Et_2O$ react with the vinylic acetals in an anti S_N2' reaction that results in diastereoselective cleavage of the chiral acetal ring. The resulting enol ethers were easily hydrolyzed to enantiomerically enriched β-substituted aldehydes with recovery of the chiral diol. They obtained the highest diastereoselectivity (95%) with PhCu, BF_3, and P(*n*-Bu)$_3$ as a copper(I) ligand. Conjugate addition to chiral ketals was also performed with some success (Table 15). This methodology was used to synthesize the California red scale pheromone **29** (Scheme 12).

Table 13. Diastereoselective Conjugate Addition to Scalemic Ketal Enones



reagent	% de R = Me	R = Ph	R = CH_2OBn	R = $MeOC(Me)_2$
Me_2CuLi	28	22	4	24
$Me_2Cu(CN)Li_2$	26	2	20	22
(*n*-Bu)$_3$PMeCuLi			20	12
(Th)MeCu(CN)Li_2			24	
$PhCH_2(CN)ZnBr$	25			

Yamamoto and co-workers have reported DCA of Me_3Al to vinyl acetals derived from α,β-unsaturated aldehydes and ketones and *N*,*N*,*N*^{1},*N*^{1}-tetramethyltartramide with excellent diastereoselectivity (Table 14, entries 17–21).[52] This method was used to synthesize the side chain of vitamin E (entry 21).

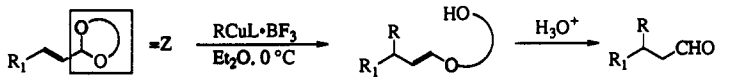
Reaction of Grignard reagents and a Cu(I) catalyst with scalemic propargylic acetals gave allenes with up to 85% de (Table 16).

Berlan et al. have reported DCA of organocuprate reagents to α,β-unsaturated oxazolidines with de's of up to 85% (Table 17).[53] The enantioselectivity of this reaction is highly dependent on solvent and salts present in solution. A number of mechanistic studies have been carried out which suggest the reaction occurs by 1,2-addition to the double bond rather than by S_N2' addition.[54] Formation of more than one diastereomer of the oxazolidine from ephedrine and various α,β-unsaturated aldehydes can often be problematic leading to difficulties in implementing this method.[55]

F. Vinyl and Aryl Oxazolines

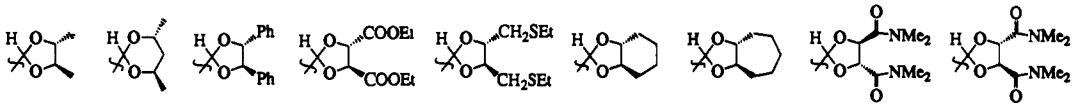
Another highly effective means of DCA, reported by Meyers, Whitten, and Smith,[56] involves the addition of organolithiums to vinyl oxazolines giving, after hydrolysis, β,β-disubstituted propionic acids (Table 18). Either enantiomer of the product can be obtained by switching R and R_1. The reaction is believed to involve, first, complexation of the organolithium reagent to the nitrogen and methoxy group of the oxazoline, followed

Table 14. Diastereoselective Conjugate Addition of Organometallic Reagents to Scalemic α,β-Unsaturated Acetals



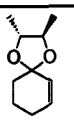
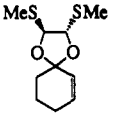
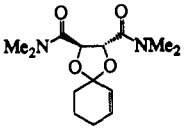
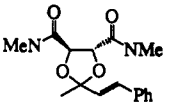
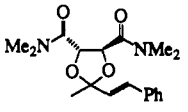
entry	R_1	Z[a]	reagent	% yield	% ee	R/S	ref
1	Me	**63**	$PhCuSMe_2$	70	76	*S*	51
2			$PhCuP(n\text{-}Bu)_3$	75	95	*S*	
3	(*Z*)-Me		PhCu	75	69	*R*	
4	*n*-Pr		$PhCuPBu_3$	71	91	*S*	
5	Me	**64**	$PhCuSMe_2$	70	77	*S*	
6		**65**		50	76	*S*	
7		*ent*-**66**		67	35	*R*	
8		*ent*-**67**		70	29	*R*	
9		**68**	$(Me_2C{=}CH)_2CuLi$	69	24	ND	
10			$(Me_2C{=}CH)Cu{\cdot}SMe_2$	72	67	ND	
11				70	85	ND	
12			$[CH_2{=}C(n\text{-}C_5H_{11})]_2CuLi$	75	50	ND	
13			$[CH_2{=}C(n\text{-}C_5H_{11})]_2CuLi{\cdot}SMe_2$	71	60	ND	
14			$CH_2{=}C(n\text{-}C_5H_{11})CuP(n\text{-}Bu)_3$	69	85	ND	
15			$(Z)\text{-}(n\text{-}C_6H_{13})HC{=}CHCuSMe_2$	70	73	ND	
16			$(Z)\text{-}(n\text{-}C_6H_{13})HC{=}CHCuP(n\text{-}Bu)_3$	68	85	ND	
17	*n*-Pr	**69**	Me_3Al	NG	96	*S*	52
18	Me		$(n\text{-}Pr)_3Al$	51	93	*R*	
19	Ph		Me_3Al	77	98	*R*	
20	4-methyl-3-pentenyl	**70**		61	96	*R*	
21	(*R*)-4,8-dimethylnonyl			55	96	*R*	

[a] Z =

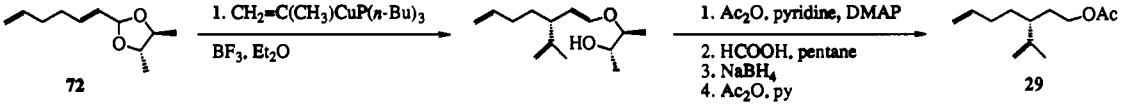


63 **64** **65** **66** **67** **68** **69** **70** **71**

Table 15. Diastereoselective Conjugate Addition of Organometallic Reagents to Scalemic Ketals

entry	substrate	reagent	% yield	% ee	R/S	ref
1		$LiCuMe_2$, $BF_3{\cdot}OEt_2$	71	26	*S*	51
2				48	*R*	
3		$AlMe_3$/toluene	97	77	*R*	52
4			84	72	*S*	
5			74	70	*S*	
6			84	54	*R*	

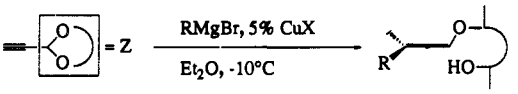
Scheme 12. Synthesis of California Red Scale Pheromone via Diastereoselective Conjugate Addition to Scalemic Vinyl Acetals



72 **29**

50% yield
85% ee

Table 16. Copper-Catalyzed Diastereoselective Conjugate Addition of Grignard Reagents to Scalemic Propargylic Acetals



entry	Z[a]	R	CuX	% de
1	**63**	Me	CuBr	56
2		*n*-Bu		70
3		*t*-Bu		100
4		Ph		45
5	**64**	Me		28
6	**65**			59
7	**66**		$CuBr{\cdot}2P(OEt)_3$	78
8	**67**		CuBr	30
9	**68**			74
10	**69**			66
11			$CuBr{\cdot}2P(OEt)_3$	85

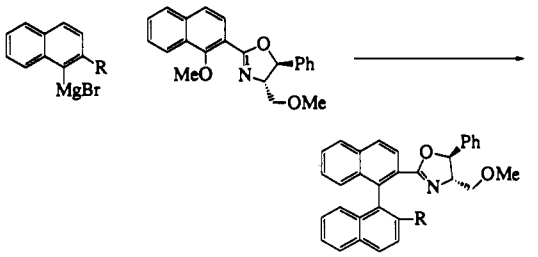
[a] See Table 14 for structures.

by nucleophilic addition of the R_1 group to the top face of the olefin (Figure 8). The phenyl group on the oxazoline apparently has little or no effect on the stereochemical outcome of the reaction.[57] Stabilized carbanions add in a conjugate fashion but with little or no diastereoselectivity. Methyl lithium is also nonstereoselective in its addition to vinyl oxazolines. More recently, vinyl oxazolines, in which the oxazoline is derived from *tert*-leucinol, have been used in this reaction and have been found to be highly effective giving products in greater than 94% ee.[58] In addition, mild procedures have been developed for removal of the oxazoline group facilitating recovery of the desired product.

This method has been used in the synthesis of *ar*-tumerone (**76**; Scheme 13)[59] and in carbomycins **78** and **79** (Scheme 14).[60]

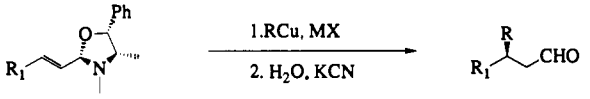
Treatment of the intermediate azaenolate with MeI results in α-alkylation with high diastereomeric excess and produces α,β,β-trisubstituted propionic acids (Scheme 15).

An interesting variation of this reaction was developed for the synthesis of scalemic biaryls (Table 19). Reaction of naphthyl Grignards with scalemic (1-methoxy-2-naphthyl)oxazolines results in displacement of the methoxy group and formation of the binaphthyl (eq 15).[61]



(15)

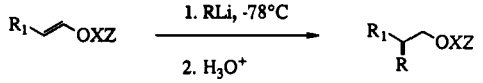
Table 17. Diastereoselective Conjugate Addition of Cuprate Reagents to Scalemic α,β-Unsaturated Oxazolidines[a]



entry	R_1	R	M	solvent	salt	*R*/*S*	% ee
1	Ph	Me	Li	ether	-	*S*	40
2				hexane		*R*	80
3		C_2H_5		ether		*S*	15
4				hexane		*R*	10
5		C_4H_9		ether		*S*	20
6				ether, hexane, THF		*S*	12
7				ether	LiBr	*S*	59
8		*t*-C_4H_9		ether, hexane	-	*R*	48
9		$CH{=}CH_2$		ether		*R*	25
10				ether, hexane, THF		*R*	35
11	*o*-ClPh	Me		ether		*R*	39
12				hexane		*R*	81
13	*o*-MeOPh			ether		*S*	7
14				hexane		*R*	70
15	1-naphthyl			ether		*S*	35
16				hexane		*R*	55
17	Me	C_2H_5		ether		*R*	5
18					LiBr	*S*	54
19		C_3H_7			-	*R*	7
20					LiBr	*S*	40
21			MgBr		-	*S*	13
22		*n*-C_4H_9	Li			*R*	12
23					LiBr	*S*	70
24			MgBr		-	*S*	25
25		*i*-C_3H_7				*S*	12
26		*t*-C_4H_9	Li			*S*	16
27					LiO*t*-C_4H_9	*R*	45
28		*c*-C_6H_{11}			-	*S*	6
29					LiBr	*R*	34
30	C_3H_7	Me			-	*S*	14
31				hexane		*S*	40
32				ether	LiBr	*R*	51
33			MgBr		-	*R*	29
34		*c*-C_6H_{11}	Li			*S*	24
35		*t*-C_4H_9			LiBr	*R*	66

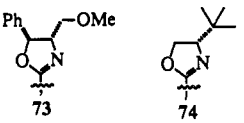
[a] The yields were in most cases ≈ 80%; the reactions were run at -40 °C.

Table 18. Diastereoselective Conjugate Addition of Organolithiums to Scalemic Vinyl Oxazolines



entry	R_1	OXZ[a]	RLi	% yield	% ee	R/S	ref
1	Me	73	Et	40	92	R	56
2			*n*-Bu	38	91	R	
3			*n*-hexyl	44	99	R	
4			Ph	44	98	S	
5	Et		*n*-Bu	55	96	R	
6			Ph	39	92	S	
7	*i*-Pr		*n*-Bu	53	99	R	
8	*t*-Bu			50	98	R	
9	cyclohexyl		Et	73	99	R	
10			*n*-Bu	79	99	R	
11	$MeOCH_2CH_2$		Et	54	95	S	
12			*n*-Pr	50	99	S	
13			*n*-Bu	66	95	S	
14			Ph	60	95	S	
15	Ph		Et	66	97	R	
16			*n*-Bu	67	99	R	
17	*o*-MeOPh		Et	83	95	R	
18			*n*-Bu	75	95	R	
19			Ph	87	95	R	
20	*n*-Bu	74		53	97	S	58
21	cyclohexyl			60	96	R	
22	Ph		*n*-Bu	53	96	R	
23			*t*-Bu	74	94	S	
24	*o*-MeOPh		*n*-Bu	61	96	R	

[a] OXZ as follows:



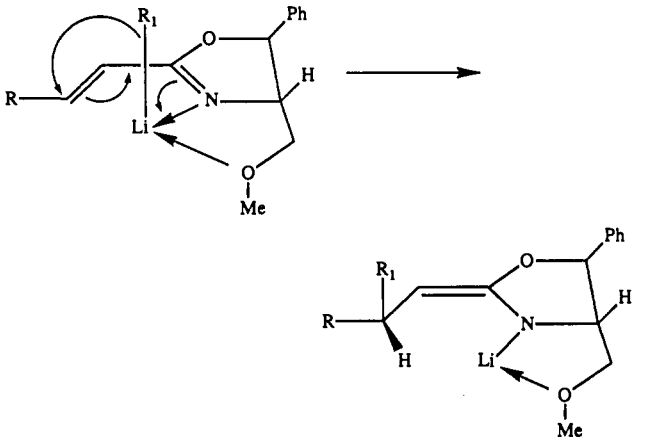
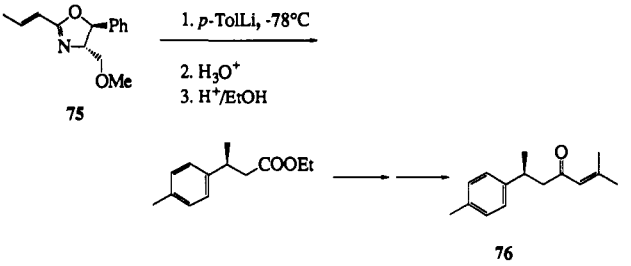


Figure 8.

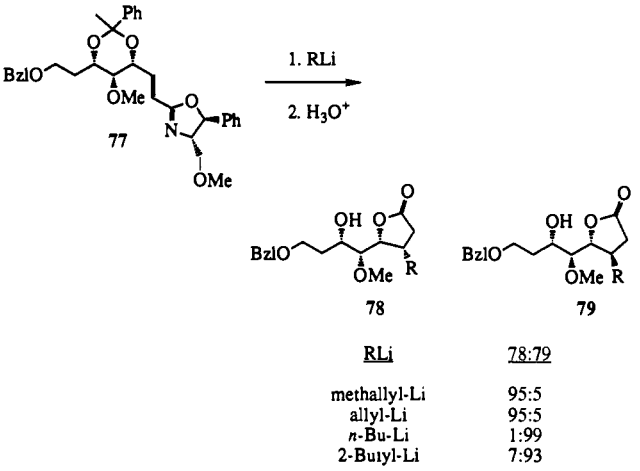
High diastereoselectivity is achieved as a result of the formation of a stereochemically preferred complex between the naphthyl Grignard and the naphthyloxazoline before coupling. In cases where the naphthyl Grignard has an alkyl group at the 2 position, attack in which the naphthyl ring points away from the complex is preferred. Where the 2 position has an alkoxy group, chelation of that group with the magnesium ion of the Grignard results in the formation of a complex which leads to the opposite diastereomer (Figure 9).

This same reaction can be accomplished using 2-(1-alkoxy)naphthyl oxazoline in which the alkoxy group is chiral (Table 20).[62]

Scheme 13. Synthesis of *ar*-Tumerone via Diastereoselective Conjugate Addition

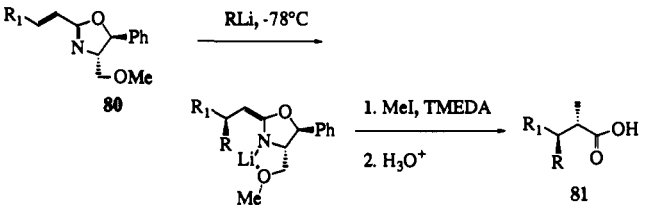


Scheme 14. Synthesis of Carbomycins via Diastereoselective Conjugate Addition



RLi	78:79
methallyl-Li	95:5
allyl-Li	95:5
n-Bu-Li	1:99
2-Butyl-Li	7:93

Scheme 15. Diastereoselective Conjugate Addition of Organolithium Reagents to Scalemic Vinyl Oxazoles Followed by Oxazaenolate Alkylation

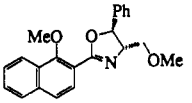
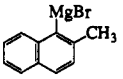
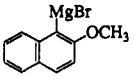
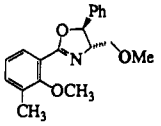
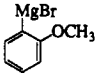
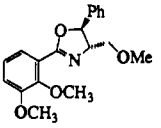
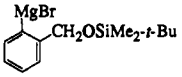
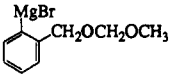
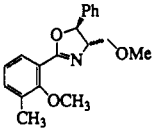
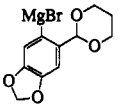
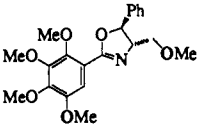
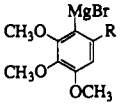
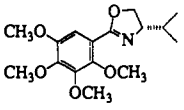
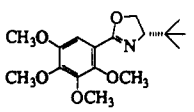


Asymmetric coupling of aromatic Grignard reagents with scalemic aryl oxazolines has also been used to synthesize scalemic biphenyl compounds. In their initial paper on the synthesis of scalemic biphenyls, Meyers and Himmelsbach reported the reaction of various 2-substituted Grignard reagents with 2-(methoxyphenyl)oxazolines in THF resulting in the formation of biphenyl compounds with up to 92% diastereoselectivity (Table 19).[63] Use of aryllithium instead of Grignard reagents results in nonstereoselective coupling. The oxazoline group must be removed under conditions mild enough to avoid racemization of the biphenyl.

This coupling reaction was used strategically to form the scalemic biphenyl portion of steganone (84, Scheme 16).[64] Tetramethoxyphenyl oxazoline 83, formed in five steps from 3,4,5-trimethoxybenzoic acid, reacts first with the Grignard to give 65% and 9% of the two diastereomeric biphenyls. Removal of the acetal and then the oxazoline rings was done under highly controlled conditions in order to avoid racemization.

A similar approach was used to synthesize (−)-schizandrin (86) and (−)-isoschizandrin (87; Scheme 17).[65]

Table 19. Diastereoselective Conjugate Addition of Aryl Grignard Reagents with Scalemic Methoxyaryl Oxazolines

entry	Grignard	oxazoline	% yield	% de	*R*/*S*	ref
1			56	90	*R*	61
2			43	87	*S*	
3			65	96	*R*	
4			59	36		63
5			72	92		
6			75	60		
7			85	0		
8			85	58		
9			95	68		
10			74	76		64
11			53	47	*S*	
	R = 2-(1,3-dioxanyl)					
12	R = 2-(1,3-dithianyl)		60	100		
13	R = CH_2OCH_3		40	47	*S*	
14	R = CH_2OTBS		68	72	*S*	65
15	R = CH_3		52	73	*S*	
16	R = CH_2OH		26	68	*R*	
17	R = CH_2OCH_3		56	56	*S*	66
18	R = CH_3		80	80	*S*	
19	R = CH_2OSiMe-*t*-Bu		90	96	*S*	
20	R = CH_2OH		16	90	*R*	
21	R = CH_2OCH_3		9	50	*S*	
22	R = CH_3		75	82	*S*	
23	R = CH_2OSiMe_2-*t*-Bu		60	0.96	*S*	

Meyers, Meier, and Rawson recently reported that oxazolines formed from valinol and *tert*-leucinol also react with high diastereoselectivities in this reaction.[66]

Meyers and co-workers also developed similar reactions involving the diastereoselective addition of organolithium and Grignard reagents to scalemic 3-

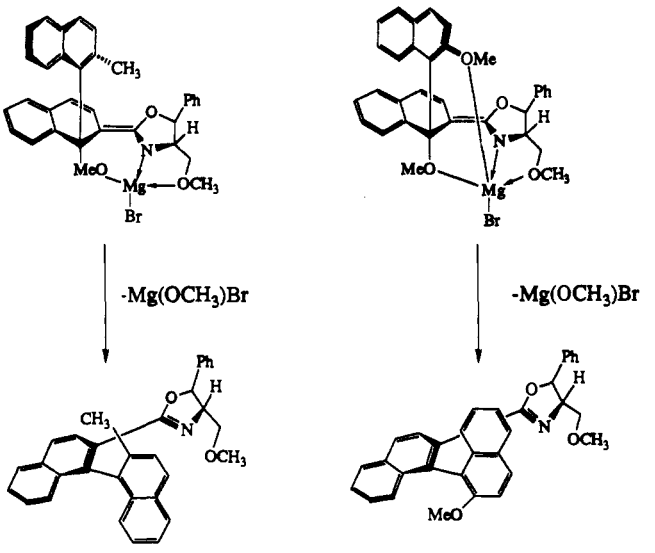
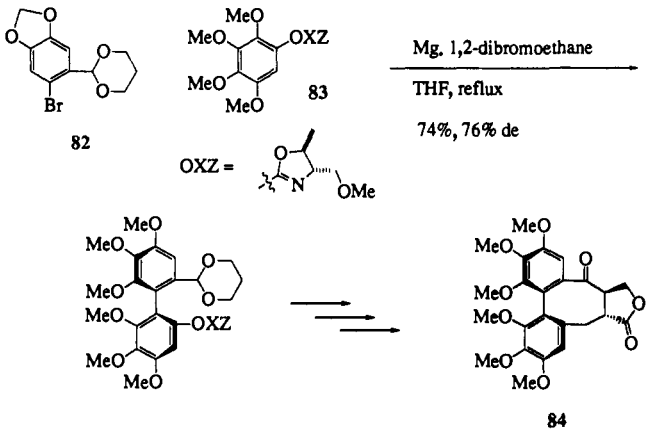


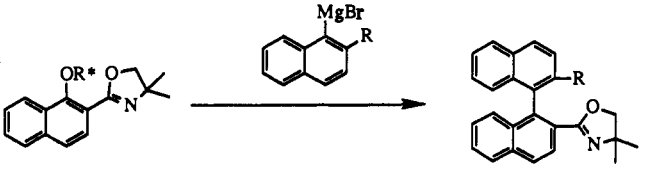
Figure 9.

Scheme 16. Enantioselective Synthesis of (-)-Steganone

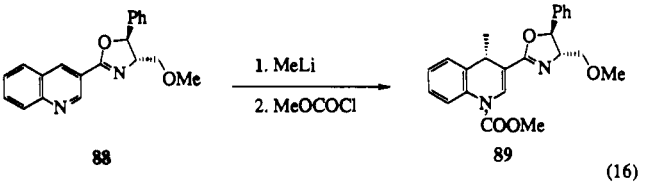


pyridyloxazolines (Table 21, entries 1–6).[67] They found that addition of organolithium or organomagnesium reagents to chiral 3-pyridyloxazoline followed by quenching with methyl chloroformate gives 4-substituted 1,4-dihydro pyridine derivatives with high diastereoselectivity. Similar results are obtained in the reaction of MeLi with a scalemic 3-quinolyloxazoline **88** to give **89** (eq 16). A similar protocol was used by Mangeney and coworkers (Table 21, entries 7–18).[68] A scalemic aminal, readily obtained from 3-pyridine-3-carboxaldehyde, was used rather than an oxazoline. Cuprate reagents in THF are used to add the allyl substituent to the pyridine ring. The reaction is performed in the presence of an acyl chloride trapping reagent. Diastereoselectivities as high as 95% are obtained. 1,6-Addition product is obtained when cuprate reagents are used in ether or when a Grignard reagent is used in THF. This method has been used in the synthesis of indoloquinolizidines **92** (Scheme 18).[69]

Table 20. Diastereoselective Coupling of Scalemic 1-Alkoxy-2-naphthoxazolines with Naphthyl Grignards



entry	R	OR*	% yield	% ee	*R/S*
1	H	*l*-menthoxy	80	67	*S*
2		quininoxy	12	80	*S*
3		quinidyl	15	81	*R*
4		α-fenchyl	78	45	*S*
5		boronoxy	83	10	*R*
6	OCH_3	*l*-menthoxy	53	78	*S*
7		quininoxy	7	94	*R*
8		quinidinoxy	27	84	*S*
9		α-fenchoxy	65	48	*S*



(16)

Scheme 17. Enantioselective Synthesis of (-)-Schizandrin and Isoschizandrin

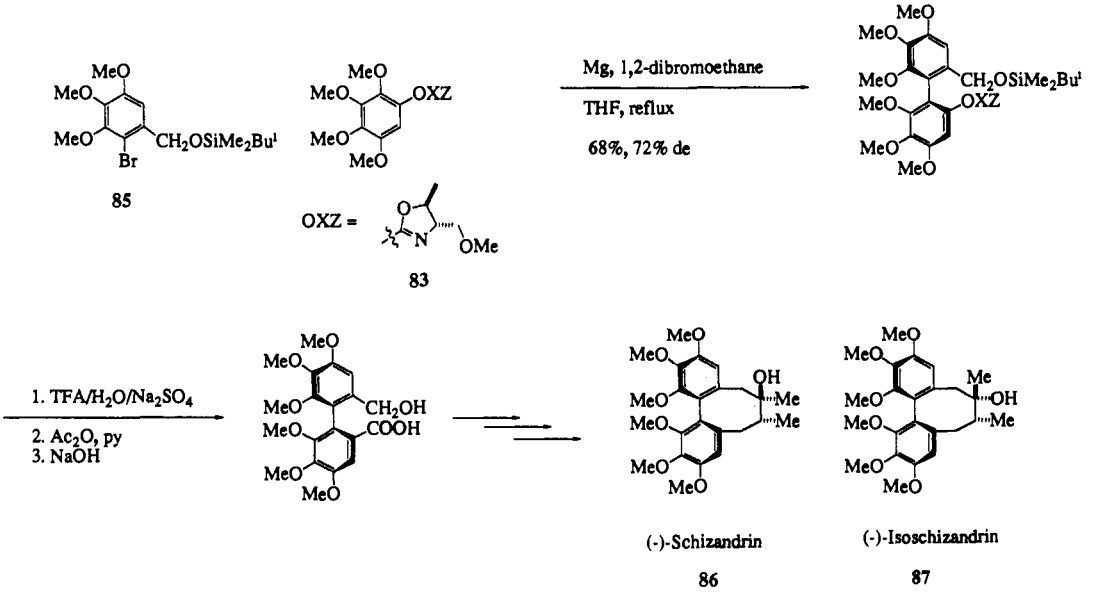
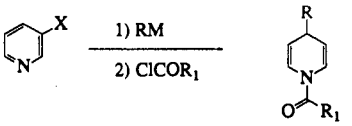
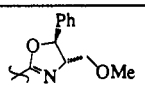
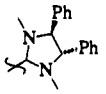
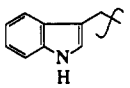
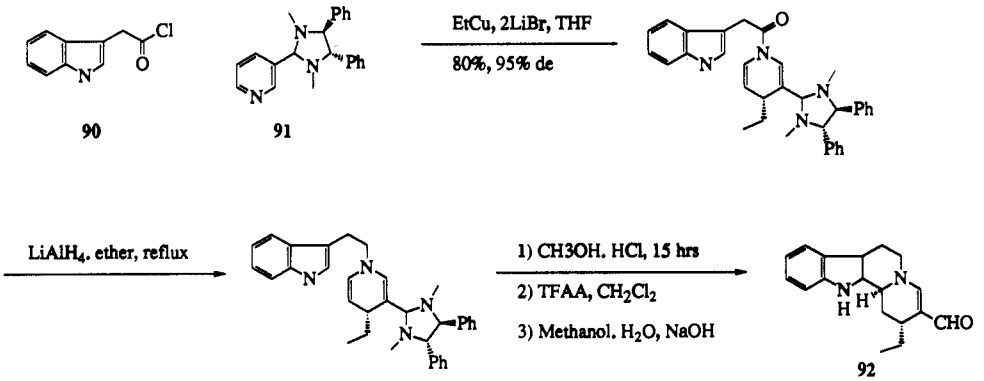


Table 21. Diastereoselective Conjugate Addition to Scalemic 3-Pyridyl Oxazolines and Imidizolidines



entry	X	RM	R_1	solvent	% yield	% de	*R*/*S*	ref
1		MeLi	OMe	THF	79	88	*S*	67
2		MeMgCl			88	82	*S*	
3		*n*-BuLi			92	86	*S*	
4		*n*-BuMgCl			98	90	*S*	
5		EtMgBr			63	84	*S*	
6		PhLi			94	84	*S*	
7		MeLi	CH_3	ether	–	–	–	68
8		MeMgBr		THF	10	93	*R*	
9		Me_2CuLi		ether	56	95	*R*	
10				THF	90	41	*R*	
11		$Me_2CuMgBr$			90	95	*R*	
12		Et_2CuLi		ether	64	32	*R*	
13		$Et_2CuMgBr$		THF	90	82	*R*	
14		Et_2CuLi			90	85	*R*	
15		*n*-Bu_2CuLi			40	95	*R*	
16		$(CH_2{=}CH)_2CuLi$			90	95	*R*	
17		$Ph_2CuMgBr$			90	95	*R*	
18		EtCu, 2LiBr			80	95	*R*	69

Scheme 18. Enantioselective Synthesis of Indoloquinolizidines



Scheme 19. Diastereoselective Conjugate Addition of Organolithiums to Scalemic Naphthyl Oxazolines

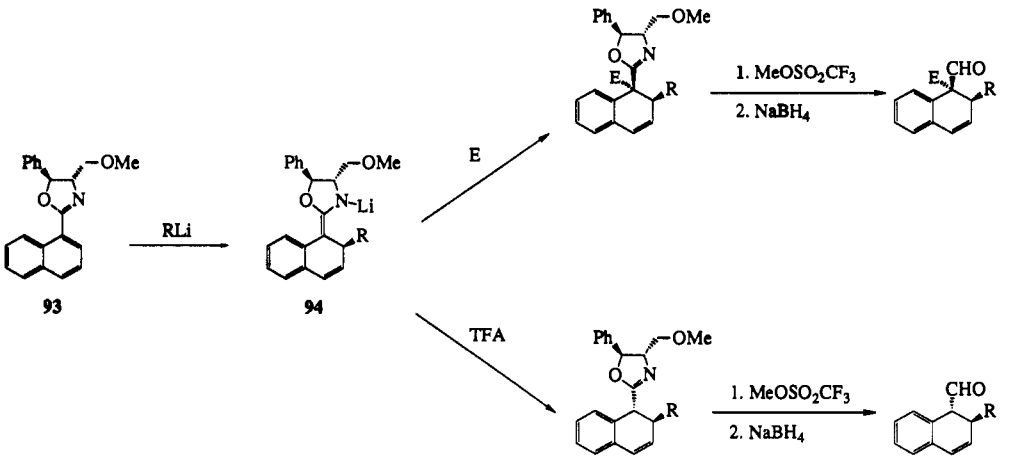
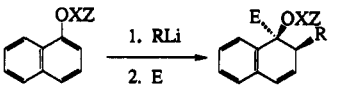
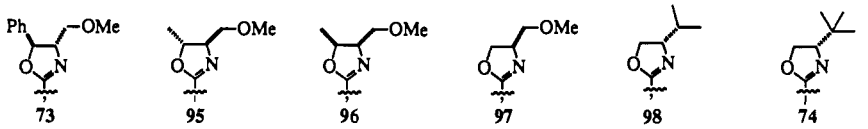


Table 22. Diastereoselective Conjugate Addition to Scalemic Naphthyl Oxazolines



entry	naphthalene	OXZ	RLi	E	% yield	% de	ref
1	1-naphthyl	**73**	*n*-BuLi	MeI	97	88	70
2				$(PhS)_2$	91	88	
3				$ClCO_2Me$	99	94	
4			MeLi	$(PhS)_2$	56	72	
5			*t*-BuLi	MeI	98	48	
6			PhLi		99	66	
7			$(H_2C{=}CMeCH_2)Li$		75	76	
8			$(H_2C{=}CH)Li$		79	80	
9			(c-1-C_5H_7)Li		73	78	
10			$(Me_3Si)Li$		70	20	
11			EtLi		92	88	
12	1-(5-methoxynaphthyl)		$(H_2C{=}CH)Li$		80	60	
13			$[H_2C{=}CH(CH_2)_3]Li$		80	90	
14			*n*-BuLi		95	94	
15	1-(6-methoxynaphthyl)		(c-1-C_5H_7)Li		50	70	
16	1-(4-methoxynaphthyl)		*n*-BuLi		95	94	
17			*t*-BuLi		95	30	
18			$[H_2C{=}CH(CH_2)_3]Li$		90	94	
19			$[H_2C{=}CMe(CH_2)_3]Li$		90	94	
20	2-naphthyl		PhLi		89	80	
21			*n*-BuLi		85	96	
22		**95**	PhLi		90	82	
23			*n*-BuLi		87	88	
24		**96**	PhLi		93	50	
25		**97**			90	82	
26			*n*-BuLi		96	86	
27	1-naphthyl	**73**			100	88	
28		**97**			93	84	
29		**73**	PhLi		100	72	
30		**96**			94	40	
31		**98**	*n*-BuLi		97	94	71
32			$(H_2C{=}CH)Li$		89	88	
33			PhLi		87	74	
34		**74**	*n*-BuLi		99	98	
35			$(H_2C{=}CH)Li$		94	98	
36			PhLi		81	90	

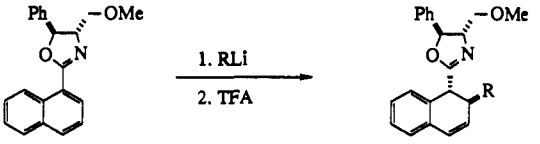
[a] OXZ as follows:



In a further extension of this work, Meyers and coworkers have developed an interesting set of protocols for DCA to scalemic naphthyloxazolines (Scheme 19).[70] Reaction of organolithium reagents with scalemic naphthyloxazolines **93** results in addition to the naphthyl ring with high diastereoselectivity to give **94**. The intermediate thus formed can be treated with an electrophile to give α substitution or with trifluoroacetic acid to protonate the aza enolate. Treatment with an electrophile gives exclusively a substitution pattern in which the R group and the oxazoline group are cis to one another (Table 22). In contrast, treatment with trifluoroacetic acid gives a product in which the R group and the oxazoline are trans to one another (Table 23). The diastereoselectivity is controlled similar to that shown above for vinyl oxazolines.

Rawson and Meyers recently reported that excellent levels of diastereoselectivity can be achieved in similar systems using valinol or *tert*-leucinol to form the oxazolines (Table 22, entries 31–36).[71] The *tert*-leucinol system in particular gives the best results seen thus far and is viewed by the authors as the system of choice.

Table 23. Diastereoselective Conjugate Addition to Scalemic Naphthyl Oxazolines

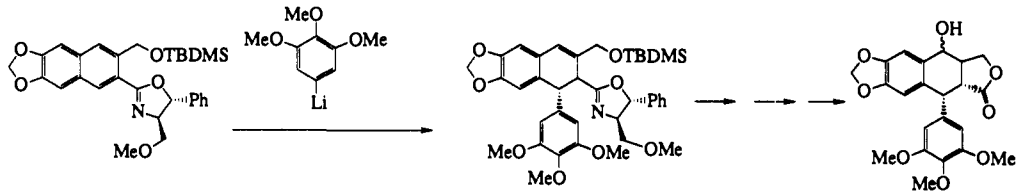


entry	naphthalene	RLi	E	% yield	% de
1	1-naphthyl	*n*-BuLi	TFA	73	88
2		PhLi		62	70
3		MeLi		42	70
4	1-(5-methoxynaphthyl)	EtLi		85	94
5		*i*-PrLi		73	92

Unfortunately, the amino alcohol currently is expensive. Valinol, however, is readily available either commercially or by synthesis.

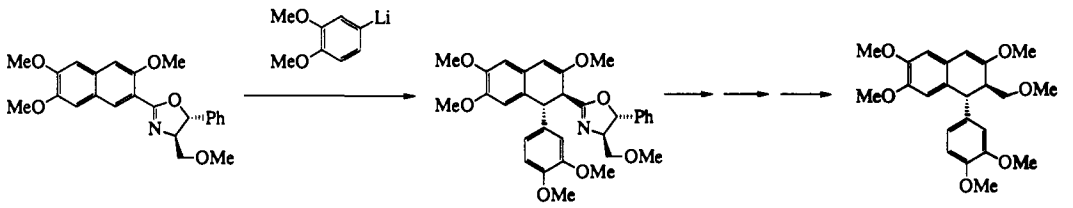
This method has been used in the synthesis of a number of natural products including (−)-podophyllotoxin (**106**; Scheme 20),[72] (+)-phyltetralin (**102**; Scheme 21),[70a] the A–B ring of alkavinone (**104**; Scheme 22),[73] and analogues to the bottom half of chlorothricolide

Scheme 20. Synthesis of Podophyllotoxin



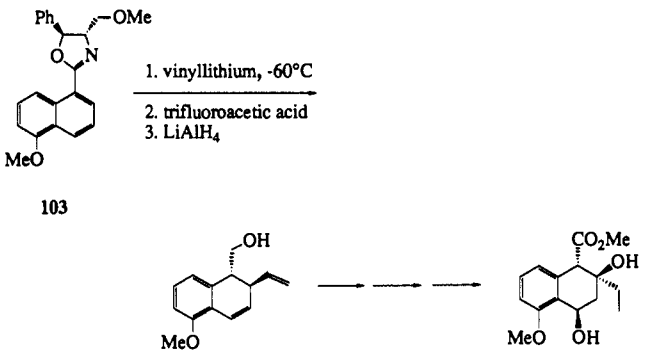
99 100

Scheme 21. Synthesis of (+)-Phyltetralin



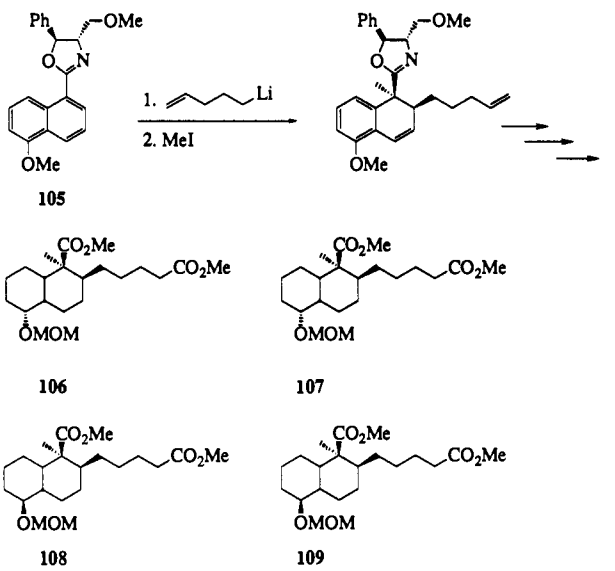
101 102

Scheme 22. Synthesis of the A-B Ring of Aklavinone



103 104

Scheme 23. Synthesis of Analogues of Chlorothricolide



105 106 107 108 109

106–109 (Scheme 23)[74] and tetracyclic terpene ring systems related to aphidicolin, scopadulcic acid, and kauranes (Scheme 24).[75]

This method can also be used to form the polycyclic compounds 113 by DCA followed by internal alkylation (Scheme 25).[76]

G. α,β-Unsaturated Aldimines

Enantiomerically enriched β,β-disubstituted aldehydes have been synthesized by reacting Grignard reagents with scalemic α,β-unsaturated aldimines derived from α,β-unsaturated aldehydes and scalemic α-amino acid esters (Table 24).[77] The mechanism is believed to involve initial chelation of the imine nitrogen and ester oxygen with the magnesium followed by addition of the R group to the bottom face of the olefin (Figure 10).

This method was also used in the synthesis of scalemic 2-substituted cycloalkanecarbaldehydes[78] (Table 25) including the natural product (+)-ivalin (115) from 114 (Scheme 26).[79]

DCA followed by alkylation of the intermediate enamine gave the 1,2-disubstituted cycloalkane carbaldehyde (Table 26).[80] The stereochemical course of the reaction depends on the method used to carry out the reaction.

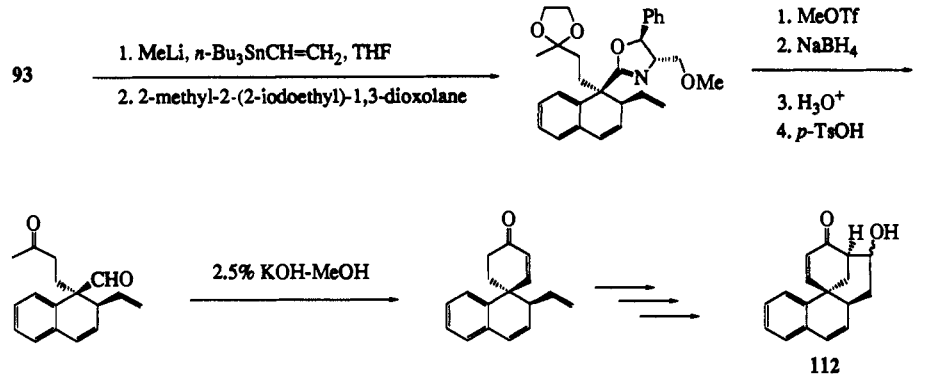
Meyers, Brown, and Laucher were able to perform similar additions of organolithiums to scalemic naphthyl aldimines 116 (Scheme 27).[81] The stereochemical outcome of these reactions was rationalized by assuming the organolithium and the naphthyl aldimine form a complex as shown, followed by transfer of the R group to the underside of the naphthyl ring (Figure 11).

III. Enantioselective Conjugate Addition of Organometallics to Prochiral α,β-Unsaturated Ketones

A. Scalemic Lithium Organo(alkoxo)cuprates

Among the early attempts to form enantioselective chiral cuprate reagents were those which involved formation of mixed cuprates derived from a chiral alcohol and an organolithium or magnesium reagent (Table 27). Initial attempts at making chiral mixed cuprates from chiral alcohols involved the use of 1,2:5,6-di-*O*-isopropylidene-α-D-glycofuranose (**2**),[82] (*S*)-prolinol (**125**),[83] cinchonidine (**131**),[84] (*R*)-(2,4,6-trimethoxybenzylidene)phenylglycinol (**134**), and (*R*)-2-

Scheme 24. Enantioselective Synthesis of Tetracyclic Terpene Ring Systems Related to Aphidicolin, Scopadulcic Acid, and Kauranes



Scheme 25. Diastereoselective Conjugate Addition to Naphthyl Oxazoline Followed by Internal Alkylation

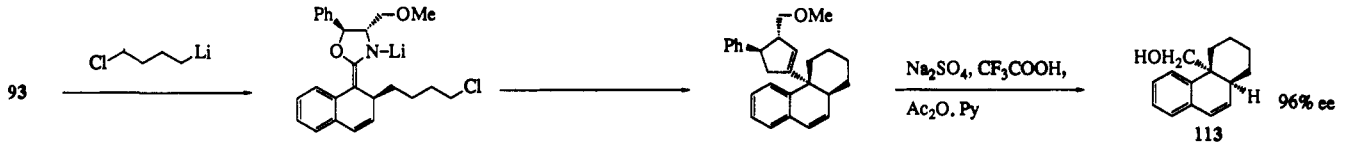
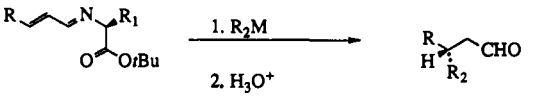
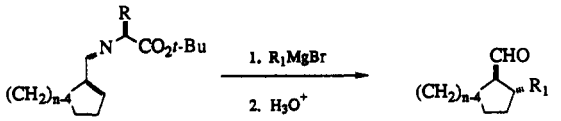


Table 24. Diastereoselective Conjugate Addition to α,β-Unsaturated Aldimines of Optically Active α-Amino Acid Esters



entry	R	R_1	R_2–M	solvent	% yield	% ee	*R/S*
1	Me	*i*-Pr	PhMgBr	ether	11	67	*R*
2				THF	55	53	
3				THF–ether (5:1)	53	57	
4				ether–THF (5:1)	49	65	
5				toluene–THF (6:1)	36	49	
6				hexane–THF (3:1)	38	44	
7			Ph_2Mg	ether	31	67	
8				THF	64	52	
9			PhMgBr–CuI	ether	12	65	
10				THF	64	52	
11			PhMgBr	ether–THF (5:1)	42	65	
12			c-C_6H_{11}Br		6	71	
13		*t*-Bu	PhMgBr		52	91	
14			c-C_6H_{11}MgBr		53	96	
15			*n*-BuMgBr		40	98	*S*
16			$[(CH_3)_2C{=}CH(CH_2)_2]$MgBr		48	98	*R*
17	Ph		EtMgBr		56	95	*S*

Table 25. Diastereoselective Conjugate Addition to Scalemic Cyclic Aldimines

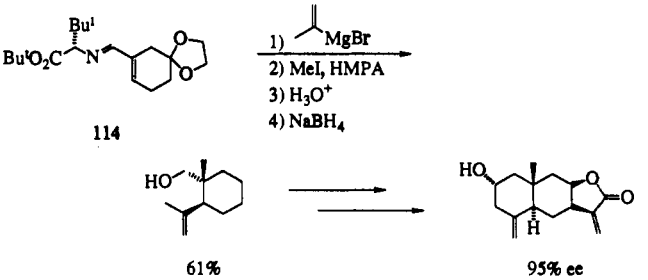


entry	*n*	R	R_1	% yield	% ee
1	5	*i*-Pr	Ph	72	61
2		*t*-Bu		82	82
3		*i*-Pr	$CH_2{=}CH$	36	71
4		*t*-Bu		69	92
5	6	*i*-Pr	Ph	52	49
6		*t*-Bu		54	91
7		*i*-Pr	$CH_2{=}CH$	31	69
8		*t*-Bu		68	93

butanol (119).[85] In all cases, the ee's observed were well below 50%. Imamoto and Mukaiyama reported the use of a cuprate formed from *N*-methylprolinol (126) and MeMgBr which, when reacted with chalcone, gives the expected product in ≤68% ee.[86]

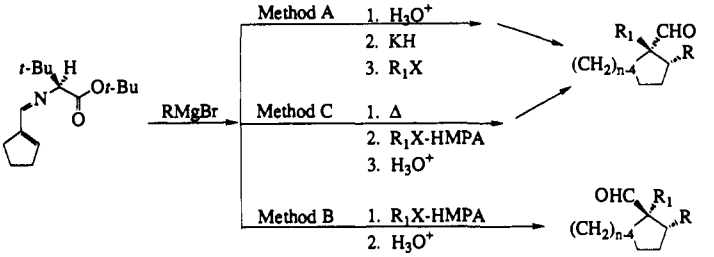
Figure 10.

Scheme 26. Enantioselective Synthesis of (+)-Ivalin



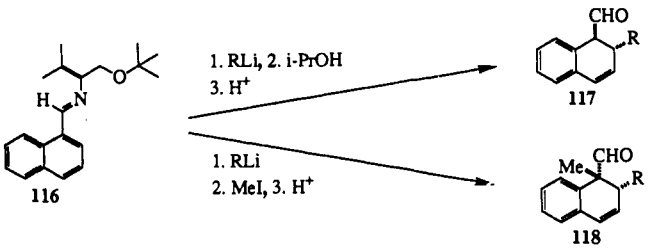
Leyendecker et al. used derivatives of proline as cuprate ligands for ECA to several ketones and obtained ee's as high as 88%.[87] Analogues of these ligands, **127**–

Table 26. Diastereoselective Synthesis of 1,2-Disubstituted Cycloalkanecarboxaldehydes



					% yield		
entry	method	n	R	R_1X	cis	trans	% ee
1	A	5	Ph	CH_3I	65	0	82
2			CH_2=CH		61	0	92
3		6	Ph		62	1	91
4			CH_2=CH		51	11	93
5	B	5	Ph		62	15	82
6			CH_2=CH		0	62	92
7		6	Ph		0	55	91
8		6	CH_2=CH		0	67	93
9				$PhCH_2I$	0	67	93
10				CH_2=$CHCH_2Br$	0	63	93
11				C_2H_5I	0	65	93
12				CH_3OCH_2Cl	0	52	93
13	C	5	Ph	CH_3I	44	2	82
14		6			49	0	91

Scheme 27. Diastereoselective Conjugate Addition to Scalemic Naphthyl Imines



	113		114	
R	% Yield	% ee	% Yield	% ee
i-Pr	78	95	-	-
n-Bu	78	95	85	95
t-Bu	85	95	75	95

129, give poor ee's. Corey, Naef, and Hannon reported a chiral mixed cuprate, $LiCu(OR^*)R_1$ in which HOR* is one of two diamino alcohols, **137** and **138**, which were derived from (1*R*,2*S*)-(−)-ephedrine and (*R*)-mandelic acid, respectively.[88] The cuprate reagent is formed by deprotonating the alcohol with an alkyllithium reagent, reacting this alkoxide with CuI in THF/dimethyl sulfide to form the copper alkoxide, and adding an additional 1 equiv of the alkyl lithium to form the reagent. The reaction is performed at −78 °C by adding the enone neat to the reaction mixture. The use of even slightly contaminated alkyllithium reagents results in lower ee's. In order to rectify this situation, a modified protocol was developed in which MeI is added to the reaction mixture in order to react with alkoxides presumed to be present as contaminants in old bottles of akyllithium reagents.

A mechanism was proposed to account for the enantioselectivity observed in this reaction (Figure 12). As shown, the cuprate is represented as a monomer in which one lithium is coordinated to the ligand through the

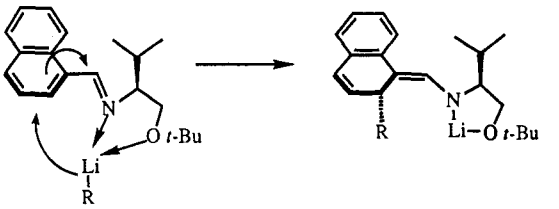
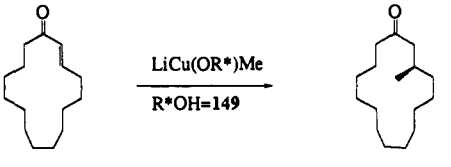


Figure 11.

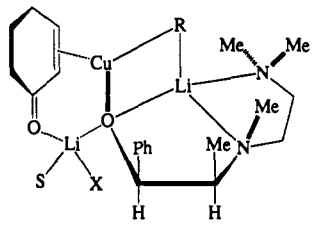
alkoxide oxygen and two nitrogen atoms and the copper is bridging between the alkoxide oxygen and the alkyl group, R. An additional lithium ion tethers the enone through the carbonyl oxygen to the alkoxide oxygen. This model suggests the predominant enantiomer in this reaction will be *R*.

Tanaka, Ushio, and Suzuki recently reported the use of 10 chiral amino alcohols, **140–149**, for use as chiral cuprate alkoxide ligands.[89] The ligands were used to form chiral methyl (alkoxy) cuprates and then reacted with (*E*)-2-cyclopentadecenone to form enantiomerically enriched Muscone (eq 17). They later reported that the enantioselectivity of this reaction, using ligands **144** and **149**, can be improved by forming the reagent in toluene with 2–10 equiv of THF. In each caseproducts of 100% ee, as determined by optical rotation, are obtained.[90]



(17)

Other scalemic alcohols and amino alcohols have been used by several groups but without great success.[91,92]



S = THF; X = I⁻ or THF

Figure 12. Proposed intermediate in conjugate addition with Corey's cuprate.

B. Scalemic Lithium Organo(amido)cuprates

A number of research groups have looked at the use of chiral lithium organo(amido)cuprates as agents for ECA to enones, particularly cyclic enones (Table 28). Bertz, Dabbagh, and Sundararajan formed mixed cuprates with phenyl as the transferable ligand and chiral primary amides as the nontransferable ligand and reacted them with 2-cyclohexenone (entries 1–50).[91] Enantioselectivities as high as 50% were reported.

Dieter and Tokles reported the use of four derivatives of proline, **198–201**, as chiral auxiliaries in organo(amido)cuprates (entries 51–111).[93] Enantiomeric excesses as high as 83% were attained in a survey that included several enones as well as the above-mentioned nontransferable ligands. They later reported some difficulties in reproducing their work and extended their original investigation to include other chiral ligands.[94]

In order to explain the enantioselectivity observed, they suggest the lithium organo(amido)cuprate forms a dimeric complex, with the organo and amido ligands occupying alternating bridging positions (Figure 13). They further suggest that the second chelating group (OMe, NC_4H_8, SMe, or SPh) occupies a ligand site in the lithium coordination sphere. The structures thus formed possess C_2 symmetry. The enone complexes to the cuprate either through a lithium–oxygen complex or a copper–olefin complex or both. The alkyl group is transferred to the face of the olefin coordinated to the copper atom. They assume preferential conjugate addition with the complex which gives the *S* isomer. The cuprate derived from ligand **198** has been used in the synthesis of (+)-confertin (Scheme 28).[95]

Rossiter and Eguchi reported a study in which a series of 11 chiral secondary amines, **168**, **171**, **173**, **184**, **207**, **208**, and **211–215**, were screened as chiral nontransferable cuprate ligands in the conjugate addition of *n*-butyl to 2-cyclohexenone (entries 112–166).[96] The structures of the chiral ligands were based on 1-phenylethaneamine. The structure of this ligand was modified systematically in order to discern relationships between the structures of the ligands and the enantioselectivity of the reaction. Of the ligands screened, ligand **208** proved to be the most successful, giving 3-*n*-butylcyclohexanone in 83% ee and up to 92% yield and 3-phenylcyclohexanone in 97% ee. The cuprate formed using ligand **208** was reacted with cyclic enones of ring sizes 5–8 in order to discern the overall selectivity of this reagent with other substrates.[97] The enantioselectivity with this series of enones increased, going from cyclopentenone to cycloheptenone, and then dropped with cyclooctenone. Reaction with cycloheptenone using either methyl or butyl as the transferable ligand gives product in 97% ee.

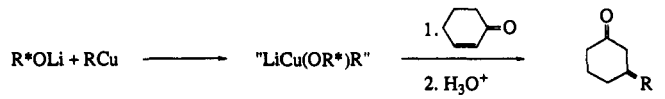
Enantioselectivity in the reactions using ligand **208** was rationalized by first assuming the amidocuprate forms a dimeric complex similar to that proposed by Dieter and Tokles (Figure 14). According to this model, the complex assumes a configuration in which both *N*-methyl groups point up relative to the plane of the complex. The piperidine groups bind to the lithium atoms and are positioned roughly where a solvent molecule would normally reside. The phenyl groups reside under the plane of the complex blocking its underside from interaction with the enone. The enone binds to one of the lithium atoms followed by interaction of the olefin with one of the copper atoms. This positions the enone directly over the stereochemically accessible side of the complex in order to obtain best orbital overlap and to avoid undesirable stereochemical interactions with the two *N*-alkyl groups. When the *re* face of the enone complexes with cuprate, the hydrogens on the 4, 5, and 6 carbons of the cyclohexenone interact unfavorably with one of the methyl groups pointing out of the plane of the complex, making this a relatively high energy complex. When the *si* face of the enone interacts with the cuprate, the same hydrogens will point toward the more stereochemically open corner of the complex. This model predicts the *S* enantiomer will be formed preferentially with the *S* ligand in conformance with experimental observation. Rossiter and co-workers also reported asymmetric amplification with this cuprate.[98] Cuprate formed with ligand of 56% ee and with *n*-butyl as the transferable ligand was reacted with 2-cycloheptenone to give 3-*n*-butylcycloheptanone in 81% ee.

Lippard and co-workers recently described a copper(I) complex capable of catalyzing the conjugate addition of Grignard reagents to enones with up to 78% ee and moderate to high chemical yields (Table 29).[99] These complexes consist of copper(I) bound to the chiral aminotropone imines H(*R*-CHIRAMPT) (**222**) and H(*R*-NEAT) (**221**). They found the enantioselectivity of these reactions is significantly increased by running them in the presence of HMPA and silyl chlorides. For example, reaction of *n*-BuMgCl with 2-cyclohexenone in the presence of 2 equiv of HMPA and Ph_2(*t*-Bu)SiCl and 0.037 equiv of Cu[*R*-CHIRAMPT] gives 3-*n*-butylcyclohexanone in 53% yield and 74% ee. Slightly higher ee's are obtained when a stoichiometric amount of the catalyst is used. An X-ray structure of the chiral copper complex has been obtained.[100]

C. Scalemic Lithium Diorganocuprates

Several groups have used scalemic cuprate reagents in which one of the ligands is (*S*)-2-[1-(dimethylamino)ethyl]phenyl or (*S*)-2-[cyclohexyl(dimethylamino)methyl]phenyl. Andersson et al. found that reaction of [(*S*)-2-[1-(dimethylamino)ethyl]phenyl](2-thienyl)copperlithium with 4-phenyl-3-buten-2-one, 2-cyclohexenone, and 2-cyclopentenone in each case gave the *S* product in which the scalemic ligand was transferred.[101] In the case of 2-cyclopentenone, conjugate addition occurred with 84% diastereoselectivity (eq 18). Gustafsson[102] and Malmberg and Nilsson performed similar experiments, but with cuprates in which the achiral ligand was transferred (eq 19).

Table 27. Enantioselective Conjugate Addition to Enones with Scalemic Organo(alkoxo)cuprates, MCu(OR*)R

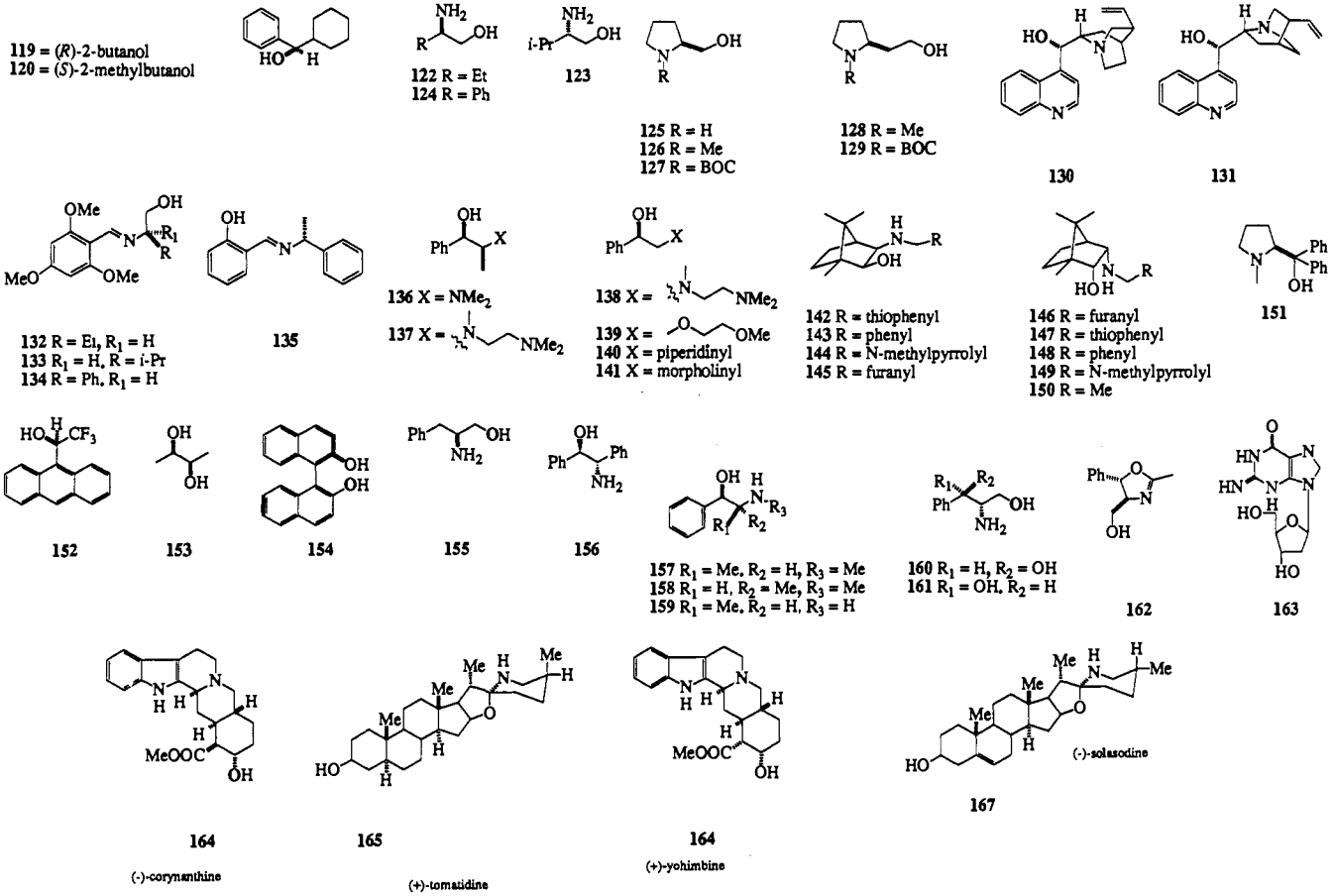


entry	substrate	HOR*[d]	RM	solvent	% yield	% ee	*R*/*S*	ref
1	2-cyclohexenone	**2**	MeLi	ether	NG	[−0.93]	*S*	82
2			*n*-BuLi		NG	[−0.8]	ND	
3			PhLi		NG	[+0.42]	ND	
4		**125**	MeLi		NG	16	*S*	83
5	1,3-diphenylpropenone	**122**			44	3	*S*	84
6		**123**			59	2	*S*	
7		**124**			35	0	-	
8		**130**			21	34	*S*	
9		**131**			8	0	-	
10		**132**	MeMgBr	THF	35	4	*R*	
11		**133**	MeLi	ether	59	15	*S*	
12			MeMgBr	THF	23	25	*S*	
13		**134**	MeLi	ether	17	31	*S*	
14			MeMgBr	THF	30	0	-	
15		**135**	MeLi	ether	75	12	*R*	
16	2-cyclohexenone	**119**	*n*-BuLi		48	6	ND	85
17	4-phenyl-3-buten-2-one				65	[−4.4]	ND	
18		**120**			70	[−3.0]	ND	
19	2-cyclohexenone	**4**		THF	42	4	ND	
20		**121**			54	8	ND	
21	(*E*)-1,3-diphenylpropenone	**126**	MeMgBr		88	61	*S*	86
22	(*Z*)-1,3-diphenylpropenone				71	68	*S*	
23	2-cyclohexenone	**125**		benzene	61	26	*S*	87a
24				THF	85	6	*S*	
25	1,3-diphenylpropenone				70	15	*S*	
26				toluene	42	20	*S*	
27	4-phenyl-3-butenone			THF	61	29	*S*	
28				toluene	36	37	*S*	
29	1,3-diphenylpropenone	**126**			32	2	*S*	
30				THF	81	41	*S*	
31	4-phenyl-3-buten-2-one			toluene	36	3	*R*	
32				THF	92	10	*S*	
33	2-cyclohexenone			benzene	64	1	*R*	
34				THF	70	5	*R*	
35	(*E*)-1,3-diphenylpropenone	**127**			55	7	*S*	87b
36		**125**			70	15	*S*	
37		**126**			80	88	*S*	
38		**128**			94	0	-	
39		**129**			86	2	*R*	
40	2-cyclopentenone	**137**	EtLi		68	77	*R*	88
41			*n*-BuLi		60	72	*R*	
42			*t*-$BuOCH_2Li$		52	81	*R*	
43	2-cyclohexenone		EtLi		90	92	*R*	
44			*n*-BuLi		90	89	*R*	
45			*t*-$BuOCH_2Li$		73	85	*R*	
46		**138**	MeLi	ether/toluene	60	90	*R*	
47		**139**	*n*-BuLi	THF	68	16	*R*	92
48		**140**			63	14	*R*	
49		**141**			68	15	*R*	
50	(*E*)-2-cyclopentadecenone	**142**		toluene	82	49	*S*	89
51		**143**			72	39	*S*	
52		**144**		toluene/THF	89	100	*S*	90
53		**145**		toluene	86	50	*S*	89
54		**146**			90	33	*R*	
55		**147**		toluene/THF	80	95	*R*	90
56		**148**		toluene	90	64	*R*	89
57		**149**		toluene/THF	90	100	*S*	90
58		**150**			70	39	*R*	89
59		**151**			59	15	*S*	
60	2-cyclohexenone	**124**	PhLi	ether	38	10	*R*	91
61		**125**			52	10	*S*	
62		**152**			31	10	*R*	
63		**153**			53	0	-	
64		**154**			15	20	*R*	
65		**155**			37	10	*R*	
66		**156**			14	10	*R*	
67		**157**			94	50	*R*	
68[a]					91	20	*R*	
69[b]					48	40	*R*	
70[c]					72	20	*R*	
71				THF	34	50	*R*	

Table 27. (Continued)

entry	substrate	HOR* [d]	RM	solvent	% yield	% ee	R/S	ref
72[a]					46	10	R	
73[b]					39	50	R	
74[c]					38	0	-	
75				ether	65	20	R	
76			PhMgBr		41	10	S	
77			PhLi	THF	39	50	R	
78			PhMgBr		7	50	S	
79			PhLi	DME	30	30	R	
80				$(i\text{-Pr})_2O$	45	20	R	
81				Me_2O	39	0	-	
82				dioxane	12	0	-	
83				Me_2S	98	0	-	
84		158		ether	73	0	-	
85		159			44	0	-	
86		160			53	10	R	
87		161			51	20	R	
88		162			36	10	R	
89		163			14	20	R	
90		164			33	0	-	
91		165			27	0	-	
92		166			6	20	S	
93		167			34	10	R	

[a] CuBr used. [b] CuOTf used. [c] CuCN used. [d] R*OH =



Another approach to stereoselective conjugate addition involves the reaction of scalemic copper and zinc azaenolates with cyclic enones (Table 30).[104] The azaenolates are formed by reacting scalemic 1,2-amino ethers with acetone to form the imine, deprotonating at the α-position of the imine with *n*-butyllithium, and treating this azaenolate with a copper salt or dimethyl zinc. Reaction of these complexes with 2-cyclopentenone and 2-cyclohexenone gives, after hydrolysis, 3-acetonylcyclopentanone and 3-acetonylcyclohexanone,

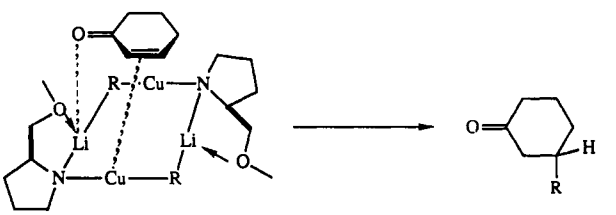
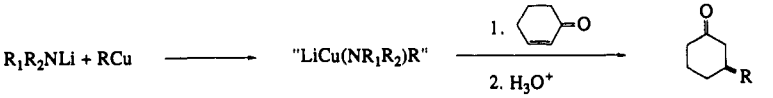


Figure 13.

respectively. This protocol was used in the synthesis of *trans*-dihydrindandione systems (Scheme 29).[105]

Table 28. Enantioselective Conjugate Addition to Enones with Chiral Organo(amido)cuprates, $LiCu(NR^1R^2)R$



entry	ligand[b]	substrate	R	solvent	CuX	% yield	% ee	R/S	ref
1	**168** (*S*)	2-cyclohexenone	Ph	ether	CuI	69	30	*S*	91
2				THF		12	30	*R*	
3	**168** (*R*)			ether		72	30	*R*	
4	**169** (*R*)					62	40	*R*	
5						72	30	*R*	
6					CuBr	47	40	*R*	
7					CuOTf	34	20	*R*	
8					CuCN	35	0		
9					CuI/LiCN	54	40	*R*	
10					CuCN/LiI	52	30	*R*	
11					CuI/LiI	46	40	*R*	
12					CuI/$LiBPh_4$	41	40	*R*	
13	**169** (*S*)				CuI	74	30	*S*	
14			*a*			2	0		
15				THF		6	10	*R*	
16			*a*			11	10	*R*	
17				ether		78	20	*S* (0 °C)	
18						79	10	*S* (25 °C)	
19	**170**					50	40	*S*	
20	**175**					23	40	*R*	
21	**176**					74	0		
22	**177**					88	10	*S*	
23	**178**					48	10	*S*	
24	**179**					86	20	*S*	
25	**180**					69	10	*S*	
26	**181**					42	0		
27	**182**					31	30	*R*	
28	**183**					32	10	*S*	
29	**184** (*S,S*)					32	20	*R*	
30	**185**					34	40	*R*	
31	**186**					12	10	*R*	
32	**187**					49	10	*R*	
33				THF		22	60	*R*	
34	**188**			ether		62	50	*R*	
35			*a*			29	10	*R*	
36				THF		26	0		
37			*a*			10	10	*R*	
38				hexane		51	30	*S*	
39				Me_2S		53	10	*R*	
40				Et_2S		56	0		
41	**189**			ether		72	10	*R*	
42	**190**					66	10	*R*	
43	**191**					47	10	*S*	
44	**192**					59	10	*S*	
45	**193**					8	10	*S*	
46	**194**					24	50	*R*	
47	**195**					6	40	*R*	
48	**196**					47	10	*R*	
49	**197**					33	0		
50	**198**					36	20	*R*	
51			Me		CuBr	77	82	*S* (−25 °C)	93
52					CuBr/LiBr	35	63	*S*	
53					CuBr	69	79	*S* (−110 °C)	
54				THF		60	53	*R* (−78 °C)	
55				$PhCH_3$		63	70	*R*	
56				ether	CuSCN	57	75	*R*	
57				$PhCH_3$		68	83	*R*	
58				ether	CuBr	24	20	*R*	
59		2-cyclopentenone				50	20	*S* (−25 °C)	
60						36	23	*S* (−78 °C)	
61				$PhCH_3$		70	37	*R*	
62				ether	CuSCN	51	33	*R*	
63				$PhCH_3$		77	41	*S*	
64			*t*-Bu	ether	CuBr	56	35	*S*	
65		2-cyclohexenone	*n*-Bu			42	28	*S* (−25 °C)	
66			*t*-Bu			83	52	*S*	
67						25	67	*S* (−78 °C)	
68		*trans*-3-penten-2-one	*n*-Bu			32	49	*S* (−25 °C)	
69						36	64	*S* (−78 °C)	
70				THF		62	38	*R*	
71				ether	CuSCN	37	68	*R*	

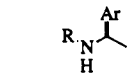
Table 28. (Continued)

entry	ligand[b]	substrate	R	solvent	CuX	% yield	% ee	R/S	ref
72		*trans*-3-octen-2-one	Me		CuBr	46	58	*R*	
73					CuSCN	56	75	*R*	
74	**199**	2-cyclohexenone	Me	ether	CuBr	39	8	*S*	
75		2-cyclopentenone				35	1	*S*	
76	**200**			$PhCH_3$		58	32	*R*	
77						60	35	*R*	
78		2-cyclohexenone		THF		70	52	*R*	
79				ether		78	71	*S*	
80				$PhCH_3$		71	80	*R*	
81		2-cyclopentenone	*t*-Bu	ether		50	50	*S*	
82		*trans*-3-penten-2-one	*n*-Bu	THF		48	46	*R*	
83				ether		51	61	*S*	
84		*trans*-3-octen-2-one	Me			42	74	*R*	
85	**201**	2-cyclohexenone				68	80	*S*	
86			*n*-Bu			46	58	*S*	
87			*t*-Bu			51	69	*S*	
88		2-cyclopentenone	Me			60	33	*S*	
89		*trans*-3-penten-2-one	*n*-Bu			52	64	*S*	
90		*trans*-3-octen-2-one	Me			78	83	*R*	
91	**123**	2-cyclohexenone				54	69	*R*	
92	**198**				CuI		20	*R*	94
93					CuBr		30	*R*	
94			*n*-Bu		CuI	98	8	*R*	
95					CuBr	56	22	*R*	
96	**202**		Me		CuI	100	30	*R*	
97					CuBr	95	46	*R*	
98				$PhCH_3$	CuI	–	17	*R*	
99					CuBr	–	40	*R*	
100				THF		29	0	–	
101			*n*-Bu	ether		45	22	*R*	
102					CuI	100	10	*R*	
103				THF	CuBr	100	0	–	
104	**205** (*R*,*S*)			ether	CuI		37	*R*	
105					CuBr		70	*R*	
106					CuBr/*n*-Bu_3P	84	52	*R*	
107	**205** (*R*,*R*)				CuI		25	*R*	
108					CuBr		66	*R*	
109					CuBr/TMSCl	91	0	–	
110	**206**				CuI	82	26	*S*	
111					CuBr	60	28	*S*	
112	**168** (*R*)		*n*-Bu	DMS	CuI	88	4	*R*	96
113				ether		66	15	*R*	
114		2-cycloheptenone				19	11	*R*	92
115	**169**	2-cyclohexenone				88	9	*R*	
116						62	13	*R*	
117	**171**			DMS		84	50	*S*	96
118				ether/DMS		53	24	*R*	
119				ether		46	21	*R*	
120			Ph	ether/DMS		44	10	*R*	
121		2-cycloheptenone	*n*-Bu	ether		26	12	*R*	92
122	**172**	2-cyclohexenone		DMS		74	51	*S*	
123				DMS/ether		45	18	*R*	
124				ether		51	6	*R*	
125	**173**			DMS		64	29	*R*	96
126				ether/DMS		28	8	*S*	
127	**174**			DMS		59	29	*R*	92
128				ether/DMS		11	7	*R*	
129	**184**			DMS		43	43	*R*	96
130				ether/DMS		25	3	*S*	
131		2-cycloheptenone		ether		45	2	*S*	92
132	**203**	2-cyclohexenone				77	7	*R*	
133	**204**			DMS		7	8	*S*	
134	**207**					92	68	*S*	96
135				ether/DMS		79	16	*S*	
136	**208**	2-cyclopentenone	Me	ether		40	32	*R*	97
137			*n*-Bu			51	45	*S*	
138		2-cyclohexenone	Me			57	58	*S*	
139			*n*-Bu			92	83	*S*	
140				DMS		60	83	*S*	96
141				THF		22	1	*S*	
142			Ph	ether		30	97	*S*	
143		2-cycloheptenone	Me			60	97	*S*	97
144			*n*-Bu			63	96	ND	
145		2-cyclooctenone	Me			48	67	ND	
146			*n*-Bu			50	86	ND	

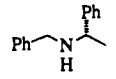
Table 28. (Continued)

entry	ligand[b]	substrate	R	solvent	CuX	% yield	% ee	R/S	ref
147	209	2-cyclohexenone		ether		69	84	S	92
148		2-cycloheptenone				57	8	S	
149			Me			4	95	S	
150	210	2-cyclohexenone	n-Bu			71	55	S	
151	211	2-cyclohexenone	n-Bu			52	19	S	96
152				DMS		49	10	S	
153		2-cycloheptenone		ether		76	4	S	92
154	212	2-cyclohexenone	n-Bu	DMS		100	71	S	96
155				ether		75	55	S	
156				THF		20	6	S	
157			Ph	ether/DMS		51	71	S	
158	209		n-Bu	DMS		39	4	S	
159	214			ether		79	25	S	
160		2-cycloheptenone				35	68	S	92
161	215	2-cyclohexenone				28	28	S	96
162	216					63	19	R	92
163	217			DMS		2	1	S	
164	218					25	11	R	
165	219					58	32	R	
166	220					20	35	R	
167	198	2-methyl-2-cyclopentenone	2-propenyl			76	76	R	95

[a] PhMgBr used instead of PhLi. [b] The ligands are as follows:

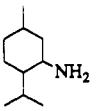


168 R = H, Ar = Ph
169 R = H, Ar = 1-naphthyl
170 R = H, Ar = 2-naphthyl
171 R = Me, Ar = Ph
172 R = Me, Ar = 1-naphthyl
173 R = i-Pr, Ar = Ph
174 R = c-Hexyl, Ar = Ph

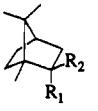


175

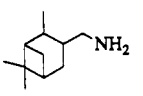
176 = (S)-2 aminoheptane
177 = (S)-1-amino-2-methylbutane



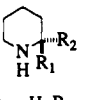
178



179 $R_1 = NH_2$, R_2 = H
180 R_1 = H, $R_2 = NH_2$

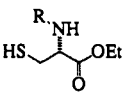


181



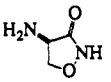
182 R_1 = H, R_2 = n-Pr
183 R_1 = 3-pyridyl, R_2 = H

184 Ar = Ph
185 R = 2-Methoxyphenyl

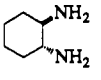


186 R = H
187 R = $COCH_3$

188



189



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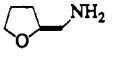

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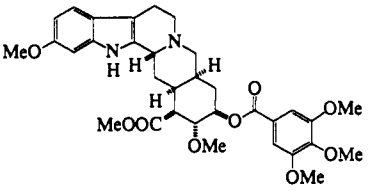
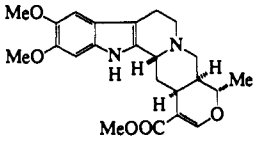


192



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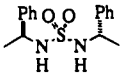

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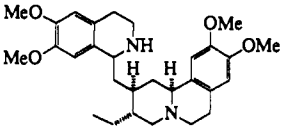

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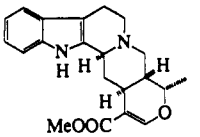
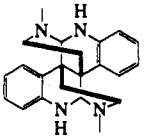
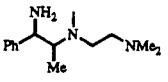


196

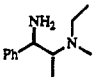


197

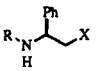
198 X = OMe
199 X = c-NC_4H_8
200 X = SPh
201 X = SMe
202 X = OCH_2OCH_3
203 X = c-NC_5H_{10}
204 X = $N(Me)CH_2CH_2N(Me)_2$



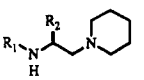
205



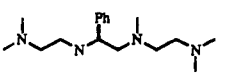
206



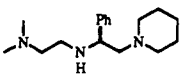
207 R = Me, X = OMe
208 R = Me, X = 1-piperidinyl
209 R = Me, X = 1-(4-methylpiperidinyl)
210 R = Me, X = 1-(3,3-dimethylpiperidinyl)
211 R = i-Pr, X = 1-piperidinyl
212 R = Me, X =
213 R = c-Hexyl, X =



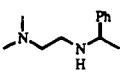
214 R_1 = Me, R_2 = i-Pr
215 R_1 = Me, R_2 = t-Bu
216 R_1 = Bzl, R_2 = i-Pr



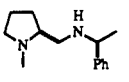
217



218



219



220

D. Lithium Diorganocuprates with Scalemic Noncovalently Bound Ligands

Several groups have synthesized and tested reagents made from various organometallic species and scalemic neutral organic ligands. One of the first examples of ECA was reported by Kretchmer in which Grignard reagents plus catalytic CuCl were combined with sparteine (226) and reacted with several enones (Table 31).[106] The highest reported ee was 6%.

Several years later, Langer and Seebach reported using the chiral cosolvent, 2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine (DDB, 227), to promote ECA to various substrates (Table 32).[107] Three types

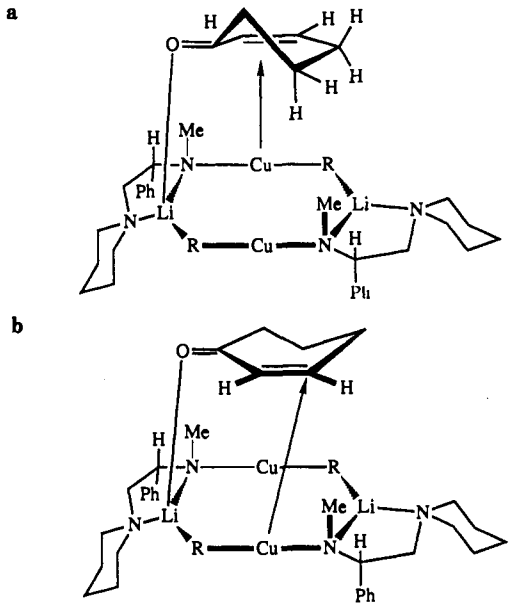
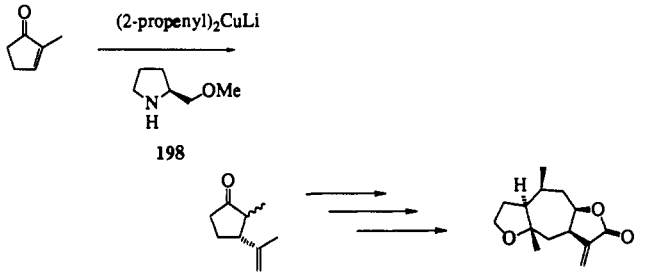


Figure 14.

Scheme 28. Enantioselective Synthesis of (+)-Confertin

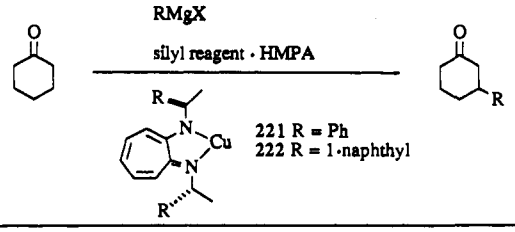


of reagent were used: organocuprates, organozincates, and organolithiums. In general, the ee's were low although one reaction reached as high as 43% ee. The solvent, in principle, is available in substantial quantities. Given the expense of making or purchasing this solvent and the low ee's obtained in these reactions, it is currently not a useful approach for stereoselective conjugate addition.

Leyendecker examined a series of chiral ligands **228–237** derived from hydroxyproline in the reaction of lithium dimethyl cuprate with chalcone (Table 33).[108] In one case, ee's of 94% were obtained. They previously found that bidentate ligands give better results than unidentate ligands and reasoned that tridentate ligands would perform even better. They also discovered that N-carboalkoxylated and N-acylated ligands **230–232** and **234–237** gives better results than N-alkylated ligands **228**, **229**, and **231** and that dilution of the reaction mixtures does not change enantioselectivities. They postulated that simultaneous chelation of lithium and copper is important in order to attain high enantioselectivities (Figure 15). The proposal that the ligand chelates with copper runs counter to the suggestion of van Koten and Noltes that copper(I) in cuprates does not readily chelate with electron-rich ligands and therefore will not be an important aspect of enantioselective cuprate reagents.[109]

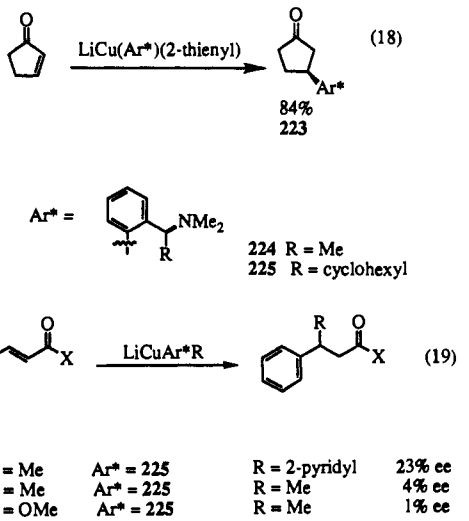
Recently, Alexakis, Mutti, and Normant reported using chiral phosphorus compounds derived from HMPT with *n*-BuCu to attain ECA with 2-cyclohexenone (Table 34).[110] The highest ee observed was 76% and depended in part on having 4 equiv of LiBr present

Table 29. Catalytic Enantioselective Conjugate Addition of RMgX to 2-Cyclohexen-1-one



entry	catalyst	R	silyl reagent	% yield	% ee	*R/S*
1	**221**	*n*-Bu	–	96	20	*S*
2	**222**			89	15	*S*
3			Me_3SiCl	95	51	*S*
4				98	60	*S*
5				63	0	
6			$Ph_2(t\text{-Bu})SiCl$	26	70	*S*
7				53	74	*S*
8	**221**			57	74	*S*
9				97	78	*S*
10				51	27	*S*
11	**222**		$(i\text{-Pr})_3SiOTf$	98	44	*S*
12	**221**		$(t\text{-Bu})_2Si(OTf)_2$	67	40	*S*
13		Me	Me_3SiCl	54	30[a]	*R*
14		Et		87	14	*S*
15		vinyl		92	9	*S*
16		Ph		96	0	
17		Me	$(t\text{-Bu})_2MeSiOTf$	95	10[a]	*R*
18		Et		54	35	*S*
19		Ph	$(t\text{-Bu})_2MeSiOTf$	57	0	

[a] The enantiomeric form of the ligand was used.

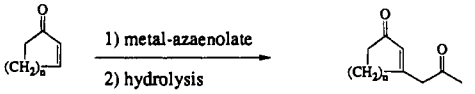


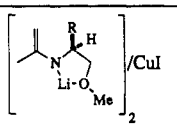
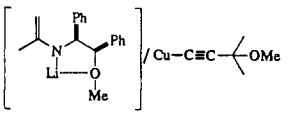
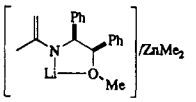
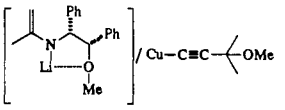
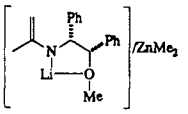
in the reaction mixture. Forming the organocopper reagent from Grignard reagents or using LiI gives poorer results than those reactions in which organolithium reagents and LiBr are used.

E. Dialkylzinc Reagents and Scalemic Catalysts

Luche et al. found that Ni(II) salts facilitate the conjugate addition of dialkylzinc to enones.[111] Several groups have taken this reaction and rendered it enantioselective. In their initial studies, Soai et al. reported that ECA to prochiral enones is possible using dialkylzinc reagents and $Ni(acac)_2$ in the presence of a chiral auxiliary.[112,113] The catalyst is formed by stirring 1 equiv of $Ni(acac)_2$ or $NiBr_2$ with *N,N*-dibutylnorephedrine (**251**) in toluene at 80 °C (Table 35, entries 1–6). The substrate is added, the reaction mixture is cooled to −30 °C, and Me_2Zn or Et_2Zn is added. The enantioselectivity in these reactions is partially a function of

Table 30. Enantioselective Conjugate Addition of Scalemic Azaenolates with 2-Cycloalkenones



entry	substrate	metal–azaenolate	% yield	% ee	R/S	ref
1	2-cyclopentenone		54	17	R	104a
		R = CH_2Ph				
2		R = Pr^i	75	27	S	
3		R = Bu^t(R enantiomer)	89	75	R	
4		R = CH_2Ph	41	28	R	
5		R = Pr^i	46	23	R	
6		R = Bu^t	30	44	S	
7		R = Bu^t(R enantiomer)	31	44	R	
8			78	78	R	104b
9			73	92	R	
10	2-cyclohexenone		78	71	S	
11			48	88	S	

Scheme 29. Enantioselective Synthesis of the Scalemic *trans*-Dihydrindandione System

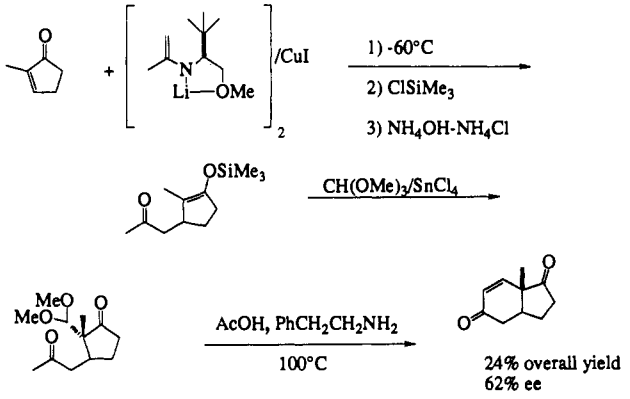
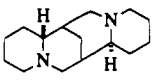


Table 31. Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to Enones with Sparteine (226)



226

entry	substrate	Grignard	solvent	% yield	% ee
1	2-cyclohexenone	MeMgI/CuCl	ether	17	6
2		PhMgBr/CuCl		17	<1
3[a]	1,2-diphenyl-propenone	MeMgI/CuCl	benzene	45	3
4				50	5
5	3-penten-2-one	EtMgBr/CuCl	ether	10	5

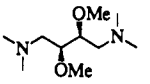
[a] No copper(I) salt used.

the ratio of catalyst to substrate. Increasing the amount of catalyst gives better ee's.

Soai et al. later reported that the enantioselectivity of these reactions could be improved significantly by using a combination of Ni(II)–2,2′-dipyridyl chiral ligand in acetonitrile/toluene to form the catalyst.[114] ECA of dialkylzinc to aryl substituted enones affords β-substituted ketones in up to 90% ee (entries 15 and 16). In addition to the chiral ligand and Ni(II), both the achiral ligand and acetonitrile were essential in obtaining the product with high ee. Other achiral ligands were used as well, but not with the same degree of success.

Bolm and Ewald recently published the use of nickel-catalyzed ECA of organozinc reagents to α,β-unsaturated ketones using the chiral 2,2′-dipyridyl ligand **254**.[115] Optically active β-substituted ketones are obtained in high yields and with ee's as high as 74%. They have also observed asymmetric amplification with their system.[116] For example, when ligand **257** of 10% ee is used, product of 44% ee is obtained. Bolm suggests asymmetric amplification occurs as a result of the formation of dimeric nickel catalysts. If the nickel complexes with an unequal mixture of enantiomeric ligands, one can form *SS* (where *S* is the predominant enantiomer) and *SR* complexes. If the *SR* (meso) complex is relatively unreactive as a catalyst, one would expect the enantioselectivity of the reaction to be higher than the enantiomeric purity of the ligand. Although this reaction is catalytic in Ni, better ee's are obtained

Table 32. Enantioselective Conjugate Addition of Organometallic Reagents to Enones with DDB (227) as Cosolvent



227

entry	substrate	reagent	solvent	% yield	% ee	*R/S*
1	2-cyclohexenone	Me_2CuLi	ether	54	14	*S*
2		Me_3ZnLi		63	[−0.74]	
3		$(n\text{-Bu})_2CuLi$		84	15	*S*
4				65	7	*S*
5				81	5	*S*
6				45	[−0.78]	
7		$(n\text{-Bu})_3ZnLi$		84	16	*S*
8				81	24	*S*
9				52	[−1.04]	
10		$(PhS)_3CLi$		80	[−5.48]	
11	2-cyclopentenone	$(n\text{-Bu})_2CuLi$		64	[−10.0]	
12		$(n\text{-Bu})_3ZnLi$		78	[+6.93]	
13		$[Me_3Si](Me_2S)_2CLi$		38	5	
14	crotonaldehyde	$(n\text{-Bu})_2CuLi$		63	[−0.32]	
15		$(n\text{-Bu})_3ZnLi$		39	[−0.32]	
16	cinnamaldehyde	Me_2CuLi		54	[−0.10]	
17		$(n\text{-Bu})_2CuLi$		51	[+0.61]	
18	1,3-diphenyl-2-propenone	$(n\text{-Bu})_2CuLi$		75	[−0.75]	
19	2-(2-cyclohexenylidene)-1,3-dithiane	*n*-BuLi		78	[−9.5]	
20	nitropropene		pentane	49	28	*R*
21		$(n\text{-Bu})_2CuLi$		49	27	*R*
22			pentane/ether	54	15	*R*
23		$(n\text{-Bu})_3ZnLi$		59	27	*R*
24				54	15	*R*
25			pentane	72	43	
26				62	[+0.054]	
27				80	[−4.25]	
28	β-nitrostyrene	*n*-BuLi		60	[+1.22]	
29				55	[+0.43]	
30	nitropropene			48	[−0.39]	
31				70	6/[+0.12]	
32				75	[+0.10]	
33				57	12/[+0.64]	
34	β-nitrostyrene			68	10/[+1.25]	

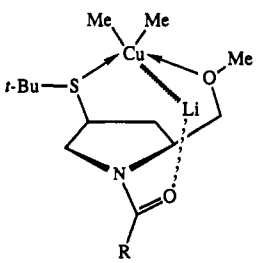


Figure 15.

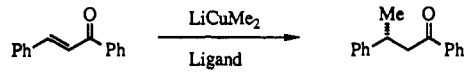
when more reagent is used (compare entries 27 and 28 vs 32–34).

Soai et al. have also described ECA of diethylzinc to enones using chiral β-amino alcohol, 1-phenyl-2-(1-piperidinyl)propan-1-ol **255** and **256** in catalytic and stoichiometric amounts to facilitate the reaction. No additional transition metal catalyst is added.[117] When enones **246** and **248–250** are reacted with Et_2Zn using 0.25 equiv of the 1*S*,2*R* isomer, **255**, the corresponding ketone products are obtained with 60–80% ee (entries 37, 40, and 42). When a stoichiometric amount of **255** is employed, ee's of the product increase to 81–94% (entries 38, 39, 41, 43, and 44). Reaction times appear to be considerably longer than those employing nickel catalysts.

F. Grignard Reagents Catalyzed by Scalemic Arenethiolatocopper(I) Complexes

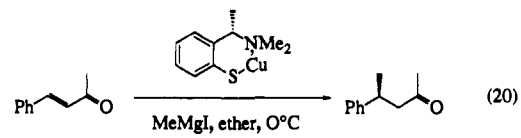
van Koten et al. recently described the catalytic conjugate addition of MeMgI to 4-phenyl-3-buten-2-

Table 33. Enantioselective Conjugate Addition of $LiCuMe_2$ to Chalcone Using Noncovalently Bound Hydroxyproline-Derived Ligands



entry	ligand	% yield	% ee
1	**228**, R = neopentyl	98	2
2	**229**, R = methyl	97	7
3	**230**, R = *t*-BOC	95	33
4	**231**, R = acetyl	71	33
5	**232**, R = trimethylacetyl	93	68
6	**233**, R = *t*-Bu	95	75
7	**234**, R = 1-phenylcyclohexylcarbonyl	95	50
8	**235**, R = isobutanoyl	>90	58
9	**236**, R = benzoyl	>90	85
10	**237**, R = 1-naphthoyl	>90	94

one in up to 57% ee using the chiral arenethiolatocopper(I) complex shown below (eq 20).[118] This complex is similar to achiral complexes that have been developed and structurally characterized.[119] The reaction is performed by dissolving the thiolato complex and 4-phenyl-3-buten-2-one in ether at 0 °C and adding MeMgI slowly. When excess MeMgI is present in the reaction mixture, the enantioselectivity of the reaction is low (ca. 3%). The mixed cuprate, LiCu(SAr)(Me) gives predominantly 1,4-addition but is not enantioselective.

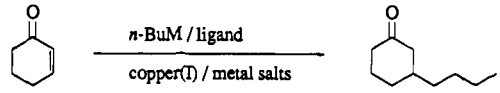


(20)

G. Grignard Reagents with Scalemic Zinc Catalysts

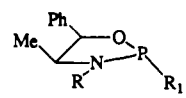
Isobe et al. found that lithium trialkylzincates react with enones to give conjugate addition.[120] Others discovered that alkoxides could be substituted for some of the alkyl groups as nontransferable ligands.[121] Jansen and Feringa subsequently found that *N,N,N',N'*-tetramethylethylenediamine complexes of $ZnCl_2$ catalyze the conjugate addition of Grignard reagents to enones.[122] Using this reaction, Jansen and Feringa screened a number of chiral ligands to see if they could render this reaction enantioselective (Table 36).[123] They looked at the conjugate addition of various alkyl moieties to 2-cyclohexenone. As part of their study, they also looked at the influence of solvent, counterions, rate of addition, and temperature. The advantage of this system is that it is catalytic and uses inexpensive and readily prepared Grignard reagents. In general, the reactions proceed with high chemical yields and selectivity for 1,4 vs 1,2 addition. The enantioselectivities, however, are poor, reaching only as high as 33% in one case. They found the highest enantioselectivities are attained by preparing the catalyst in situ from the lithium salt of the chiral diamino alcohol ligand and performing the reaction in THF. A mechanism was suggested for this reaction in which 2-cyclohex-

Table 34. Enantioselective Conjugate Addition to 2-Cyclohexenone with Organocopper Reagents and Scalemic Noncovalently Bound Phosphorus Ligands

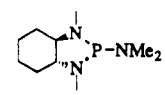


entry	*n*-BuM	ligand[a]	copper source and added salts	ligand equiv	solvent	% yield	% ee
1	BuLi/hexane	**238**	CuI	1	THF	30	22
2				2		35	38
3				3		43	19
4				2	Et_2O	43	22
5			CuI + TMSCl		THF	15	0
6			CuI + 4LiBr			56	65
7			CuI + 4LiI			45	44
8			CuBr–Me_2S + 4LiBr			45	40
9	BuLi–LiBr/Et_2O		CuI + 3LiBr			62	62
10	BuMgBr/Et_2O		CuI + 4LiBr			28	19
11	0.5 equiv BuLi/hexane					27	75
12	2 equiv BuLi/hexane					>90	0–75
13	BuLi/hexane	**239**				61	76
14		**240**				10	62
15		**241**				12	14
16		**242**				55	rac
17		**243**				62	23

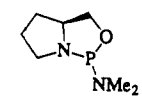
[a] The ligands are as follows:



238 R = Me, R_1 = NMe_2
239 R = Me, R_1 = Ph
240 R = *i*-Pr, R_1 = NMe_2
241 R = Me, R_1 = morpholinyl

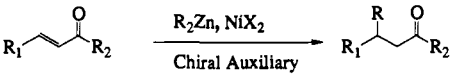


242



243

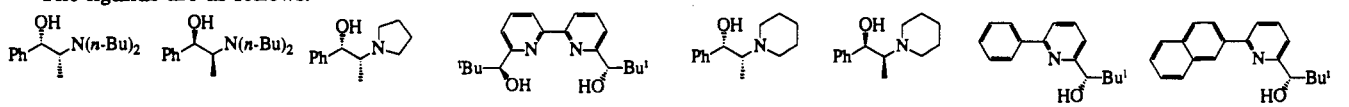
Table 35. Catalyzed Enantioselective Conjugate Addition of Dialkylzinc to Enones



244 R_1, R_2 = Ph
245 R_1 = Ph; R_2 = Me
246 R_1 = Me; R_2 = Ph
247 R_1 = Ph; R_2 = *p*-MeOPh
248 R_1 = Ph; R_2 = CPh_3
249 R_1 = Ph; R_2 = Bu^t
250 R_1 = Ph; R_2 = Adamantyl

entry	NiX_2	ligand[a]	substrate	R	Ni:L*:S	% yield	% ee	*R/S*	ref
1	$Ni(acac)_2$	**251**	**244**	Me	1:1.2:1.7	72	40	*R*	112
2				Et	1:1.2:2.0	75	45	*R*	
3					1:1.2:17	94	20	*R*	
4		**252**			1:1.2:17	89	22	*S*	
5		**251**	**245**		1:1.2:1.7	63	12	*R*	
6			**246**		1:1.2:2.0	78	44	*R*	
7	$NiBr_2$		**244**		1:1.2:4.0	32	48	*R*	113
8					1:1.2:33	NR	36	*R*	
9					1:1.2:2.5	NR	32	*R*	
10	$NiCl_2$				1:1.2:4	NR	30	*R*	
11	NiI_2					NR	3	*R*	
12	$NiBr_2$			*n*-Bu		16	43	ND	
13			**245**	Et		32	18	*S*	
14			**246**			40	14	*S*	
15	$Ni(acac)_2$	**251**/2,2′-bipyridyl	**244**		1:2.4:14	47	90	*R*	114
16		**253**/2,2′-bipyridyl			1:2.4:17	63	82	*R*	
17		**251**/piperazine				44	87	*R*	
18		**251**/1,10-phenanthroline				72	81	*R*	
19		**251**/2,2′-bipyridyl		*n*-Bu	1:2.4:14	47	74	*R*	
20		**251**/2,2′-bipyridyl	**247**	Et		58	80	*R*	
21		**251**/2,2′-bipyridyl ketone	**244**		1:2.4:17	87	71	*R*	
22		**251**/2,2′-biquinoline				92	70	*R*	
23		**251**/1,2-DPPE				89	71	*R*	
24		**251**/morpholine				84	71	*R*	
25		**251**/quinuclidine				85	72	*R*	
26		**251**/pyridine				84	71	*R*	
27		**254**			1:30:100	55	72	*R*	115
28					1:20:100	75	72	*R*	
29					1:10:100	82	54	*R*	
30					1:5:100	74	20	*R*	
31					1:5:50	66	48	*R*	
32					1:3:50	73	18	*R*	
33					1:3:20	58	58	*R*	
34					1:1:20	69	18	*R*	
35			**247**		1:10:20	68	74	ND	
36			**245**		1:5:20	76	2	*R*	
37		**255**	**248**		0:1:4	81	80	(+)	117
38					0:1:1	96	94	(+)	
39		**256**				95	93	(−)	
40		**255**	**249**		0:1:4	82	72	*R*	
41					0:1:1	84	81	*R*	
42			**250**		0:1:4	88	60	ND	
43					0:1:1	84	82	ND	
44			**246**			34	82	*R*	
45		**257**	**244**		0:30:100	62	86	*R*	116
46		**258**	**244**		1:20:100	NG	86	*R*	

[a] The ligands are as follows:



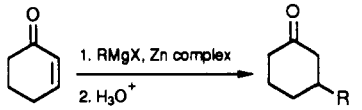
251 **252** **253** **254** **255** **256** **257** **258**

enone is tethered to the chiral tetracoordinated alkylzinc complex through the carbonyl oxygen (Figure 16). The Grignard reagent also becomes tethered to the zinc complex through the alkoxide oxygen. The enone and Grignard, having been brought into close proximity, react with transfer of the alkyl group to the β-position of the enone. The mechanism does not attempt to account for the stereochemical outcome of the reaction.

IV. Enantioselective Conjugate Addition of Organolithium Reagents to Prochiral α,β-Unsaturated Aldimines

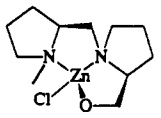
Tomioka, Shindo, and Koga have developed a protocol for ECA of organolithium compounds to α,β-unsaturated aldimines using enantiomerically pure C_2 symmetric diethers and a diamine to direct the ster-

Table 36. Enantioselective Conjugate Addition of Grignard Reagents to 2-Cyclohexenone Using Chiral Zinc Complexes

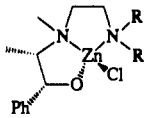


entry	catalyst[a]	R	X	note	% yield	% ee
1	**259**	*i*-Pr	Br		91	18
2	**260**				90	16
3					90	26
4					95	26
5	**259**	Et	Br		68	4
6		*n*-Bu			74	5
7		*i*-Pr	Cl		97	22
8			I		65	9
9		*n*-Bu	Cl		96	9
10			I		69	0
11	**260**	*i*-Pr	Cl		97	17
12			Br		92	26
13			I		49	3
14			Cl	0 °C	81	7
15	**262**			0 °C	75	7
16				−90 °C	97	17
17	**263**			LiO*t*-Bu	95	21
18				NaO*t*-Bu	89	11
19				KO*t*-Bu	93	17
20	**261**	*i*-Pr	Br		87	17
21	**264**				83	14
22	**265**		Cl		93	17
23	**266**				91	21
24	**267**				85	17
25	**159**				95	15
26	**160**				92	16
27	**128**				96	13
28	**129**				87	5
29	**268**				89	21
30	**269**				97	3
31	**270**				95	11
32	**152**				91	21
33	**271**				88	4
34	**272**				87	4
35	**273**				95	6
36	**274**				96	8
37	**275**				94	16
38	**276**				99	17
39	**277**				87	6
40	**278**				89	10

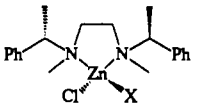
[a] Catalysts are as follows:



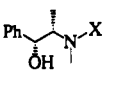
259



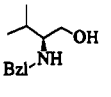
260 R = Me
261 R = Et



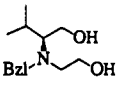
262 X = Cl
263 X = OBu^t



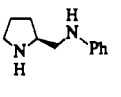
264 X = CH_2CH_2SMe
265 X = H



266

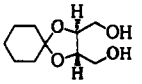


267

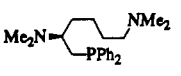


268

269



270



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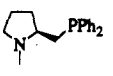
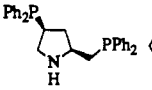
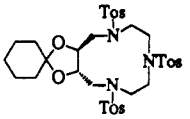


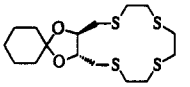
272



273



274



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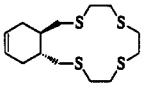

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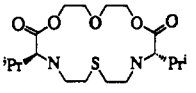
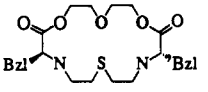


277



278

eochemical course of addition (Table 37).[124] The reaction does not occur readily in the absence of the chiral diethers or diamine. As shown, the reaction works well with both cyclic and acyclic aldimines.

The reaction is believed to occur by forming a lithium complex which includes the bidentate chiral ligand, the alkyl group and the aldimine via complexation with the nitrogen (Figure 17). Transfer of the R group to

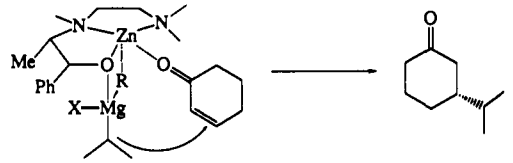
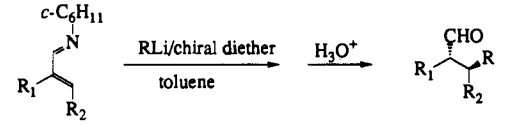


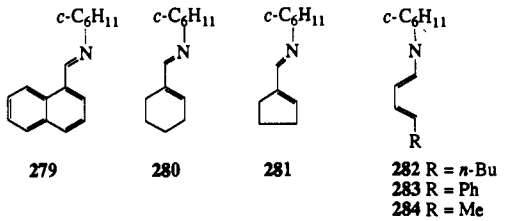
Figure 16. Mechanism of zinc-catalyzed conjugate addition of Grignard reagents.

Table 37. Enantioselective Conjugate Addition of Organolithium Reagents to α,β-Unsaturated Aldimines in the Presence of Chiral C_2 Symmetric Diethers



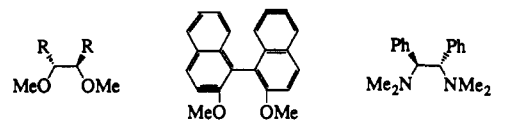
entry	imine[a]	R	chiral diether[b]	% yield	% ee	config
1	**279**	*n*-Bu	**285**	80	91	1*R*,2*S*
2			**286**	92	53	
3			**287**	46	6	
4			**288**	26	11	1*S*,2*R*
5		Ph	**285**	82	94	1*R*,2*S*
6			**286** (*S*,*S*)	68	90	1*S*,2*R*
7	**280**		**285**	61	96	1*S*,2*S*
8			**286** (*S*,*S*)	69	80	1*R*,2*R*
9	**281**		**285**	59	98	1*S*,2*S*
10			**286** (*S*,*S*)	76	90	1*R*,2*R*
11	**282**		**285**	58	>99	*S*
12			**286** (*S*,*S*)	45	93	*R*
13	**283**	*n*-Bu	**285**	40	82	*R*
14	**284**	Ph	**285**	48	>99	*S*
15			**286** (*S*,*S*)	42	94	*R*

[a]Imines are as follows:



279 **280** **281** **282** R = *n*-Bu; **283** R = Ph; **284** R = Me

[b]Chiral diethers are as follows:



285 R = Ph; **286** R = Me **287** **288**

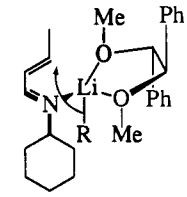


Figure 17.

the bottom face of the olefin yields, after hydrolysis, the product.

IV. Summary

Over the last 25 years, many approaches to the problem of asymmetric conjugate addition to α,β-unsaturated substrates have been investigated. A variety of very successful methods have been developed for diastereoselective conjugate addition to acyclic and cyclic scalemic α,β-unsaturated substrates. In a few instances, high enantioselectivities have been achieved in the conjugate addition of scalemic reagents with prochiral cyclic and acyclic α,β-unsaturated ketones. Good asymmetric induction has also been demonstrated with acyclic aldimines. The ideal reagent for asymmetric conjugate addition, of course, is a scalemic catalyst which promotes enantioselective conjugate addition of readily available organometallic reagents such as Grignard and organolithium reagents to a wide variety of cyclic and acyclic α,β-unsaturated substrates in high chemical yield and high enantioselectivity. The reagent capable of doing this has not yet been developed and remains an important challenge in synthetic organic reagent development.

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