Review

Asymmetric Synthesis of Tertiary Alcohols and #-Tertiary Amines via Cu-Catalyzed C#C Bond Formation to Ketones and Ketimines

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Asymmetric Synthesis of Tertiary Alcohols and α-Tertiary Amines via Cu-Catalyzed C−C Bond Formation to Ketones and Ketimines

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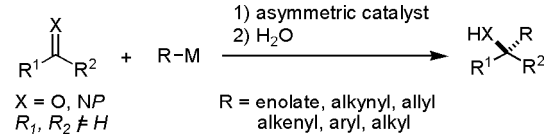
1. Introduction

Chiral tertiary alcohols and α-tertiary amines are important building blocks of naturally occurring and artificial biologically active molecules. Although there are catalytic asymmetric oxidation[1,2] and amination[3] reactions to access these chiral building blocks, the catalytic asymmetric addition of carbon nucleophiles to ketones and ketimines, which can simultaneously construct a carbon skeleton and tetrasubstituted stereogenic center, is synthetically more efficient (Scheme 1).[4] Realizing the catalytic asymmetric addition to ketones and ketimines (tetrasubstituted carbon synthesis), however, is generally more challenging than addition to aldehydes or aldimines (trisubstituted carbon synthesis) for two main reasons: (1) ketones and ketimines are significantly less reactive than aldehydes and aldimines; (2) enantio-face differentiation of ketones and ketimines is more difficult due to the smaller steric and electronic differences between the two substituents on prochiral carbons. Therefore, asymmetric catalysts that promote C−C bond-formation to ketones and ketimines should have high catalyst activity and enantioselectivity.

Scheme 1



Despite the potential difficulties, practical catalytic asymmetric methods that access enantiomerically enriched tertiary alcohols and α-tertiary amines are in high demand. The current most advanced catalytic asymmetric method, asymmetric hydrogenation, cannot be used to synthesize these chiral building blocks. The sequential racemization−optical resolution process, which could produce the desired enantiomer in high yield (>50%) and is frequently utilized in large-scale process synthesis, is also not applicable because racemization of the tetrasubstituted carbon is impossible. Enzymatic C−C bond-formation to ketones and ketimines is ineffective as well because the products are generally thermodynamically less stable than the starting materials. The development of catalytic asymmetric C−C bond-forming reactions to ketones and ketimines is a challenging frontier of the asymmetric catalysis field.[5–7]

In this review, Cu-catalyzed asymmetric tetrasubstituted carbon-forming reactions via the addition of carbon nucleophiles to ketones and ketimines are discussed, classified by the nucleophiles. Copper exists abundantly on earth and is utilized as a multifunctional element in organic synthesis. Copper can catalytically promote a wide variety of useful transformations by acting as a Lewis acid, activating nucleophiles via transmetalation or as a Brönsted base, mediating redox chemistry,[8] or as a component of carbene[9] or nitrene[10] complexes, depending on the reaction conditions. Historically, the first homogeneous asymmetric catalysis was copper-catalyzed cyclopropanation.[9a] The Lewis acidic character and nucleophile activation ability (transmetalation and deprotonation) of a copper catalyst have been utilized in asymmetric C−C bond-formation to ketones

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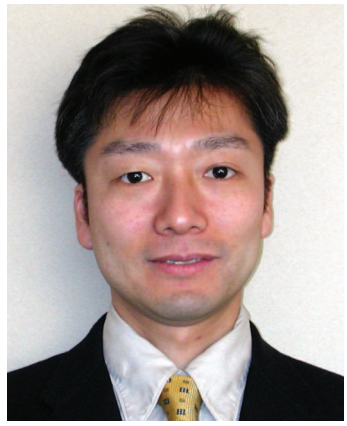
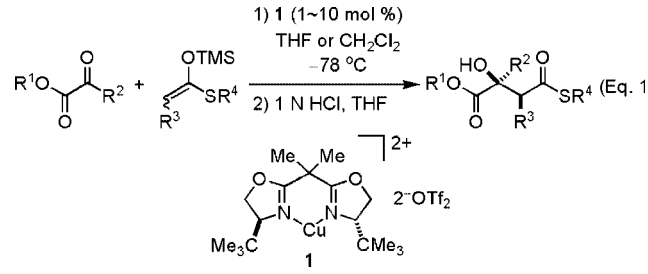
Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his Ph.D. from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido University before returning to the University of Tokyo as a professor in 1991. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young scientists (1981), Inoue Prize for Science (1994), Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), the Molecular Chirality Award (1999), the Naito Foundation Research Prize for 2001 (2002), ACS Award (Arthur C. Cope Senior Scholar Award; 2002), the National Prize of Purple Ribbon (2003), the Toray Science Award (2004), The Japan Academy Prize (2005), Takamine Memorial Sankyo Award, 2006 (Japan), The Rare Earth Society of Japan Award, 2006 (Japan), Centenary Medal and Lectureship (Royal Society of Chemistry), 2008, ACS Award: Creative Work in Synthetic Organic Chemistry, 2008, and Prelog Medal, 2008. Moreover, he has been selected as a Fellow of the Royal Society of Chemistry (1997) and a Honorary Fellow of Chemical Research Society of India in 2003. His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.



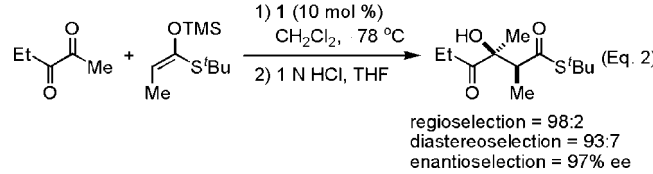
Motomu Kanai was born in 1967 in Tokyo, Japan, and received his Ph.D. from Osaka University in 1995 under the direction of Professor Kiyoshi Tomioka before doing postdoctoral studies with Professor Laura L. Kiessling at the University of Wisconsin. In 1997 he returned to Japan and joined Professor Shibasaki's group in the University of Tokyo as an assistant professor. He is currently an associate professor in Shibasaki's group. He has received The Pharmaceutical Society of Japan Award for Young Scientists (2001) and Merck-Banyu Lectureship Award (2005). His research interests entail design and synthesis of functional molecules.

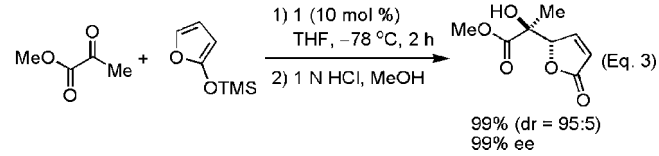
and ketimines. Lewis acidic cationic copper-catalyzed tetrasubstituted carbon-forming reactions generally produce excellent enantioselectivity, but substrates are restricted to

Table 1. Cu(II)−Box-Catalyzed Asymmetric Aldol Reaction between α-Keto Esters or 1,2-Diketone and Silyl Enolates Reported by Evans[11a,a]



entry	R^2	R^3	time	yield (%)	ee (%)
1[b]	Me	H	<24 h	96	99
2	Et	H	n.d.[h]	84	94
3[c]	^{i}Bu	H	< 24 h	94	94
4	^{i}Pr	H	n.d.[h]	36	36
5[d]	Me	(*Z*)-Me	8 h	96 (94:6)[g]	96
6[d,e]	Me	(*E*)-Me	1 d	90 (95:5)[g]	98
7[d]	Me	(*Z*)-^{i}Bu	1 d	88 (90:10)[g]	93
8[d,f]	Me	(*Z*)-^{i}Pr	12 h	80 (90:10)[g]	99





[a] Representative results (R^1 = Me, R^4 = ^{t}Bu, **1** = 10 mol %, solvent = THF) were selected from ref 11. [b] Loading of **1** = 1 mol %. [c] Loading of **1** = 2 mol %. [d] Solvent = CH_2Cl_2. [e] Reaction required 0.9 equiv of TMSOTf for completion. [f] Reaction temperature = −50 °C. [g] *syn*/*anti* ratio. [h] Not described.

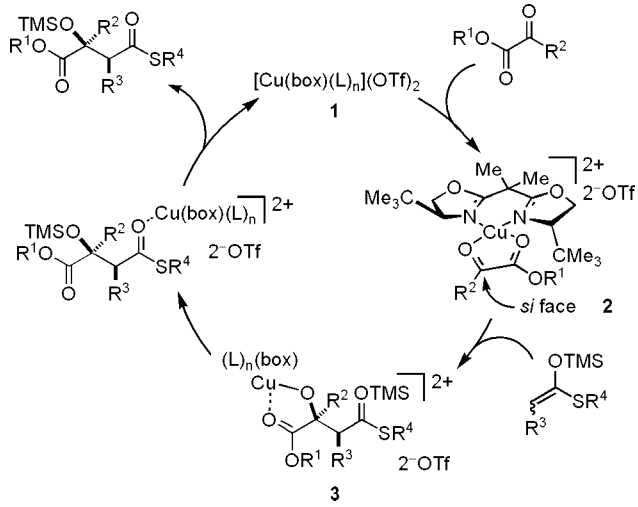
activated ketones, such as pyruvate esters. The excellent enantioselectivity is attributed to chelate coordination of the substrates to copper containing a well-defined geometry. On the other hand, catalytic asymmetric C−C bond formation to simple ketones and ketimines is promoted through activation of the nucleophile side via transmetalation. This mechanism is relatively new and has high potential.

2. Catalytic Asymmetric Aldol and Mannich-Type Reactions to Ketones and Ketimines: Addition of Enolates and Related Nucleophiles

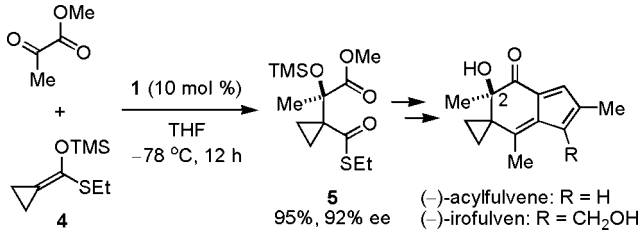
2.1. Chiral Lewis Acid Cu(II)-Catalyzed Aldol Reactions

The first example of a catalytic asymmetric aldol reaction of silyl enolates to pyruvate esters was reported by Evans and co-workers using cationic Cu(II)−box and pybox complexes.[11] The optimal catalyst was determined to be $Cu(OTf)_2$−^{t}Bu−box complex **1** (Table 1, eqs 1−3). The characteristics of this reaction were (1) a variety of alkyl groups were tolerated at the ester moiety of pyruvates (Table 1, eq 1, R^1); (2) high yield and enantioselectivity were

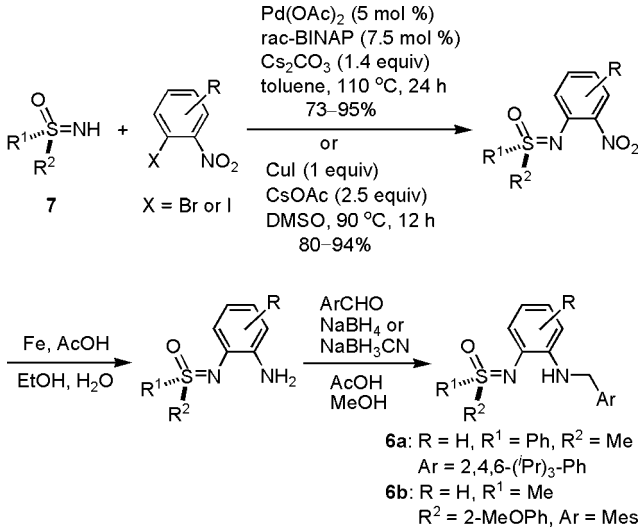
Scheme 2. Proposed Catalytic Cycle



Scheme 3. Movassaghi's Application of Evans' Method to Asymmetric Synthesis of Acylfulvene and Irofulven[13]

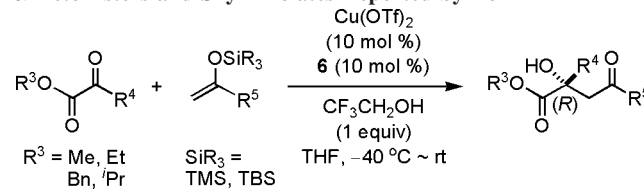


Scheme 4. Synthesis of Chiral Aminosulfoximine Ligands



obtained when the α-position of pyruvate ketone carbonyl was CH_2, whereas an α-branched substrate (R^2 = ^{i}Pr) produced less satisfactory results (entry 4); (3) various α-substituted silyl enolates can be used, producing *syn* isomers as the major product irrespective of the geometry of silyl enolates (entries 5−8); (4) addition of a stoichiometric amount of TMSOTf significantly accelerated the reaction (entry 6), suggesting that the silylation step of the intermediate copper tertiary alkoxide **3** (Scheme 2) was the catalyst turnover-limiting step; (5) vicinal diketones were competent substrates, giving the corresponding product with excellent regio-, diastereo-, and enantioselectivity (Table 1, eq 2); and (6) a lactone-derived silyl enolate can be used as a nucleophile, producing a densely functionalized product useful for natural product synthesis (Table 1, eq 3).

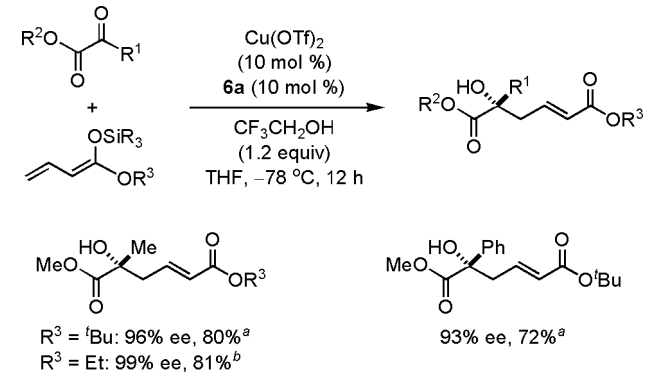
Table 2. Cu(II)-Catalyzed Asymmetric Aldol Reaction between α-Keto Esters and Silyl Enolates Reported by Bolm[16]



entry	R^4	R^5	time (h)	yield (%)	ee (%)
1[a]	Me	Ph	15	89	98
2[a]	$(CH_2)_2Ph$	Ph	40	86	96
3[a]	Et	Ph	20	78	89
4[a]	Me	Me	46	71	91
5[b]	Me	S^{t}Bu	6	76	91
6[b]	$(CH_2)_2Ph$	S^{t}Bu	6	58	91
7[b]	Et	S^{t}Bu	6	76	93

[a] **6a** was used as a chiral ligand. (*R*)-Products (shown in the reaction scheme) were obtained. [b] **6b** was used as a chiral ligand. (*S*)-Products (the opposite configuration to that shown in the reaction scheme) were obtained.

Scheme 5. Cu(II)-Catalyzed Asymmetric Vinylogous Aldol Reaction between α-Keto Esters and Silyl Dienolates Reported by Bolm[20a]



[a] (a) Using *t*-butyldimethylsilyl enolate; (b) using trimethylsilyl enolate.

A probable catalytic cycle was proposed as shown in Scheme 2. In Cu(II)−box catalysis, substrate chelation ability is necessary for high reactivity and enantioselectivity.[12] Based on X-ray crystallographic studies, molecular modeling, and EPR data, copper atoms chelated by the substrate had a distorted square planar structure (**2**). Addition of silyl enolate to the activated pyruvate proceeded from the *si*-face (the downside), opposing the steric bulkiness (^{t}Bu group) of the box ligand. A linear transition state was proposed based on the experimental finding that the *syn*-diastereomer was the major product, irrespective of enolate geometry (Table 1, entries 5−8). This transition state model can explain the product stereochemistry (enantio- and diastereoselectivity). Subsequent *O*-silylation of copper tertiary alkoxide intermediate **3** was the catalyst turnover-limiting step. Crossover experiments using two distinct silyl enolates indicated that this silicon transfer is an intermolecular process. Therefore, the addition of a stoichiometric amount of TMSOTf effectively accelerated the reaction (e.g., Table 1, entry 6). TMSOTf is an extremely powerful Lewis acid but did not promote a background reaction independent of the asymmetric catalyst. As a result, the enantioselectivity was not affected by the presence of TMSOTf.

Movassaghi applied this synthetic method to the enantioselective total synthesis of (−)-acylfulvene and (−)-

irofulven, highly cytotoxic antitumor drug candidates (Scheme 3).[13] Methyl pyruvate and highly strained silyl enolate **4** were coupled under Evans' conditions, giving the desired tertiary alcohol **5** in 95% yield with 92% ee. The produced tetrasubstituted carbon corresponded to the C-2 of the target molecules.

Steric tuning of the box ligand[14] or introduction of a perfluoroalkyl group to the ligand to facilitate catalyst recovery[15] was studied in Cu(II)-catalyzed asymmetric aldol reactions of α-keto esters. The efficiency of those catalysts, however, did not exceed that of the original catalyst reported by Evans.

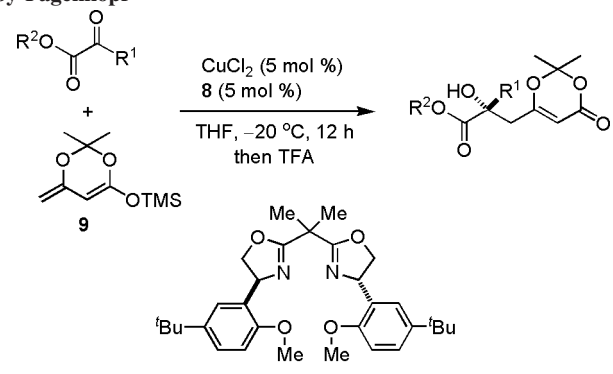
Bolm et al. developed chiral C_1-symmetric aminosulfoximine ligands **6** for Cu(II)-catalyzed asymmetric aldol reactions of α-keto esters.[16] A series of chiral ligands was modularly synthesized from **7**[17] in three steps, using Buchwald−Hartwig amination or copper mediated cross coupling followed by reductive amination as key steps (Scheme 4). Structures of the sulfoximine moiety, the core aryl moiety, and the *N*-substituent were independently optimized. The optimal chiral ligands were identified as **6a** for reactions using ketone-derived silyl enolates and **6b** for those using thioester-derived silyl enolates. Addition of 1 equiv of CF_3CH_2OH significantly accelerated the reaction rate,[18] which allowed for improving the enantioselectivity by conducting the reaction at lower temperature. Under the optimized conditions, excellent enantioselectivity was produced from linear alkyl-substituted pyruvate derivatives (Table 2). Results using α-substituted enolates, which produced unsatisfactory results in Evans' reaction, are not described.

This reaction was extended to a catalytic enantioselective vinylogous aldol reaction[19] of α-keto esters (Scheme 5).[20] Chiral ligand **6a** was identified as the optimal ligand in this case. Phenyl- and methyl-substituted keto esters afforded excellent enantioselectivity.

A substituted aryl−box **8**−$CuCl_2$ complex is an efficient asymmetric catalyst of vinylogous aldol reactions between α-keto esters and silyl dienolate **9** (Table 3).[21] The substituent effects of the aromatic rings of **8** on enantioselectivity and catalyst activity were significant: the product derived from methyl pyruvate was obtained in 35% yield and 40% ee using $CuCl_2$−Ph−box, and in 85% yield and 92% ee using $CuCl_2$−**8**. The absolute configuration of the products was consistent with Evans' model **2**.

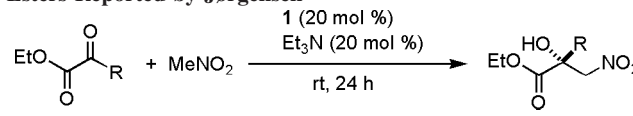
The above reactions utilized preactivated nucleophiles (silicon enolates). Catalytic asymmetric C−C bond-formation mediated by in situ nucleophile generation from stable organic molecules, however, is more favorable in terms of total efficiency and atom economy.[22] The nitroaldol reaction is an excellent template for this type of reaction development.[23] Due to the relatively high acidity of nitroalkanes (pK_a of α-proton ∼ 17), chemoselective deprotonation of nitroalkanes to form an active nucleophile (nitronates) is possible in the presence of electrophiles [aldehydes (pK_a of α-proton ∼ 23), ketones, imines, etc.]. Jørgensen reported a catalytic enantioselective nitroaldol reaction of α-keto esters using a combination catalyst of a $Cu(OTf)_2$−^{t}Bu−box complex (20 mol %) and Et_3N (20 mol %; Table 4).[24] Nitromethane was used as a prenucleophile as well as the solvent. Use of $Cu(OTf)_2$ as a Lewis acid, Et_3N as a Brønsted base, and the 1:1 ratio of Cu and Et_3N were all critical for the excellent yield and enantioselectivity of the products. For example, use of $Cu(OTf)_2$ (20 mol %)−Et_3N (10 mol %) and $Cu(OTf)_2$ (20 mol %)−Et_3N (30 mol %) afforded the product in only 11% yield with 49% ee and >95% yield with 26% ee, respectively (vs > 95% yield and 92% ee under the optimized conditions described in Table 4, entry 1). An exact ratio of these catalytic components was required because both

Table 3. Cu(II)-Catalyzed Asymmetric Vinylogous Aldol Reaction between α-Keto Esters and Silyl Dienolates Reported by Pagenkopf[21]



entry	R^1	R^2	yield (%)	ee (%)
1	Me	Me	81	94
2	Ph	Me	91	96
3	4-$MeOC_6H_4$	Et	82	93
4	4-MeC_6H_4	Et	75	94
5	4-IC_6H_4	Et	90	98
6	4-$CF_3C_6H_4$	Et	74	84
7	4-$NO_2C_6H_4$	Et	77	80
8	*n*-C_6H_{13}	Et	85	96
9	*i*-Pr	Et	75	91
10	(*E*)-PhCH=CH	Et	81	91
11	2-benzophenone	Et	78	81

Table 4. Catalytic Asymmetric Nitroaldol Reaction of α-Keto Esters Reported by Jørgensen[24]



entry	R	yield (%)	ee (%)
1	Me	95	92
2[a]	Et	73	87
3[a]	$(CH_2)_2Ph$	47	77
4	hexyl	91	93
5	but-3-enyl	97	94
6	pent-4-enyl	92	94
7	3-methylbutyl	90	94
8	*i*-Bu	99	92
9	Ph	81	86
10	*p*-ClC_6H_4	91	88
11	*p*-$NO_2C_6H_4$	99	93
12	*p*-$MeOC_6H_4$	68	57

[a] At 50 °C for 48 h.

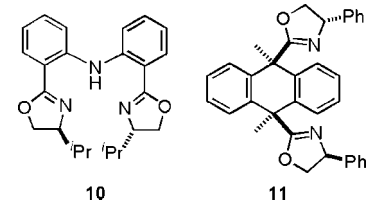
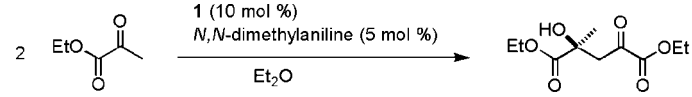
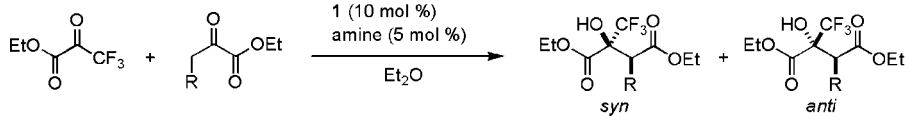


Figure 1. Modified box ligands for catalytic enantioselective nitroaldol reaction of α-keto esters.

Table 5. Catalytic Asymmetric Direct Aldol Reaction of α-Keto Esters[28]

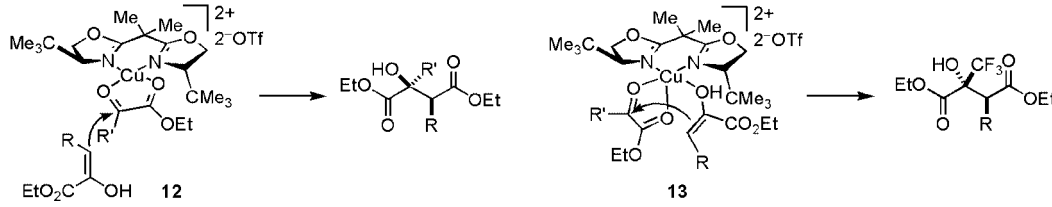


(Eq. 1)



(Eq. 2)

entry	R	amine	temp. (°C)	time (h)	yield (%)	*syn*:*anti*	ee (%)
1 (Eq. 1)	H	*N*,*N*-dimethylaniline	r.t	40	>80	...	96
2 (Eq. 2)	H	–	r.t	n.d.	>80	–	42
3 (Eq. 2)	Me	*N*,*N*-dimethyl-*p*-toluidine	−15	48	40	1:1.8	89/92
4 (Eq. 2)	CH_2–*c*-C_6H_{11}	*N*,*N*-dimethyl-*p*-toluidine	−15	72	32	1:1.2	68/84
5 (Eq. 2)	$CH_2CH_2CH{=}CH_2$	*N*,*N*-dimethyl-*p*-toluidine	−24	144	52	1:1.4	85/96
6 (Eq. 2)	*n*-C_5H_{11}	*N*,*N*-dimethyl-*p*-toluidine	−15	120	28	1:1.2	92/91
7 (Eq. 2)	*i*-Bu	*N*,*N*-dimethyl-*p*-toluidine	−15	74	66	1:1.2	62/75



the inactive acid [$Cu(OTf)_2$]/base (Et_3N) complex formation and the racemic background reaction catalyzed by the amine should be minimized. Copper nitronate generated in situ via deprotonation of nitromethane with Et_3N was proposed to be the active nucleophile.

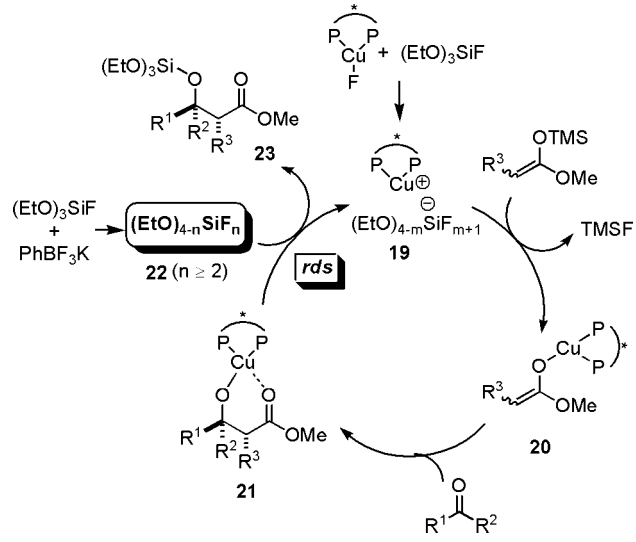
Modification of the box ligand was attempted (**10**[25] and **11**;[26] Figure 1) in the nitroaldol reaction of α-keto esters. Complexes of **10** and **11** with $Cu(OTf)_2$ were used as asymmetric catalysts in the presence of Et_3N. The enantioselectivity and substrate generality, however, did not exceed those of Jørgensen's reaction.

When ketones or ester equivalents are used as a prenucleophile, a direct catalytic asymmetric aldol reaction is possible.[27] Gathergood and Jørgensen's group developed a direct catalytic asymmetric aldol reaction of pyruvates.[28] In a homoaldol reaction of ethyl pyruvate, the optimum result (>80% conversion and 96% ee) was obtained using a combination of 10 mol % of the $Cu(OTf)_2$−^{t}Bu−box complex (**1**) and 5 mol % of *N*,*N*-dimethylaniline (Table 5, entry 1). In a cross-aldol reaction, highly electrophilic trifluoropyruvate was used as an acceptor ketone. Whereas less satisfactory enantioselectivity (42% ee) was produced when using ethyl pyruvate as the prenucleophile (Table 5, entry 2), products with excellent enantioselectivity were obtained using α-substituted pyruvates (Table 5, entries 3−7). The low diastereoselectivity was due to the low face-selectivity at the acceptor (trifluoropyruvate) side, resulting in low stereoselectivity at the tetrasubstituted carbon of the products. Two competing transition states, **12** and **13**, giving (*S*)- and (*R*)-tetrasubstituted carbons, respectively, were proposed.

2.2. Chiral Cu(I)-Catalyzed Aldol Reactions

A chiral Cu(I)F-catalyzed aldol reaction of silicon dienolate to aldehydes was first reported by Carreira.[29] Spectroscopic studies revealed that the active nucleophile of this

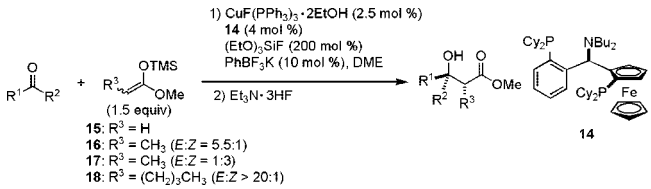
Scheme 6. Plausible Catalytic Cycle of CuF-Catalyzed Asymmetric Aldol of Ketones[31b]



reaction was the corresponding copper dienolate, which was generated via transmetalation. Our group developed a general aldol reaction of ketones and silicon enolates using the CuF·3Ph_3P·2EtOH catalyst.[30] The reaction proceeded under neutral and mild conditions. The addition of a stoichiometric amount of $(EtO)_3SiF$ was key to the success of the reaction. This reaction also proceeded via copper enolates. Based on kinetic studies, catalyst regeneration from the intermediate copper tertiary aldolate (**21** in Scheme 6), generated after addition of a copper enolate to a ketone, was the rate-determining step. Facilitation of this step by the electrophilic silicon additive [$(EtO)_3SiF$ in the racemic reaction] was critical for high product yield.

This reaction was a platform for developing a general catalytic asymmetric aldol reaction of unactivated ketones

Table 6. Catalytic Asymmetric Aldol Reaction of Simple Ketones[31b]



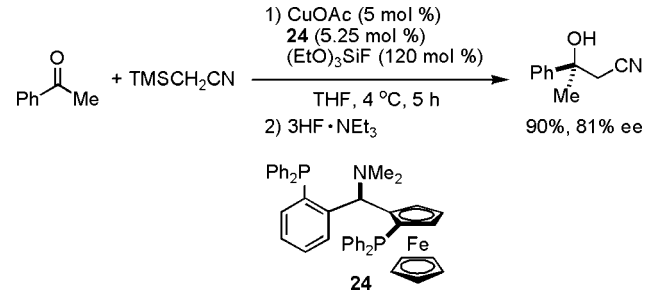
entry	ketone	enolate	product	temp. (°C)	time (h)	yield (%) [dr]	ee (%)
1	R = H	15		−20	19	93	92
2	R = OMe	15		−20	42	95	91
3	R = Cl	15		20	38	85	87
4		15		−20	19	92	90
5		15		−20	40	88	83
6[a]		15		−20	42	92	90
7		15		−20	42	73	84
8[b]		15		rt	37	93	79
9		16		rt	37	96 [80/20]	91/75
10		17		rt	62	58 [86/14]	94/78
11		18		rt	35	97 [81/19]	91/82
12[b]		15		rt	17	89	78

[a] 5 mol % of CuF and 8 mol % of **14** were used. [b] 20 mol % of $PhBF_3K$ was used.

(Table 6).[31,32] Taniaphos[33] derivative **14**, which constructs a deep chiral environment around Cu by coordination, was the optimum ligand for the enantioselectivity. The activity of the CuF−**14** complex, however, was significantly decreased compared to the platform racemic reaction using the CuF·3Ph$_3$P·2EtOH catalyst, possibly due to steric hindrance around the Cu catalytic center. To facilitate the reaction, further acceleration of the rate-determining catalyst regeneration step was examined using a stronger trapping reagent. The optimized additives were a combination of a stoichiometric amount of $(EtO)_3SiF$ and a catalytic amount of $PhBF_3K$. These additives generated polyfluorinated silicon species **22** [$(EtO)_{4-n}SiF_n$: $n > 2$] in the reaction mixture (determined by NMR studies), which functioned as powerful trapping reagents of the copper aldolate **21**. High product yield and enantioselectivity were obtained from both aromatic and aliphatic ketones. Moreover, diastereo- and enantioselective aldol reaction of ketones was possible. The *anti*-isomer was the major product irrespective of the geometry of the silyl enolate (Table 6, entries 9−11). This result can be rationalized by considering that the aldol addition to ketones proceeded after rapid *E*/*Z* isomerization of copper enolate **20** to the more stable (*E*)-enolate and through a chair six-membered Zimmerman−Traxler transition state[34] (see discussion in section 4.2 for more details).

The catalytic cycle was proposed as shown in Scheme 6. Because CuF has the mismatched characteristics of soft metal and hard anion conjugation,[35] it rapidly transferred hard fluoride onto $(EtO)_3SiF$ to generate the ate complex **19**. Transmetalation occurred between **19** and silyl enolate, and highly nucleophilic copper enolate **20** was generated. Aldol addition of **20** to a ketone substrate afforded copper aldolate **21**. This step was fast and did not significantly impact the total reaction kinetics. Trapping **21** with silicon is key for promoting the catalytic cycle. If this process is not efficient,

Scheme 7. Catalytic Enantioselective Cyanoalkylation of Acetophenone[36,37]



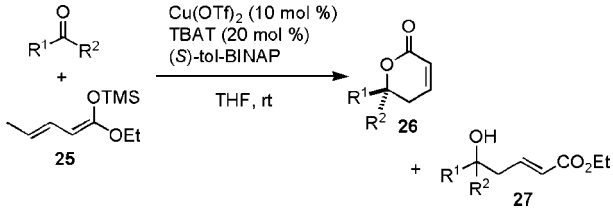
side reactions such as retroaldol reaction and/or base (copper alkoxide **21**)-catalyzed reactions could proceed. In the presence of the combined additive [$(EtO)_3SiF$ + $PhBF_3K$], highly electrophilic **22** smoothly trapped **21**, and the active catalyst **19** was efficiently regenerated with liberation of the silicon-trapped aldol product **23**.

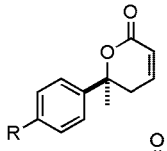
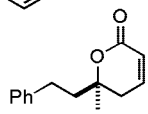
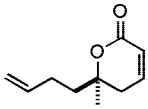
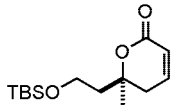
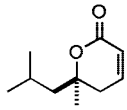
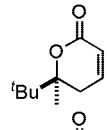
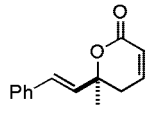
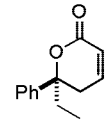
This finding was extended to a catalytic enantioselective cyanoalkylation of ketones using $TMSCH_2CN$ as the nucleophile (Scheme 7).[36] The chiral CuOAc or CuF catalyst activated $TMSCH_2CN$ through transmetalation. Interaction of soft copper with the soft nitrile of $TMSCH_2CN$ to polarize the relatively stable C−Si bond was essential for this transmetalation. Indeed, no reaction proceeded when $TMSCH_2CO_2{}^tBu$ was used as the nucleophile. The maximum enantiomeric excess was 81% using Taniaphos **24** as the chiral ligand.[37]

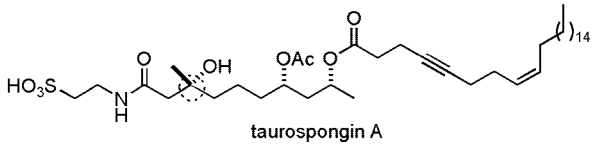
Campagne's group developed a catalytic enantioselective vinylogous aldol reaction of silyl dienolate **25** to ketones, forming δ,δ-disubstituted lactones **26** (Table 7).[38] A CuF−tol-BINAP complex, generated in situ from $Cu(OTf)_2$ and TBAT (tetrabutylammonium difluorotriphenylsilicate), was used as the catalyst. The addition of an electrophilic silicon species [such as $(EtO)_3SiF$], which was an essential additive for the aldol reaction of silyl enolate to ketones,[30,31,36] was not necessary in the vinylogous aldol reaction. This fact suggests that silyl dienolate is more susceptible to transmetalation than is simple silyl enolate. There were two distinct reaction pathways, one producing lactone **26** and the other producing linear aldol product **27**. Whereas **26** was obtained with high enantioselectivity, **27** was almost racemic (<10% ee); therefore, **27** cannot be a precursor of **26**. The ratio of these two products depended on the substrate ketones. For example, linear **27** was the major product when *p*-nitroacetophenone was used as a substrate (entry 4). Aliphatic ketones are competent substrates for this reaction. Catalytic asymmetric synthesis of taurospongin A was achieved using this methodology (the reaction shown in entry 7) to construct a tetrasubstituted stereogenic carbon.

The above two reports demonstrated that copper enolates are sufficiently nucleophilic to facilitate the addition to ketones once they are generated. Conjugate addition of copper-based nucleophiles (such as alkylcopper and copper hydride) to α,β-unsaturated carbonyl compounds is an alternative method for copper enolate formation [Scheme 8 (2)]. Preactivation of the nucleophile as silyl enolates, which was required in the previous transmetalation strategy for Cu enolate generation [Scheme 8 (1)], is not necessary. When this alternative Cu enolate generation method was applied to an aldol reaction of ketones, the reaction mixture contained three substrates, that is, the triggering nucleophile for conjugate addition, an α,β-unsaturated carbonyl compound (conjugate addition acceptor), and a ketone. In this multi-

Table 7. Catalytic Asymmetric Vinylogous Aldol Reaction of Ketones[38]



entry	product		26 yield (%)	26 ee (%)
1		R = H	71	80
2		R = MeO	39	59
3		R = Br	58	81
4		R = NO_2	19	75
5			70	87
6			81	90
7			72	88
8			40	93
9			39	92
10			17	24
11			73	60[a]



taurospongin A

[a] BINAP was used instead of tol-BINAP.

component reaction, the asymmetric catalyst should promote the reaction in a highly ordered manner. Conjugate addition of the triggering nucleophile to an α,β-unsaturated carbonyl compound should proceed preferably to the 1,2-addition to ketones. The copper enolate, generated through conjugate addition, should chemoselectively react with ketones in the presence of the conjugate addition acceptor.

This advanced strategy for catalytic asymmetric aldol reaction to ketones was first realized in a reductive intramolecular aldol reaction reported by Lam (Table 8).[39,40] From a $Cu(OAc)_2$−chiral bisphosphine [SEGPHOS (**28**)[41] or 3,5-xylyl-methoxy-BIPHEP (**29**)[42]] complex and 1,1,3,3-tetramethylhydrosiloxane (TMDS), chiral copper(I) hydride species **32** was generated through transmetalation (Scheme

Scheme 8. Two Strategies for Copper Enolate Generation

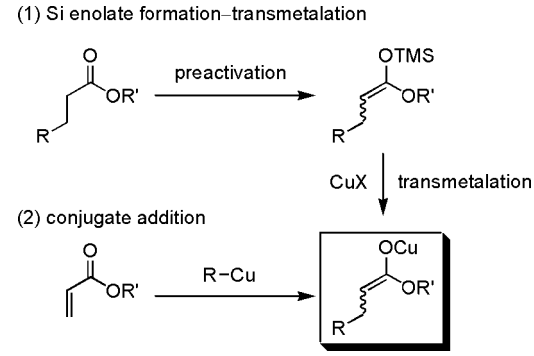
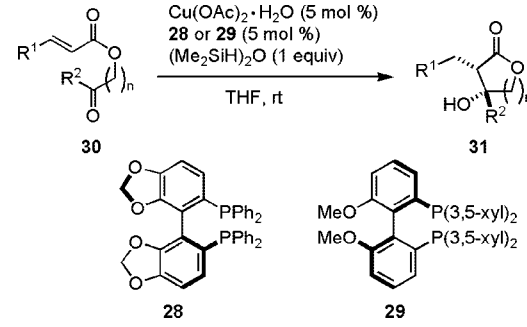


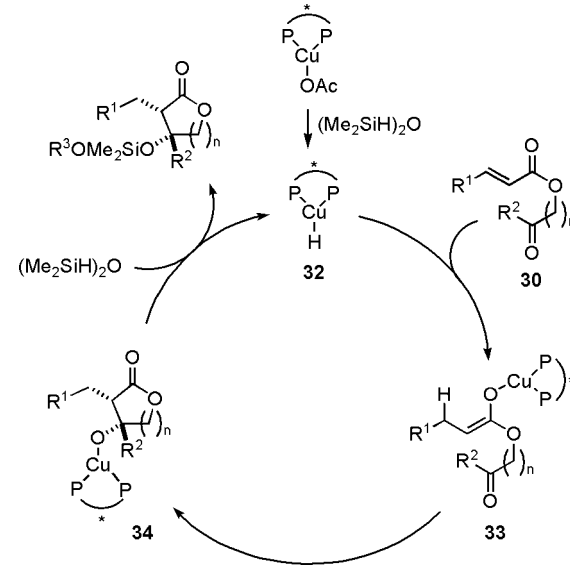
Table 8. Catalytic Asymmetric Reductive Intramolecular Aldol Reaction of Ketones[39]



entry	substrate	ligand	yield (%)	ee (%)
1	R^1 = Ph, R^2 = Me, n = 2	**28**	62	74
2	R^1 = 4-ClC_6H_4, R^2 = Me, n = 2	**29**	71	83[a]
3	R^1 = 4-ClC_6H_4, R^2 = Me, n = 2	**28**	73	82
4	R^1 = $PhCH_2CH_2$, R^2 = Me, n = 2	**28**	68	80
5	R^1 = $PhCH_2CH_2$, R^2 = Ph, n = 1	**29**	51	49[a]

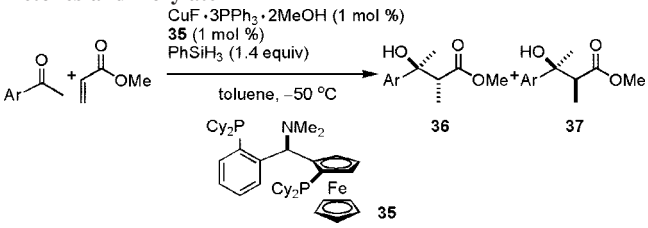
[a] The enantiomer of the depicted structure was obtained.

Scheme 9. Proposed Catalytic Cycle of Lam's Reductive Aldol Reaction of Ketones



9). This species then chemoselectively adds to the α,β-unsaturated ester moiety of substrate **30**,[43] generating copper enolate **33**. Intramolecular aldol reaction of the copper enolate to the ketone moiety produced intermediate lactone **34** containing contiguous tri- and tetrasubstituted stereogenic centers. Copper hydride **32** was regenerated through silylation

Table 9. Catalytic Asymmetric Reductive Aldol Reaction of Ketones and Acrylate[44]



entry	Ar	time (h)	yield (%)	36:37	ee of 36 (%)	ee of 37 (%)
1	Ph	1	98	92:8	95	72
2	*p*-F-C_6H_4	1	88	91:9	92	73
3	*p*-CF_3-C_6H_4	1	87	80:20	83	72
4	*p*-MeO-C_6H_4	1	31	92:8	90	56
5	*p*-Cl-C_6H_4	1	95	86:14	90	77
6	*m*-Cl-C_6H_4	1	70	88:12	82	n.d.
7[a]	2-thienyl	2	94	96:4	90	15
8	3-thienyl	2	95	95:5	95	65

[a] 3 mol % of catalyst was used.

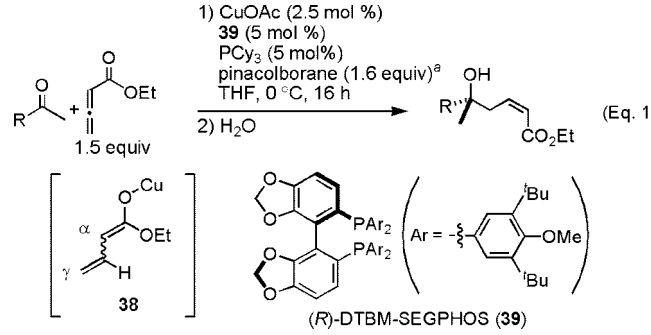
of the intermediate copper alkoxide **34** with TMDS. Although diastereoselectivity was high, enantiomeric excess was up to 83% ee.

A more general three-component catalytic asymmetric reductive aldol reaction of ketones was developed independently by Riant's group and our group. Riant's group utilized the CuF•3PPh_3•2MeOH−Taniaphos **35** complex as a catalyst, $PhSiH_3$ as a triggering nucleophile, and methyl acrylate as an acceptor for conjugate addition.[44] Excellent enantioselectivity as well as diastereoselectivity were produced from aromatic ketones (Table 9). The reactivity was also noteworthy, and the reaction was completed within 2 h at −50 °C using 1 mol % of catalyst.

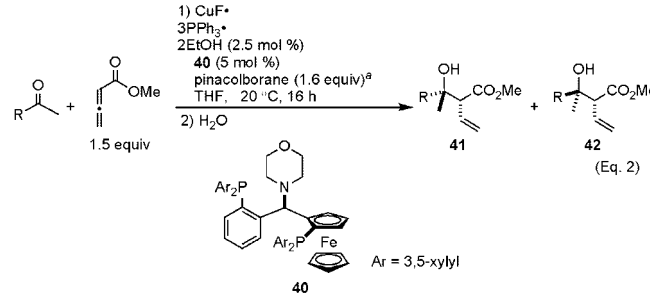
Our group developed a catalytic asymmetric reductive aldol reaction of ketones and allenic esters using pinacolborane as the triggering reducing reagent.[45] If silanes such as $(EtO)_3SiH$ were used instead of pinacolborane, the reaction was very sluggish. Copper dienolate **38**, containing two possible nucleophilic centers (α- and γ-carbon), was generated after conjugate reduction.[19] The reaction site of the copper dienolate can be switched depending on the reaction conditions. When the CuOAc−DTBM−SEGPHOS (**39**)[41] complex was used as the catalyst in the presence of Cy_3P, the γ-aldol products with *cis* olefin configuration were obtained with excellent enantioselectivity and substrate generality, including aliphatic ketones (Table 10, eq 1). On the other hand, α-aldol products were obtained as the major product with high diastereoselectivity when using CuF•3PPh_3•2EtOH-Taniaphos (**40**) as the catalyst (Table 10, eq 2). This α-selective reductive aldol reaction proceeded with moderate to high enantioselectivity from aromatic ketones. The mechanism underlying the reaction pathway switch was not clear.

An alkylative aldol reaction of ketones is possible when copper-catalyzed conjugate addition of alkyl groups is utilized as the copper enolate-forming step. In this reaction, the structural diversity of the products was significantly increased compared to the reductive variant. Although catalytic asymmetric alkylative aldol reactions of aldehydes using Rh or Cu catalysts have been reported,[46] there were no examples targeting ketones reported prior to our work in 2007.[47] We developed an asymmetric alkylative aldol reaction of ketones using Cu-DIFLUORPHOS (**44**)[48] as the catalyst and dialkylzinc as the triggering nucleophile (Table

Table 10. Catalytic Asymmetric Reductive Aldol Reaction of Ketones and Allenic Esters[45]



entry	ketone (R)	γ/α ratio	yield/%	ee/%
1	phenyl	25/1	96	99
2	*p*-Cl-C_6H_4	13/1	93	98
3	*p*-Me-C_6H_4	9/1	90	97
4	*m*-Cl-C_6H_4	9/1	90	99
5[b]	cinnamyl	30/1	97	84
6[b]	phenylethyl	3/1	70	96
7	homoallyl	>8/1	86	89
8	*n*-butyl	>6/1	86	88
9[c]	isopropyl	>8/1	80	98



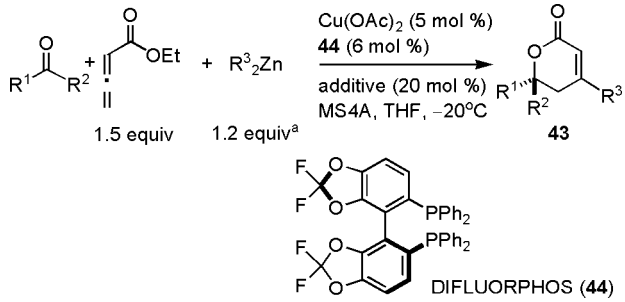
entry	ketone (R)	41/42	41	
			yield/%	ee/%
1	phenyl	10/1	90	84
2	*p*-Cl-C_6H_4	8/1	89	83
3	*m*-Cl-C_6H_4	8/1	89	82
4	*p*-I-C_6H_4	7/1	86	84
5	2-naphthyl	10/1	91	84
6	cinnamyl	9/1	87	67

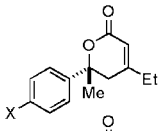
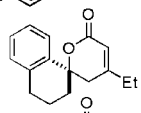
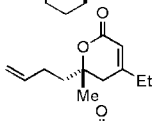
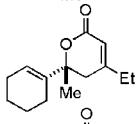
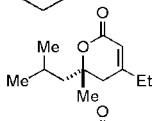
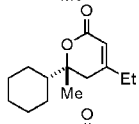
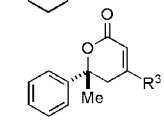
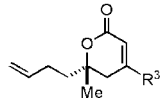
[a] Slow addition over 4 h. [b] Temperature = −20 °C. [c] 5 mol % of catalyst was used.

11). $Cu(OAc)_2$ was used as a copper source, which should be reduced to Cu(I) under the reaction conditions. Enantiomerically enriched δ-lactones **43** were produced with excellent selectivity and generality, including aliphatic ketones. A hard Lewis basic additive, such as sulfoxides or HMPA, was the key to controlling the reaction site-selectivity (α- or γ-addition) of the intermediate copper dienolate.

The catalyst cycle was proposed as shown in Scheme 10. Conjugate addition of alkylcopper **46**, generated via transmetalation from Zn to Cu, to allenic ester afforded copper enolates **47** and **48**. The α-aldol pathway was kinetically favored, producing **45**. The additive Lewis base coordinated to Zn of **45**, thus polarizing the Zn−O bond and facilitating the retroaldol reaction (**45** to **47** and **48**). Although the γ-aldol reaction pathway was kinetically less favorable than the α-aldol pathway, intermediate Zn γ-aldolate **49** was able to cyclize to give stable lactone **43**. The catalyst turned over to **46** through ligand exchange between the resulting copper ethoxide **50** and dialkylzinc. The conversion of **45** to **43** was not efficient in the absence of the additive Lewis base. The additive can be considered to function as a proofreader of the reaction pathway.

Table 11. Catalytic Asymmetric Alkylative Aldol Reaction of Ketones and Allenic Esters[47]



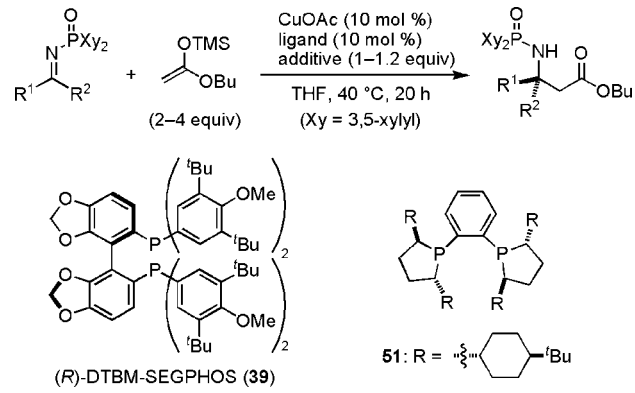
entry	product		additive	temp./°C	time/h	yield/%	ee/%
1		X = H	DMSO	−20	15	92	96
2		X = Br	HMPA	20	14	91	94
3		X = OMe	HMPA	20	14	73	95
4			HMPA	−20	14	93	92
5			Ph_2S=O	−20	14	95	87
6[b,c]			DMSO	10	14	79	98
7[b,c]			DMSO	−10	15	76	96
8			DMSO	20	42	67	94
9		R^3 = Me	DMSO	−30→−10	19+24	89	94
10		R^3 = ^{i}Pr	Ph_2S=O	−20→−10	10+12	78	84
11[b,c]		R^3 = ^{n}Bu	Ph_2S=O	10	14	73	92
12[c]		R^3 = Me	DMSO	−20→−10	17+24	61	86
13[b,c]		R^3 = ^{i}Pr	DMSO	0	48	50	78
14[b,c]		R^3 = ^{n}Bu	Ph_2S=O	−20→−10	17+24	80	88

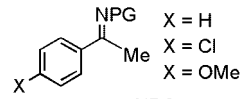
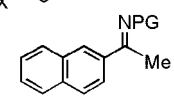
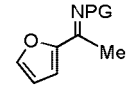
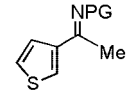
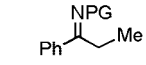
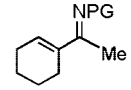
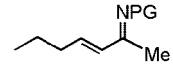
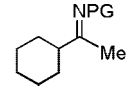
[a] Slow addition over 1.5 h. [b] 10 mol % of Cu, 12 mol % of ligand, and 1.6 equiv of dialkylzinc were used. [c] CuTC was used instead of $Cu(OAc)_2$.

2.3. Chiral Cu(I)-Catalyzed Mannich-Type Reaction of Ketimines

The catalytic asymmetric Mannich-type reaction (addition of enolate to imines) is fundamental for the synthesis of nitrogen-containing versatile chiral building blocks.[49] The substrate scope of this method was limited to aldimines and iminoesters[50] before our contribution in 2007.[51] We extended the Cu(I)-catalyzed activation of silyl enolates, which was previously developed in the catalytic asymmetric aldol reaction of ketones,[31] to the Mannich reaction of ketimines. The optimized conditions for aromatic ketimines utilized the CuOAc−DTBM−SEGPHOS (**39**) complex as a catalyst and $(EtO)_2Si(OAc)_2$ as a trapping reagent of the intermediate copper amide generated after the addition of the copper enolate to ketimines (Table 12, entries 1−7). These conditions were not effective for aliphatic ketimines. For aliphatic ketimines, use of sterically modified DUPHOS (**51**) as a ligand and $(EtO)_3SiF$ as a trapping reagent produced moderate to high enantioselectivity (entries 8−10). The nucleophile was limited to acetate, and α-substituted enolates did not react with ketimines even under optimized conditions. The Mannich products were converted to enantiomerically enriched β,β-disubstituted amino acids in high yield through acid and base hydrolysis.

Table 12. Catalytic Asymmetric Mannich-Type Reaction of Ketimines[51]



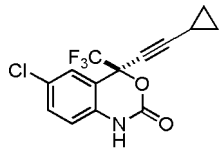
entry	substrate		conditions[a]	yield (%)	ee (%)
1		X = H	A	81	95
2		X = Cl	A	82	97
3		X = OMe	A	87	97
4			A	74	96
5			A	74	96
6			A	92	97
7			A	61	91
8			B	99	81
9			B	65	77
10			B	45	80

[a] Condition A: ligand = **39**, additive = $(EtO)_2Si(OAc)_2$ (1 equiv). Condition B: ligand = **51**, additive = $(EtO)_3SiF$ (1.2 equiv).

3. Catalytic Enantioselective Alkynylation of Ketones

Chiral tertiary propargylic alcohols are important pharmaceutical intermediates. One of the most structurally attractive pharmaceuticals containing such a chiral building block is Merck's anti-HIV drug Efavirenz (**52**; Figure 2).[52] The large-scale synthesis of **52** currently relies on an enantioselective addition of a lithium alkynide to a ketone using a stoichiometric amount of a norephedrine-derived chiral ligand.[53] Although the ligand is recovered and recycled efficiently, the development of a catalytic asymmetric variant with

comparable enantioselectivity is desirable. Such a reaction, however, has yet to be developed.

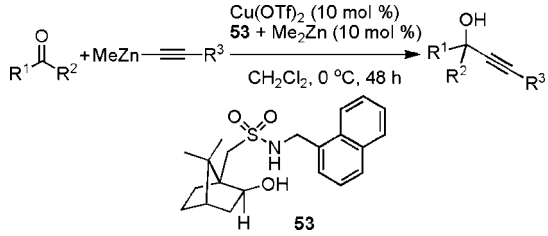


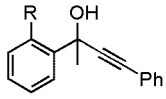
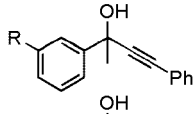
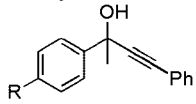
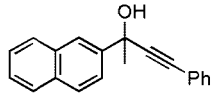
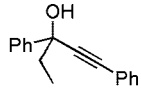
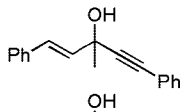
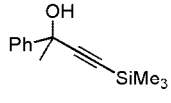
Efavirenz (**52**)

Figure 2.

Catalytic enantioselective alkynylation of ketones can be classified into two categories: (1) reactions using preactivated metal alkynides (such as zinc and silyl alkynides) as a nucleophile and (2) direct reactions using alkynes and chiral Brønsted base catalysts. The first example in the former category was developed by Cozzi using zinc acetylides as a nucleophile and bifunctional zinc−salen complex as a catalyst.[54,55] The $Cu(OTf)_2$−amido alcohol (**53**)-catalyzed reaction of zinc phenylacetylide and aromatic ketones developed by Chan afforded higher enantioselectivity than Cozzi's reaction (Table 13).[56] Aliphatic ketones and alkynes other than phenylacetylene produced less satisfactory enantioselectivity (entries 12 and 13).

Table 13. Catalytic Enantioselective Addition of Zinc Acetylide to Ketones[56]



entry	product		yield (%)	ee (%)
1		R = H	92	88
2		R = Br	65	96
3		R = Cl	94	97
4		R = F	91	96
5		R = Me	49	96
6		R = Br	80	82
7		R = Me	83	86
8		R = Br	75	91
9		R = Me	77	92
10			75	85
11			57	71
12			85	73
13			n.d.	54

Although the results were rather preliminary, a CuF catalyst can activate silylated alkynes through transmetalation. This method was utilized in a catalytic enantioselective alkynylation of trifluoroacetophenone (**54**) with trialkoxysilylated phenylacetylene (Scheme 11, eq 1).[57] The chiral catalyst, a CuF−DTBM−SEGPHOS (**39**) complex, was generated via reduction of $CuF_2 \cdot 2H_2O$ with the chiral phosphine (2 equiv to Cu). The active nucleophile was the corresponding copper acetylide, because consistent enantioselectivity was obtained under the direct conditions described below (Scheme 11, eq 2).

Direct catalytic enantioselective alkynylation of category 2 was initially developed by Carreira using aldehydes as substrates.[58,59] This type of reaction is more atom economical than those in category 1 but is more challenging because the nucleophile (metal alkynides) should be generated through chemoselective deprotonation of terminal alkynes ($pK_a \sim 29$) in the presence of aldehydes (pK_a of α-proton ~ 23) or ketones (pK_a of α-proton ~ 26).

The catalytic enantioselective alkynylation of ketones in this category is currently limited to reactions with activated ketones. A direct catalytic enantioselective alkynylation of α-keto esters was reported by Jiang using a $Zn(OTf)_2$−chiral amino alcohol complex catalyst in the presence of a catalytic amount of Et_3N.[60] Only nonenolizable substrates produced satisfactory results. When an enolizable ketone, ethyl pyruvate, was used as a substrate, the product was obtained in only 11% yield due to the undesired deprotonation of the pyruvate. In contrast, we developed a general racemic direct catalytic alkynylation of trifluoromethyl ketones using CuO^tBu[61] (generated in situ from CuOTf·0.5 toluene complex and KO^tBu[62] or $Cu(OTf)_2$ and 2 equiv of KO^tBu, followed by in situ reduction by alkynes[63])-xantphos or 1,10-phenanthroline complex.[64] This reaction was applicable to various alkynes and trifluoromethyl ketones, including enolizable ketones (pK_a of α-proton ~ 15). The broad applicability was due to the unique characteristics of copper alkoxide. Selective interaction of the soft metal (Cu) with alkynes acidified the alkyne terminal protons, leading to chemoselective deprotonation to generate a copper alkynide species **56**, even in the presence of trifluoromethyl ketones containing acidic α-protons (Scheme 12). This in situ-generated nucleophile reacted with trifluoromethyl ketones, producing a copper alkoxide species **57**, which in turn acted as a Brønsted base after the second cycle.

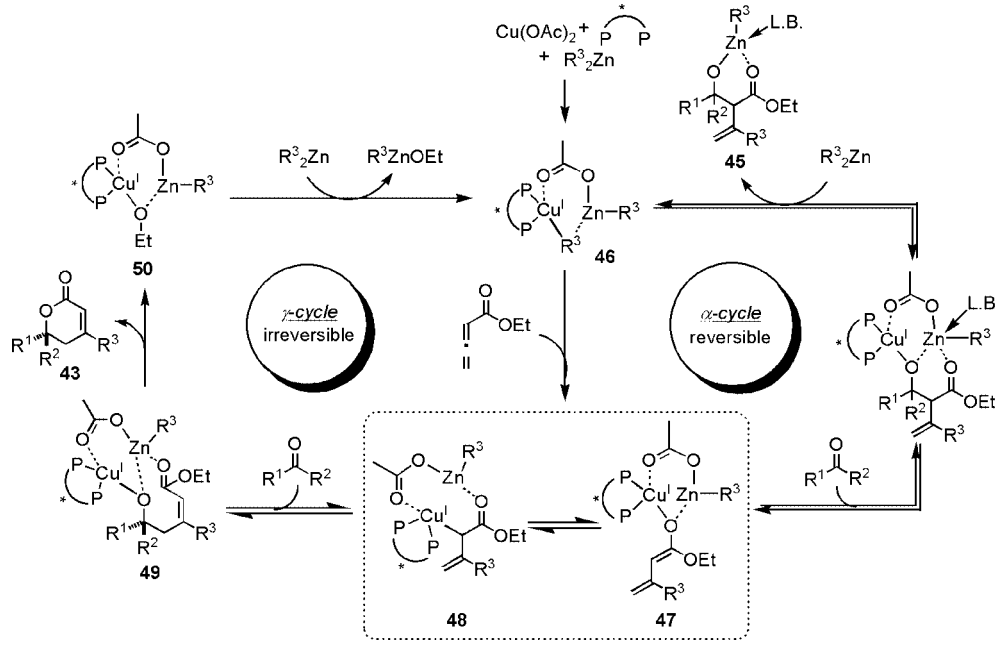
This basic reaction was extended to a direct catalytic enantioselective alkynylation of trifluoroacetophenone **54** (Scheme 11, eqs 2 and 3). The optimized chiral ligand was identified as DTBM-SEGPHOS (**39**) or pybox **55**. The enantioselectivity, however, remained only moderate. Consistent enantioselectivity was obtained using commercially available copper phenylacetylide as a catalyst in the presence of **39**. This result indicates that the active nucleophile is a chiral copper alkynide complex.

4. Catalytic Asymmetric Carbonyl-Ene and Allylation Reactions of Ketones and Ketimines (Tertiary Homoallylic Alcohol and α-Tertiary Homoallylic Amine Syntheses)

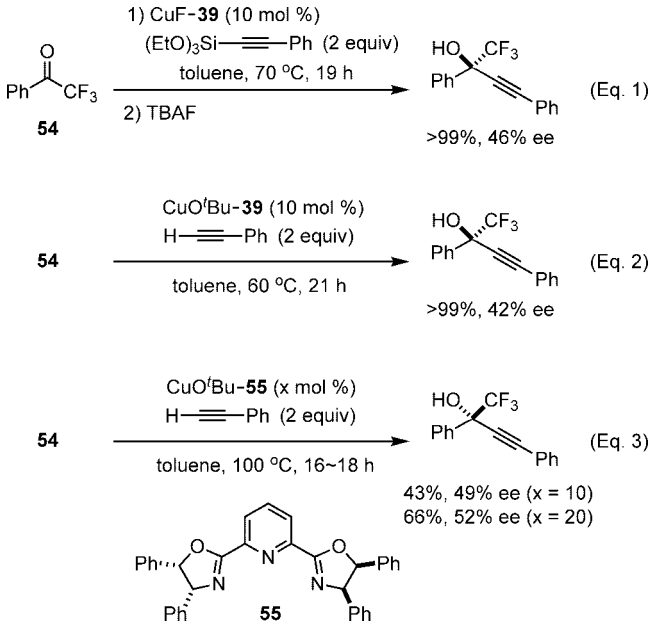
4.1. Catalytic Asymmetric Carbonyl-Ene Reactions of α-Keto Esters Using Lewis Acid Cu(II) Catalyst

The carbonyl-ene reaction produces synthetically versatile homoallylic alcohols from carbonyl compounds and olefins. Preactivation of the nucleophile via the formation of organometallic reagents is not necessary. C−C bond formation occurs

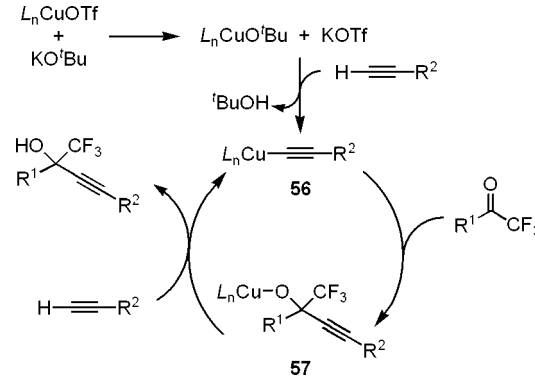
Scheme 10. Proposed Catalytic Cycle of Alkylative Aldol Reaction of Ketones[47]



Scheme 11. Catalytic Enantioselective Alkynylation of Trifluoromethyl Ketones[57,64]



Scheme 12. Proposed Catalytic Cycle of Copper Alkoxide-Catalyzed Direct Alkynylation of Trifluoromethyl Ketones[64]

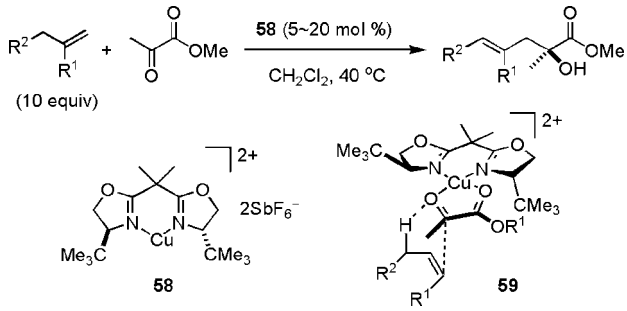


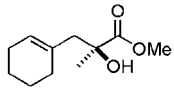
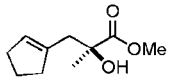
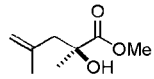
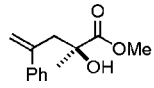
simultaneously with proton transfer from the allylic position of donor olefins to product alcohols. The first catalytic asymmetric carbonyl-ene reaction was reported by Yamamoto and co-workers using BINOL-Al complexes.[65,66] An extension to the catalytic enantioselective ketone carbonyl-ene reaction was not achieved till Evans' work using cationic Cu(II)−^{t}Bu−box (**58**) as a catalyst (Table 14).[67] $Cu(SbF_6)_2$ complex **58** afforded higher conversion and enantioselectivity than $Cu(OTf)_2$ complex **1**. The catalyst turnover step appeared to be rate-determining, and the energy barrier of this step was overcome simply by increasing the reaction temperature to 40 °C. Although excellent enantioselectivity was obtained, the substrate generality was limited to 1,1-disubstituted alkenes and methyl pyruvate. The absolute configuration of the products was explained from model **59**, which was similar to that of the Mukaiyama aldol reaction using the related catalyst (section 2.1).

The Cu-catalyzed asymmetric carbonyl-ene reaction was applied to an intramolecular variant by Yang (Scheme 13).[68] The optimum catalyst was $Cu(OTf)_2$−Ph−box (**60**) complex (20 mol % loading). The enantioselectivity was excellent for six-membered ring formation (Scheme 13, eq 1), whereas a five-membered ring product was obtained with moderate enantioselectivity (Scheme 13, eq 2). In both cases, diastereoselectivity was very high. Significant ligand acceleration was observed using **60** but not using ^{t}Bu−box and pybox ligands. The reaction was also extended to a diastereoselective version using a substrate containing a stereogenic center (Scheme 13, eq 3).

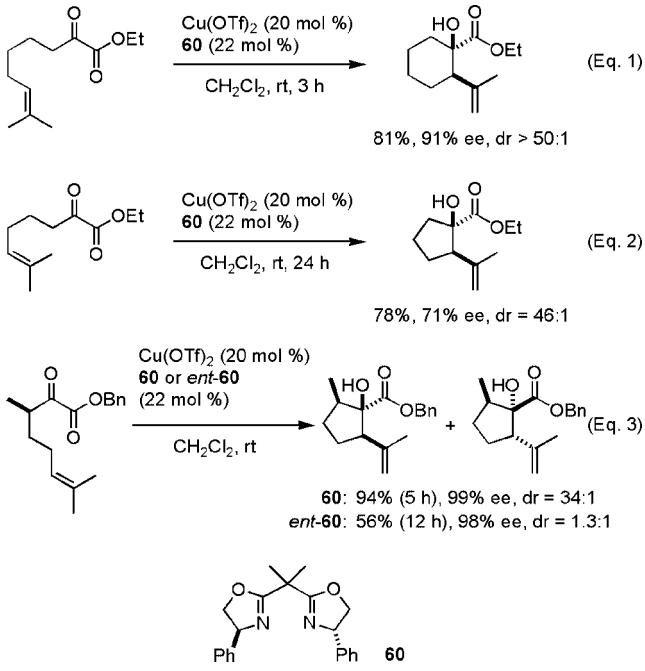
Bolm applied the modularly assembled aminosulfoximine ligand **61** to a catalytic enantioselective carbonyl-ene reaction of methyl pyruvate (Scheme 14).[69] Cu counterions had a significant effect on the catalyst activity and enantioselectivity. $Cu(ClO)_2$ was identified as the optimum Cu source, affording better results than $Cu(OTf)_2$, $Cu(SbF_6)_2$, $Cu(BF_4)_2$, and $Cu(PF_6)_2$. Although excellent enantioselectivity was obtained, catalyst activity was not satisfactory.

Table 14. Catalytic Enantioselective Carbonyl-Ene Reaction of Methyl Pyruvate Reported by Evans[67]



entry	product	58 (mol %)	yield (%)	ee (%)
1		20	84	98
2		5	95	98
3		10	76	98
4		5	94	98

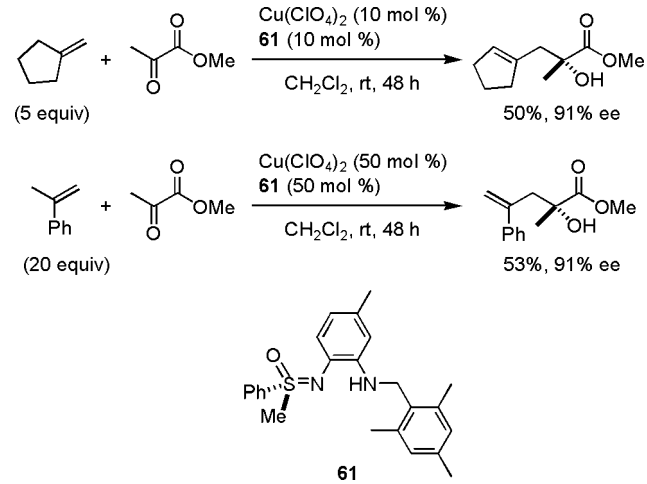
Scheme 13. Catalytic Asymmetric Intramolecular Carbonyl-Ene Reaction[68]



4.2. Catalytic Asymmetric Allylation of Simple Ketones Using Cu(I) Catalyst

Although the carbonyl-ene reaction is ideal with regard to atom economy, it is difficult to expand the substrate generality to unactivated ketones due to its large transition state energy barrier. More practical catalytic asymmetric methods for homoallylic alcohol synthesis use activated nucleophiles, such as allyltin, allylsilane, or allylboron reagents. Although there are many successful examples of

Scheme 14. Catalytic Enantioselective Carbonyl-Ene Reaction of Methyl Pyruvate Reported by Bolm[69]

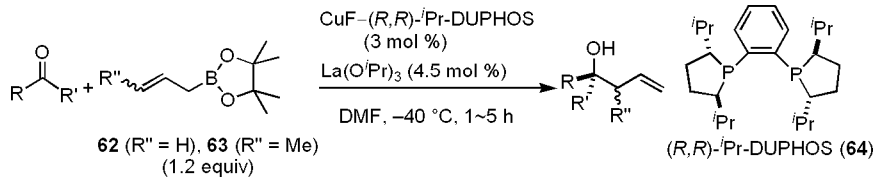


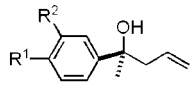
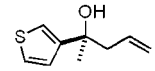
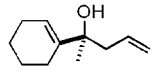
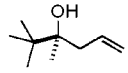
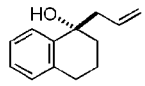
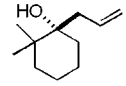
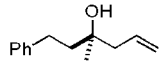
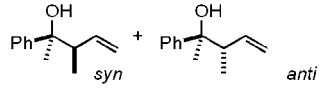
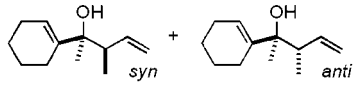
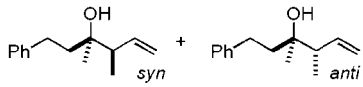
catalytic asymmetric allylation of aldehydes,[70] expansion of the substrate scope to ketones began only recently by modifying the Keck−Tagliavini−Umani−Ronchi asymmetric allylation of aldehydes[71] using the BINOL-Ti Lewis acid catalyst and the allyltin nucleophile.[72] The drawbacks of this strategy, however, are the requirements of high catalyst loading (20−30 mol %) and toxic organotin compounds.

In 2002, our group developed a general catalytic allylation using CuF (generated from CuCl and TBAT) as a catalyst and allyltrimethoxysilane as a nucleophile.[73] This basic methodology for allylation covers substrates including aldehydes, ketones, aldimines, and ketimines. Simple extension of this method to a catalytic asymmetric allylation of ketones using chiral bisphosphines, however, was only partially successful (up to 86% ee) due to the deceleration effects of the chiral ligands. After 2 years of studies, we developed an asymmetric allylboration of ketones using a CuF−^{i}Pr−DUPHOS (**64**) complex catalyst [generated via reduction of CuF·2H$_2$O with **64** (2 equiv to Cu); Table 15].[74] Addition of La(O^{i}Pr)$_3$ as a cocatalyst dramatically improved catalyst activity without affecting the enantioselectivity. Products were obtained with moderate to high enantioselectivity from both aromatic and aliphatic ketones. Our method was the first to overcome the above-mentioned problems in the previous reactions using allyltin. Moreover, high catalyst activity allowed us to extend this method to the first catalytic asymmetric crotylation of ketones. Although the diastereoselectivity must be improved, products containing contiguous tetrasubstituted−trisubstituted carbons were obtained with excellent enantioselectivity (entries 10−15). The (*E*)- and (*Z*)-crotylboronates (**63**) afforded the corresponding *anti*- and *syn*-isomers, respectively, as the major products in the case of aromatic ketones (entries 10 and 11), whereas *anti*-isomers were the major products irrespective of the geometry of crotylboronate in the case of aliphatic ketones (entries 12−15).

There are two noteworthy points regarding the mechanism of this reaction. First, the active nucleophile was an allylcopper species that was generated through transmetalation from B to Cu. Identical enantioselectivity was produced using allylboronate **62**, allyltrimethoxysilane, or allyltributyltin as an allylating reagent, suggesting that an identical species, most probably allylcopper, acted as the actual nucleophile. Generation of allylcopper from **62** in

Table 15. Catalytic Asymmetric Allylboration of Ketones[74]

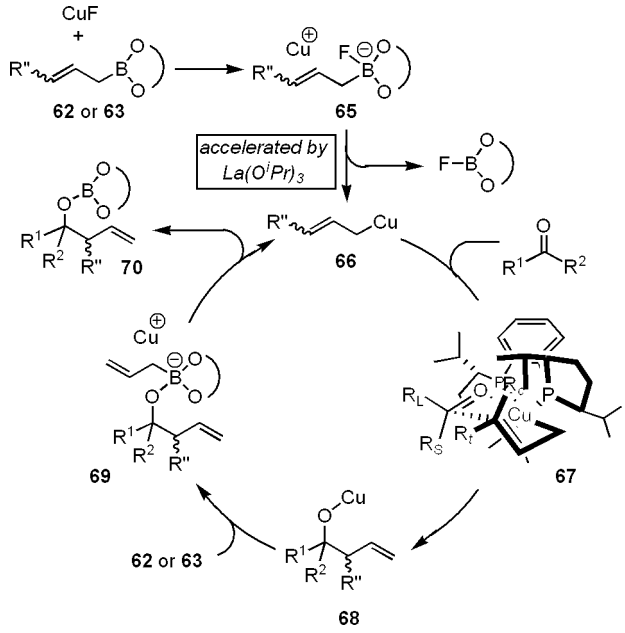


entry	product	yield (%)	ee (%)
1	 R¹, R² = H	94	82
2	R¹ = Me, R² = H	89	84
3	R¹ = H, R² = Me	83	83
4		87	90
5		87	90
6		99	91
7		88	84
8		98	84
9		96	67
10		(*E*)-**63**: 73 (30/70)	75/90
11	syn + anti	(*Z*)-**63**: 94 (84/16)	87/74
12		(*E*)-**63**: 80 (27/73)	90/93
13	syn + anti	(*Z*)-**63**: 90 (38/62)	90/92
14		(*E*)-**63**: 100 (34/66)	16/85
15	syn + anti	(*Z*)-**63**: 100 (36/64)	21/85

the presence of the CuF catalyst was also supported by NMR observation. Second, cocatalyst La(O^{i}Pr)$_3$ accelerated the rate-determining transmetalation step without affecting the enantiodifferentiation step (addition of allylcopper to ketones). The catalytic cycle was proposed as shown in Scheme 15. CuF transferred hard fluoride onto hard boron, affording copper borate **65**. The soft allyl ligand on the boron atom was then transferred back to the soft Cu, generating the active nucleophile, allylcopper **66**. This transmetalation was not very efficient in the absence of La(O^{i}Pr)$_3$. Once allylcopper **66** was generated, it rapidly reacted with ketones through a putative cyclic transition state **67**. This addition step defined the enantioselectivity but was not rate-determining. The resulting copper alkoxide **68** again had a mismatched soft−hard combination, and quickly transferred the alkoxide ligand onto the boron atom of **62** or **63**. Through the ate complex **69**, allylcopper was regenerated with liberation of product **70**.

A cyclic transition state model **67** was proposed for the addition step of allylcopper to ketones. This model was based on the fact that the geometry of crotylboronates **63** reflects the relative stereochemistry of the products in the case of aromatic ketones (Table 15, entries 10 and 11). In contrast, *anti*-isomers are the major products irrespective of the geometry of **63** in the case of aliphatic ketones. This difference, which depends on the substrate ketones, is due to differences in the relative rate of metallotropic equilibrium[75] versus addition to ketones. Allylic metal compounds with ionic characteristics (such as allyllithium, magnesium, and zinc reagents) are configurationally unstable, existing as a mixture of rapidly equilibrating (*E*)- and (*Z*)-isomers through 1,3-metal transposition. Allylcopper is in this category, which is supported by the fact that the linear product was the only observed isomer (46% yield) in the Cu-catalyzed crotylation of a bulky ketone, *t*-butyl methyl ketone, using (*E*)- and (*Z*)-**63**. The rate of the crotylcopper addition to aromatic ketones might be faster than that to aliphatic ketones. Therefore, the addition could proceed before *E*/*Z* equilibrium of crotylcopper in the case of aromatic ketones, whereas the addition proceeded after equilibrium in the case of aliphatic ketones. Model **67** rationalizes both the absolute and the relative configurations of the products.

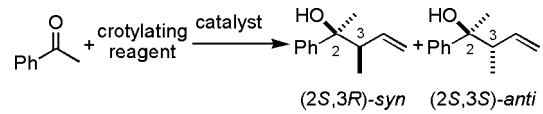
Scheme 15. Proposed Catalytic Cycle of CuF-Catalyzed Allylboration of Ketones[74]



4.3. Comparison of Four Methodologies of Catalytic Asymmetric Allylation of Ketones

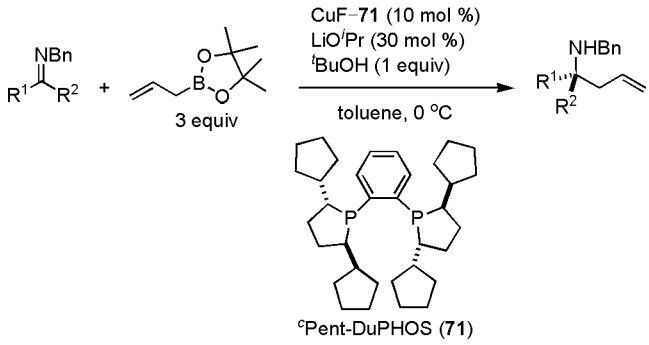
After our report, three groups reported catalytic asymmetric allylation of ketones using nucleophiles other than toxic allyltin. Interestingly, all of those methods involved activation of the nucleophile side. First, Yamamoto developed a AgF-DIFLUORPHOS catalyzed asymmetric allylation of ketones using allyltrimethoxysilane as the nucleophile (Table 16, entry 2).[76] Before this achievement, his group developed an AgF-BINAP catalyzed allylation of aldehydes in MeOH.[77] Allysilver generated via transmetalation was proposed to be the active nucleophile. By reducing the amount of MeOH to 1 equiv to the substrate, ketone allylation proceeded in high yield. Addition of MeOH was essential to regenerate the catalyst from the intermediate silver alkoxide, which was produced by the allyl transfer from silver to a ketone. Excellent enantioselectivity was produced from aromatic and α,β-unsaturated ketones. Crotylation also proceeded with excellent enantioselectivity, affording the *syn*-product as a major isomer irrespective of the geometry of crotylsilane (entry 2). Second, Schaus' reaction utilized allyldiisopropoxyborane as a nucleophile in the presence of a catalytic amount of 3,3′-dibromo BINOL (entry 3).[78] The reaction was facilitated through ligand exchange on the boron atom from the isopropoxyl to the BINOL derivative. The resulting chiral allylboronate had higher Lewis acidity on the boron, thus producing enhanced reactivity.[79] Applicable substrates were restricted to aromatic ketones and α,β-unsaturated ketones. The geometry of crotylboronate was transferred to the relative stereochemistry of the products with high fidelity, which led to the proposal of a cyclic transition state model for the addition step. Third, a chiral Cr-catalyzed asymmetric Nozaki−Hiyama−Kishi reaction between allylbromides and ketones was developed by Sigman (entry 4).[80] Excellent enantioselectivity was obtained from aromatic ketones. Crotylation also proceeded, but only the results using (*E*)-crotylbromide were described. In Table 16, representative results of crotylation using the four currently available catalysts are compared, because the characteristics of each reaction are clear in crotylation.

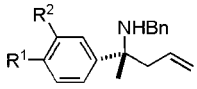
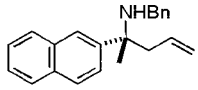
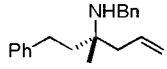
Table 16. Comparison of the Four Catalytic Asymmetric Methods of Ketone Allylation (Crotylation)



entry	catalyst	crotylating reagent	conditions	results	config. of major isomer
1[ref. 74]	(3 mol %)	BPin	DMF 40 °C, 1 h	73% (30/70) 75/90% ee	(2*S*,3*S*)
		BPin	DMF 40 °C, 5 h	94% (84/16) 87/74% ee	(2*S*,3*R*)
2[ref. 76]	(5 mol %)	$Si(OMe)_3$	THF, MeOH (1 equiv) −78 to −40 °C, 36 h	60% (90/10) 95% ee	(2*R*,3*S*)
		$Si(OMe)_3$	THF, MeOH (1 equiv) 78 to 40 °C, 36 h	95% (90/10) 93% ee	(2*R*,3*S*)
3[ref. 78]	(15 mol %)	$B(O^iPr)_2$	$PhCH_3$-$PhCF_3$ −35 °C, 15 h	72% (2/98) 98% ee	(2*S*,3*S*)
		$B(O^iPr)_2$	$PhCH_3$-$PhCF_3$ −35 °C, 15 h	75% (99/1) 97% ee	(2*S*,3*R*)
4[ref. 80]	$CrCl_3$ (10 mol %)	Br	Et_3N (20 mol %) TMSCl (4 equiv) Mn(0) (2 equiv) THF, 0 °C, 24 h	69% (21/79) 70/88% ee	(2*R*,3*R*)

Table 17. Catalytic Enantioselective Allylation of Ketimines[81]



entry	product		yield (%)	ee (%)
1		R^1, R^2 = H	92	89
2		R^1 = H, R^2 = Me	96	91
3		R^1 = H, R^2 = MeO	97	93
4		R^1 = H, R^2 = F	89	87
5		R^1 = MeO, R^2 = H	76	85
6		R^1 = Cl, R^2 = H	82	81
7			88	92
8			98	23

4.4. Catalytic Enantioselective Allylation of Ketimines

The CuF-catalyzed asymmetric allylation of ketones was extended to the first catalytic enantioselective allylation of ketimines (Table 17).[81] Tuning of three parameters was necessary: (1) sterically tuned cyclopentyl-DUPHOS (**71**) afforded higher enantioselectivity than ^{i}Pr-DUPHOS (the optimum chiral ligand for ketone allylation); (2) slow addition (over 2 h) of ^{t}BuOH accelerated the reaction through facilitating the catalyst turnover step by protonation of the intermediate copper amide generated after the addition of allylcopper to a ketimine; (3) LiO^{i}Pr, rather than La(O^{i}Pr)$_3$, was the optimum cocatalyst. High enantioselectivity was produced from aromatic ketimines (entries 1−7), whereas aliphatic substrates afforded unsatisfactory results (entry 8).[82] The *N*-benzyl protecting group can be selectively cleaved in high yield through IBX oxidation to the corresponding *N*-benzylidene imine,[83] followed by acid hydrolysis.

Based on detailed NMR studies, the cocatalyst [La(O^{i}Pr)$_3$ for ketone allylation and LiO^{i}Pr for ketimine allylation]-induced acceleration of transmetalation from allylboronate to allylcopper (see Scheme 15) was due to the generation of electron-rich alkoxyborate **73** via a facile cation exchange between initially formed copper fluoroborate **65** and lithium alkoxyborate **72** (Scheme 16). This reactive precursor (**73**), rather than fluoroborate **65**, was the major species transformed to allylcopper. La(O^{i}Pr)$_3$(the optimized cocatalyst in the allylation of ketones) should also accelerate the reaction in a similar manner as LiO^{i}Pr shown in Scheme 16.

4.5. Copper Alkoxide-Catalyzed Enantioselective Allylation of Ketones and Ketimines

Because the catalytic cycle of CuF-catalyzed allylation contains a copper alkoxide species (**68** in Scheme 15 for ketone allylation, or CuO^{t}Bu for ketimine allylation, which was generated after protonation of the intermediate copper amide with additive ^{t}BuOH) as an intermediate, a new catalytic system was developed using a CuO^{t}Bu-chiral phosphine complex as the catalyst (Table 18).[84] KO^{t}Bu (2 equiv excess to Cu) was used as the cocatalyst. Results comparable to those of the previous CuF catalysis were obtained using this new protocol using a smaller amount of the chiral phosphines.

5. Catalytic Asymmetric Arylation and Alkenylation of Ketones

Copper-catalyzed arylation and alkenylation producing tertiary alcohols is currently restricted to using activated ketones (such as trifluoromethyl ketones or α-keto esters) as substrates.[85] Lewis acid Cu(II)-catalyzed direct asymmetric arylation (Friedel−Crafts reaction) of trifluoropyruvate using electron-rich aryl groups as a nucleophile was first reported by Jørgensen (Table 19).[86] The enantioselectivity and yield strongly depended on the introduced aryl groups. When an amino group is present in the nucleophile, the amine should be protected with sterically demanding benzyl or allyl groups to prevent the coordination of amine to the catalyst (entries 13−15). The absolute configuration of the products was explained based on a model similar to those of the catalytic asymmetric aldol reaction (**2**) and carbonyl-ene reaction (**59**) promoted by the related catalyst.

Enantioselective arylation of trifluoropyruvate promoted by a silica gel-supported box−Cu(OTf)$_2$ catalyst was reported by Corma and García.[87] Solid supported catalyst **76** was synthesized through radical coupling between Cu(OTf)$_2$−Ph−box complex part **74** and solid-supported thiol **75** in the presence of AIBN (Scheme 17, eq 1). Catalyst **76** promoted the addition of 1,3-dimethoxybenzene to trifluoropyruvate with excellent enantioselectivity (Scheme 17, eq 2). The enantioselectivity and catalyst activity of **76** were significantly higher than those of homogeneous catalyst **74** (44% yield with 72% ee). This tendency is unusual but may be explained from the point of view that an undesirable complex−complex interaction was minimized by the solid surface support. Although the enantioselectivity was decreased in the second cycle, **76** was recyclable without any Cu^{2+} leaching.

Wilson[88] and Liu, Wang, and Chen[89] also reported catalytic enantioselective arylation of trifluoropyruvate using modified chiral ligands (Scheme 18).

The CuF-catalyzed nucleophile activation via transmetalation was also applicable in enantioselective alkenylation and arylation of activated ketones.[57,90] Although transmetalation of alkenylsilanes to alkenylcopper has been reported,[91] there were no examples of the use of the thus-generated alkenylcopper as a nucleophile to carbonyl compounds prior to our studies.[90a] Systematic screening of phosphine ligands for CuF revealed that alkenylation proceeded using alkenyltrimethoxysilane as a nucleophile in the presence of sterically congested bisphosphine ligands. This platform reaction was extended to a catalytic enantioselective version. DTBM-SEGPHOS (**39**) was identified as the optimum chiral ligand. The reaction produced excellent enantioselectivity from

Scheme 16. Proposed Acceleration Mechanism of the Cocatalyst

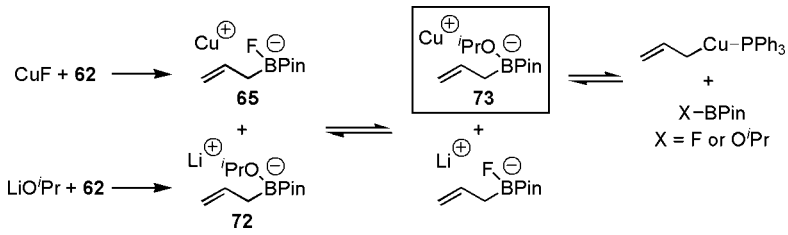
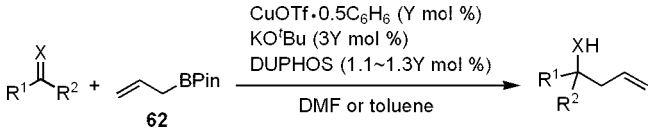
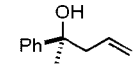
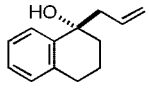
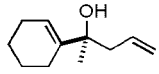
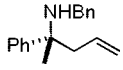
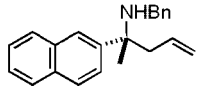


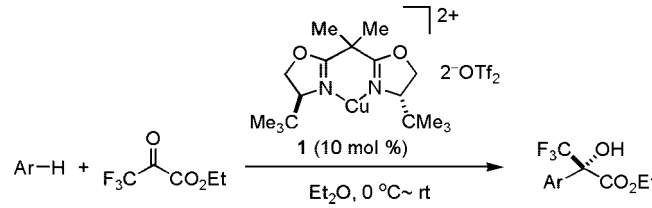
Table 18. CuO^{t}Bu-Catalyzed Enantioselective Allylation of Ketones and Ketimines[84,a]

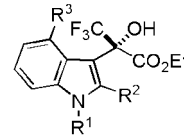
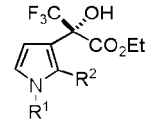
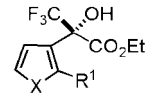
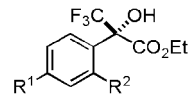
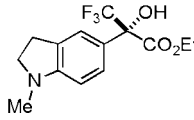


entry	Y	time (h)	product	yield (%)	ee (%)
1	3	1		89	81
2[b]	3	1		94	82
3	3	3		99	82
4[b]	3	1		88	84
5	3	3		99	91
6[b]	3	1		87	90
7	10	1		95	89
8[b]	10	0.5		92	89
9	10	10		93	87
10[b]	10	12		88	92

[a] The ketone allylation was conducted in the presence of 3 mol % of CuOTf, 9 mol % of KO^{t}Bu, 4 mol % of ^{i}Pr-DUPHOS (**64**), and 1.2 equiv of **62** in DMF at −40 °C. The ketimine allylation was conducted in the presence of 10 mol % CuOTf, 30 mol % of KO^{t}Bu, 11 mol % of ^{c}Pent-DUPHOS (**71**), and 3 equiv of **62**, with slow (2 h) addition of ^{t}BuOH (1 equiv) in toluene at 0 °C. [b] CuF catalysis. The asymmetric catalyst was prepared via reduction of $CuF_2 \cdot 2H_2O$ using the chiral phosphines (2 equiv to Cu).

Table 19. Catalytic Enantioselective Arylation of Trifluoropyruvate Developed by Jørgensen[86]



entry	product		yield (%)	ee (%)
1		R^1 = Me, R^2, R^3 = H	94	89
2		R^1, R^2 = H, R^3 = Cl	70	89
3		R^1, R^2 = H, R^3 = Ph	61	87
4		R^1, R^2, R^3 = H	93	83
5		R^1, R^2 = Me, R^3 = H	88	94
6		R^1, R^2 = H	80	83
7		R^1 = Me, R^2 = H	42	93
8		R^1 = Me, R^2 = C(O)Me	69	89
9		X = O, R^1 = Me	65	93
10		X = O, R^1 = H	15	81
11		X = O, R^1 = TMS	32	76
12		X = S, R^1 = Me	16	79
13		R^1 = NMe$_2$, R^2 = H	60	24
14		R^1 = NBn$_2$, R^2 = H	72	83
15		R^1 = N(allyl)$_2$, R^2 = H	70	85
16		R^1 = OMe, R^2 = OMe	56	86
17		R^1 = NMe$_2$, R^2 = OMe	80	10
18			71	22

various aldehydes and activated ketones including an α-keto ester (Table 20, eq 1)[90a] and trifluoromethyl ketones[57] (Table 20, eq 2). The same catalyst also promoted enantioselective phenylation reactions using dimethoxydiphenylsilane as a nucleophile. Generation of alkenylcopper or arylcopper as the active nucleophile was confirmed by NMR studies.

6. Catalytic Enantioselective Alkylation of Trifluoromethyl Ketimines

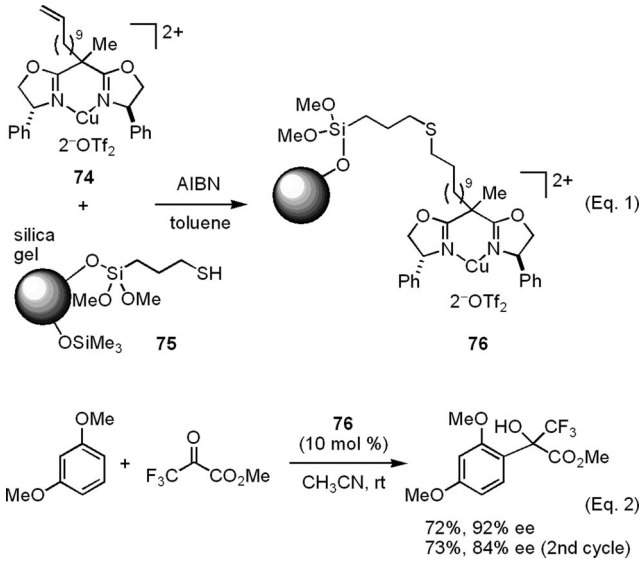
Although there are several reported examples of Cu-catalyzed enantioselective alkylation of aldimines using diorganozinc reagents as a nucleophile,[92] there is only one example that extended the substrate scope to activate ketimines (trifluoromethyl ketimines **80**, Table 21).[93,94] Stable and isolable hemiaminal **79**, synthesized through condensation of trifluoromethyl ketones and diphenylphosphinamide in the presence of $Ti(OEt)_4$, was converted to trifluoromethyl ketimine **80** under the reaction conditions of the catalytic asymmetric reaction in the presence of excess dialkylzinc. A $Cu(OTf)_2$ and bisphosphine monoxide ligand **81**[92f] complex was used as an enantioselective catalyst. The reaction scope was limited to aromatic ketimines and dialkylzinc (including Me_2Zn).

7. Cu(II)-Catalyzed Asymmetric Cycloaddition to Produce Tetrasubstituted Carbons

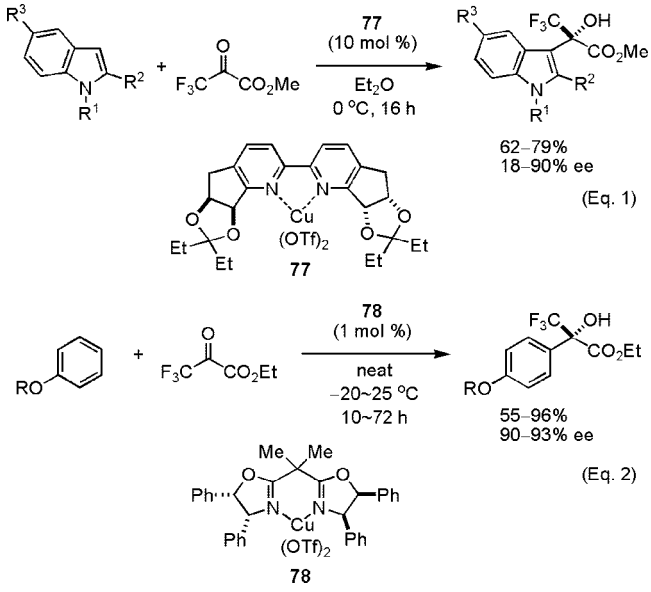
The first catalytic asymmetric hetero-Diels−Alder-type reaction between Danishefsky's diene **82**[95] and α-keto esters or 1,2-diketones was reported by Jørgensen using $Cu(OTf)_2$−^{t}Bu−box complex **1** (Table 22).[96] Excellent enantioselectivity was produced from a wide range of substrates. Catalyst loading was decreased to as low as 0.05 mol %, while the high enantioselectivity was maintained. The absolute configuration of the products was explained based on model **83**, similar to those of aldol reaction (Scheme 2, **2**) and carbonyl ene-reaction (Table 14, **59**).

A $Cu(OTf)_2$ complex of *cis*-aminoindan-2-ol-derived box ligand **84** can promote the hetero-Diels−Alder-type reaction

Scheme 17. Enantioselective Arylation of Trifluoropyruvate Using Silica-Supported Catalyst Developed by Corma and García[87]



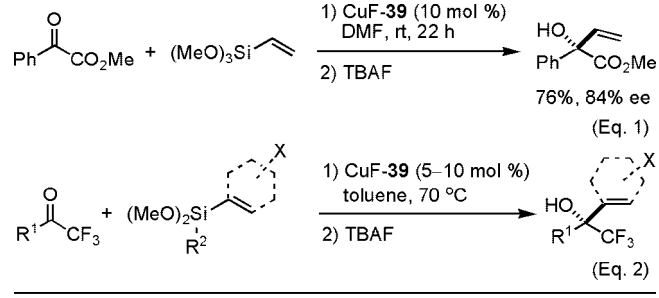
Scheme 18. Catalytic Enantioselective Arylation of Trifluoropyruvate Developed by Wilson (Eq 1)[88] and Liu, Wang, and Chen (Eq 2)[89]

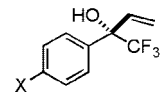
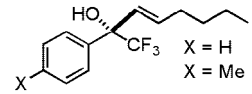
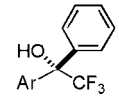


between **82** and α-keto esters with enantioselectivity comparable to that of complex **1** (Table 23).[97] This reaction was used as a platform for a catalytic asymmetric synthesis of (−)-malyngolide (**85**). The enantioselectivity of the key reaction for the total synthesis of **85**, however, was only moderate (entry 4).

A dynamic catalytic system involving in situ generation of a chiral catalyst from a mixture of diamine (**86**), cyclobutanone (**87**), and $Cu(OTf)_2$ was developed by Dalko and Cossy (Scheme 19).[98] The three components were premixed for 16 h at room temperature, during which the equilibrium shifted to the desired Cu complex **88**. The mixture was an efficient catalyst for a [4 + 2] cycloaddition reaction of Danishefsky's diene **82** and ethyl pyruvate. The premixing time of the three catalytic components was important for high enantioselectivity. The cycloaddition reaction proceeded in a stepwise manner, and an intermediate linear product resulting from a Mukaiyama aldol reaction

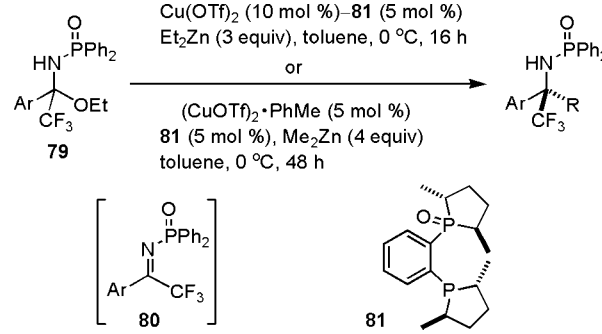
Table 20. Catalytic Enantioselective Alkenylation and Arylation of Activated Ketones[57,90a]



entry	product		time (h)	yield (%)	ee (%)
1[a,b]		X = H	39	100	84
2[a]		X = Cl	43	77	84
3[a]		X = Br	41	92	82
4[a]		X = Me	18	100	83
5[a]		X = H	17	75	80
6[a]		X = Me	45	75	80
7[c]		Ar = *p*-MeC_6H_4	10	80	67
8[c]		Ar = 2-naphthyl	37	91	49

[a] R^2 = OMe. [b] Catalyst loading = 5 mol %. [c] R^2 = Ph.

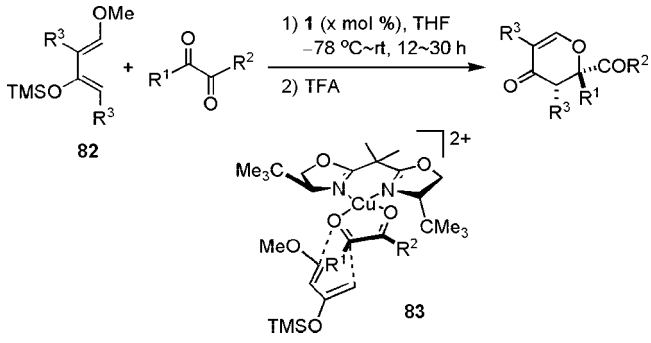
Table 21. Catalytic Enantioselective Alkylation of Trifluoromethyl Ketimines[93]



entry	Ar	R	yield (%)	ee (%)
1	Ph	Et	83	91
2	Ph	Me	85	99
3	4-BrC_6H_4	Et	71	95
4	4-BrC_6H_4	Me	89	97
5	3-MeC_6H_4	Et	78	95
6	3-MeC_6H_4	Me	84	99
7	4-MeC_6H_4	Et	77	97
8	2-naphthyl	Et	73	94
9	4-ClC_6H_4	Et	71	93

of **82** to the ketone moiety of pyruvate was also obtained. The linear product was converted to the cyclic product by treatment with catalytic amounts of TFA (step 2). The reaction did not proceed using a complex of $Cu(OTf)_2$ and diamine **86** as the catalyst in the absence of **87** or using cyclohexane 1,2-diamine instead of **86** in the presence of $Cu(OTf)_2$ and **87**. Among ketones and aldehydes investigated as the imine part of the catalyst, cyclobutanone **87** afforded the highest enantioselectivity. In addition, the Cu/ligand ratio was critical for both enantioselectivity and catalyst activity. Due possibly to such strict requirements on the reaction

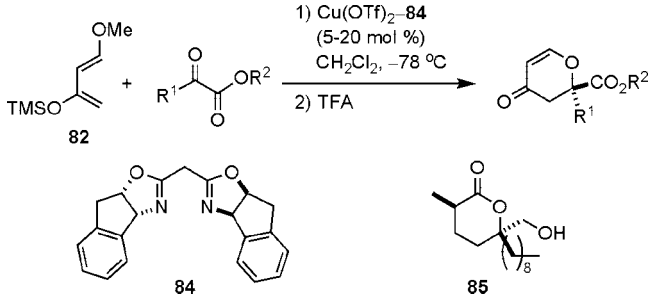
Table 22. Catalytic Enantioselective Hetero-Diels−Alder-Type Reaction of Activated Ketones Developed by Jørgensen[96a,d]



entry	product		yield (%)	ee (%)
1		R^1 = Me, R^2 = OEt	96	99
2		R^1 = Me, R^2 = OMe	96	99
3[b]		R^1 = Me, R^2 = OMe	90	98
4		R^1 = Et, R^2 = OMe	80	94
5[c]		R^1 = Et, R^2 = OMe	70	97
6		R^1 = ^{i}Pr, R^2 = OEt	42	37
7		R^1 = Ph, R^2 = OEt	77	77
8		R^1 = Me, R^2 = Me	90	94
9[b]		R^1 = Me, R^2 = Me	88	94
10		R^1 = Me, R^2 = Et	77	98
11[b]		R^1 = Me, R^2 = Et	76	98
12		R^1 = Et, R^2 = Et	84	90
13		R^1 = Me, R^2 = Ph	95	94
14[b]		R^1 = Me, R^2 = Ph	25	96
15		R^1 = Me, R^2 = OMe	75	96
16[d]		R^1 = Me, R^2 = OMe	85	97
17		R^1 = Ph, R^2 = OEt	57	99
18[d]		R^1 = Ph, R^2 = OEt	65	99
19		R^1 = Me, R^2 = Me	60	91
20[d]		R^1 = Me, R^2 = Me	81	97

[a] Catalyst loading was 10 mol % (x = 10) unless otherwise noted. [b] x = 0.05. [c] x = 0.5. [d] x = 2.5.

Table 23. Catalytic Enantioselective Hetero-Diels-Alder-type Reaction of α-Keto Esters Developed by Ghosh[97]



entry	product		yield (%)	ee (%)
1		R^2 = Me	99	87
2		R^2 = Et	52	96
3			65	83
4[a]			73	56

[a] Enantiomer of **84** was used.

conditions, results were described only for the reaction between **82** and ethyl pyruvate.

Scheme 19. Catalytic Enantioselective [4 + 2] Cycloaddition Reaction of Pyruvate Developed by Dalko and Cossy[98]

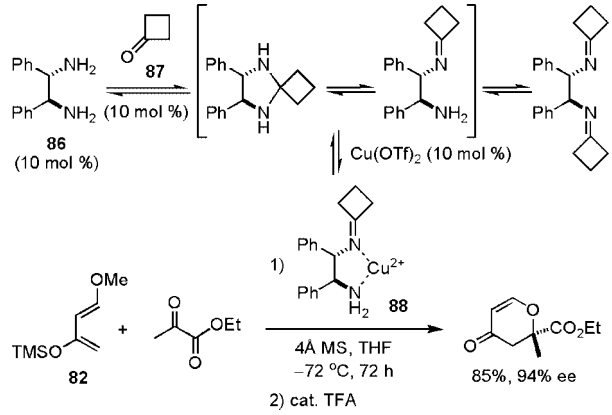
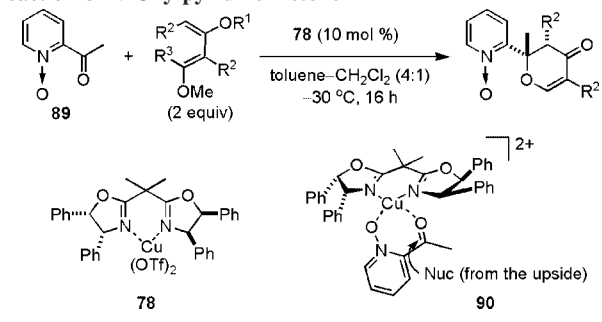


Table 24. Catalytic Enantioselective [4 + 2] Cycloaddition Reaction of *N*-Oxy-pyridine Ketone[100]



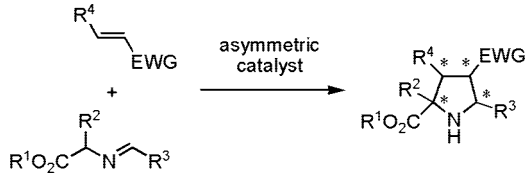
entry	diene	product	yield (%)	ee (%)
1			66	99
2			67	97
3			84	99

A sterically modified box ligand was applied to the $Cu(OTf)_2$-catalyzed hetero-Diels−Alder reaction.[14,99] The enantioselectivity, however, was significantly lower than that of the above three examples.

The dienophile scope of the catalytic asymmetric [4 + 2] cycloaddition reaction that produces tetrasubstituted carbon was extended to *N*-oxy-pyridine ketone **89** by Jørgensen (Table 24).[100] Ketone **89** is electronically activated and can form stable bidentate chelation to a Lewis acid metal. These two factors are favorable for Cu(II)−box catalysis. Excellent enantioselectivity was produced using the $Cu(OTf)_2$−box complex **78** as a catalyst. The reaction proceeded via a stepwise Mukaiyama aldol reaction followed by cyclization, and, in some cases, the intermediate noncyclized products were isolated. The absolute configuration of the products was rationalized based on model **90**, in which the nucleophile approached the activated ketone from the side opposite that of the steric bulkiness of the chiral ligand.

Chiral Lewis acid Cu catalysts can promote asymmetric 1,3-dipolar cycloaddition of azomethine ylide with electron-deficient

Scheme 20. Catalytic Enantioselective [3 + 2] Cycloaddition Reaction of Azomethine Ylide



alkenes to produce enantiomerically enriched 2,2-disubstituted pyrrolidines (Scheme 20).[101,102] This type of reaction, however, induced tetrasubstituted carbon chirality at the nucleophilic site. The reaction has yet to be extended to tetrasubstituted carbon formation at the electrophilic imine part.

8. Summary and Outlook

This review summarizes Cu-catalyzed asymmetric addition reactions of carbon nucleophiles to ketones and ketimines. The catalytic asymmetric synthesis of tertiary alcohols and α-tertiary amines is a recently emerging, highly challenging field in organic synthesis. Specifically, simple unactivated ketones and ketimines remain difficult substrates. As described in this review, Cu catalysis significantly contributes to this field. Due to the difficulties in synthesizing enantiomerically enriched tertiary alcohols and α-tertiary amines, their properties, especially as a chiral building block of drug candidates, have not been thoroughly studied. Considering their enhanced lipophilicity and stability against enzymatic degradation compared to secondary alcohols and α-secondary amines, they might have a unique biologic function. Therefore, developing practical catalytic asymmetric methods for the synthesis of tertiary alcohols and α-tertiary amines will contribute to a vast field, including medicinal chemistry and life science. In addition, novel synthetic methods producing otherwise difficult-to-access compounds generally allow synthetic chemists to use conceptually new and qualitatively more efficient strategies to synthesize complex molecules.[103] Moreover, efforts to solve the problems involved in the use of challenging substrates (especially, unactivated ketones and ketimines) should lead to the development of new concepts in asymmetric catalysis. Representative challenges in this field are (1) improving enantioselectivity and substrate generality; (2) simplifying complex molecule synthesis; and (3) discovering unique characteristics (especially, in medicinal chemistry) of tetrasubstituted carbon-containing molecules.[104]

9. References

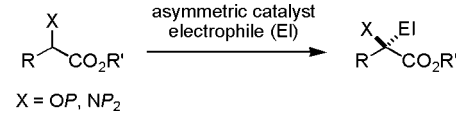
(1) The Sharpless asymmetric dihydroxylation of trisubstituted olefins can produce enantiomerically-enriched tertiary alcohols. For review, see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 357−398.

(2) For recent examples of catalytic enantioselective α-oxidation of carbonyl groups to produce tertiary alcohols, see (a) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. (b) Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5810 This reaction pattern produces α,α-disubstituted α-hydroxyl carboxylic acid derivatives.

(3) For recent examples of catalytic enantioselective electrophilic α-amination of carbonyl compounds to produce α-tertiary amines, see (a) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (b) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (c) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174. (1,3-dipolar cycloaddition). This reaction pattern produces α,α-disubstituted α-amino acid derivatives.

(4) Reactions of oxygen- or nitrogen-substituted carbon nucleophiles (such as siloxy furans, α-amino cyanoacetates, α-substituted nitroacetate, or α-substituted imino esters) with aldehydes or aldimines can be extended to catalytic asymmetric synthesis of tertiary alcohols or α-tertiary amines with induction of chirality at the nucleophile side (Scheme 21 as a representative example). An additional electron-withdrawing substituent (e.g., carbonyl or nitrile) is normally required to stabilize the nucleophile carbanion (or equivalent). Therefore, products of this reaction type are tetrasubstituted carbon-containing hydroxyl acid or amino acid derivatives. For isolated examples, see (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (b) Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810. (c) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (d) For an exceptional example (catalytic asymmetric allylic alkylation of α,α-disubstituted nitroalkanes), see Maki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 4250.

Scheme 21



(5) For reviews of catalytic asymmetric synthesis of tetrasubstituted carbons, see (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647. For the pioneering work of catalytic enantioselective C−C bond-formation to simple ketones, see (e) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445.

(6) In addition to the reactions described in this review, cyanation of ketones and ketimines are the most intensively studied catalytic asymmetric tetrasubstituted carbon synthesis. However, there are no copper-catalyzed reactions in this category. For examples of catalytic enantioselective cyanation of ketones, see (a) Belokon′, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *38*, 6669. (b) Belokon′, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968. (c) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412. (d) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691. (e) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (f) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (g) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900. (h) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009. (i) Riu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384. (j) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964. (k) Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. *J. Am. Chem. Soc.* **2005**, *127*, 12224.

(7) For catalytic enantioselective Strecker reaction of ketimines and related reactions, see (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (c) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147. (d) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (e) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147. (f) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153. (g) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784. (h) Shibasaki, M.; Kanai, M.; Mita, T. *Org. React.* **2008**, *70*, 1.

(8) For examples, see (a) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539. (b) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490.

(9) For examples, see (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239. (b) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300. Review (c) Dave, V.; Warnhoff, E. W. *Org. React.* **1970**, *18*, 217.

(10) For examples, see (a) Kwart, H.; Kahn, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1950. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (c) Evans, D. A.; Fad, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (d) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.

(11) (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

(12) For other examples of Cu(II)−box (or pybox) catalyzed asymmetric reactions, see (a) Evans, D. A.; Miller, S. J.; Lectka, T. C. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (Diels−Alder reaction). (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. T. *J. Am. Chem. Soc.* **1999**, *121*, 669. (aldol reaction). (c) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895. (hetero Diels-Alder reaction). (d) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. (carbonyl-ene reaction)

(13) Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5859.

(14) (a) van Lingen, H. L.; van de Mortel, J. K. W.; Kekking, K. F. W.; van Delft, F. L.; Songinke, T.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2003**, 317. (b) van Lingen, H. L.; van Delft, F. L.; Storcken, R. P. M.; Hekking, K. F. W.; Klaassen, A.; Smits, J. J. M.; Ruskowska, P.; Frelek, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2005**, 4975.

(15) Simonelli, B.; Orlandi, S.; Benaglia, M.; Pozzi, G. *Eur. J. Org. Chem.* **2004**, 2669.

(16) (a) Langer, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984. (b) Langer, M.; Rémy, P.; Bolm, C. *Chem.—Eur. J.* **2005**, *11*, 6254.

(17) Brandt, J.; Gais, H. J. *Tetrahedron: Asymmetry* **1997**, *8*, 909.

(18) For the original finding of acceleration effects by CF_3CH_2OH in catalytic asymmetric Michael-type reaction, see Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994.

(19) For a review of catalytic asymmetric vinylogous aldol reactions, see Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

(20) Rémy, P.; Langner, M.; Bolm, C. *Org. Lett.* **2006**, *8*, 1209.

(21) Le, J. C.-D.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 4097.

(22) Trost, B. M. *Science* **1991**, *254*, 1471.

(23) For the first example of a catalytic asymmetric nitroaldol reaction of aldehydes, see (a) Sasai, H.; Suzuki, S.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) For a review, see Shibasaki, M.; Gröger, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin-Heidelberg, 1999; Chapter 29.3.

(24) (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875.

(25) (a) Lu, S.-F.; Du, D. M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433. (b) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712.

(26) Makino, K.; Ogawa, I.; Hamada, Y. *Heterocycles* **2005**, *66*, 433.

(27) For the first example of a catalytic enantioselective direct aldol reaction of aldehydes, see (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M *J. Am. Chem. Soc.* **1999**, *121*, 4168. (c) For a review, see Shibasaki, M.; Yoshikawa, N.; Matsunaga, S. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin-Heidelberg, 2004; Chapter 29.4.

(28) Gathergood, N.; Juhl, K.; Poulsen, T. B.; Thordrup, K.; Jørgensen, K. A. *Org. Biol. Chem.* **2004**, *2*, 1077.

(29) (a) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (b) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124.

(30) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644.

(31) (a) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164. (b) For a preliminary ligand optimization, see Oisaki, K.; Zhao, D.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2005**, *46*, 4325.

(32) (a) For the first example of a catalytic enantioselective aldol reaction of ketones, see Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (b) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235.

(33) (a) Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem.—Eur. J.* **2002**, *8*, 843. The structure of Taniaphos in this original paper was incorrect (personal communication from Prof. Knochel). (b) Fukuzawa, S.-i.; Yamamoto, M.; Hosaka, M.; Kikuchi, S. *Eur. J. Org. Chem.* **2007**, 5540.

(34) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(35) CuF itself is unstable and not isolable in the absence of phosphine ligands. See (a) Cotton, F. A.; Wilkinson, G.; Murrillo; C. A.; Bochmann, M. In *Advanced Inorganic Chemistry*; Wiley-Interscience: New York, 1999. (b) Phosphine ligands stabilize CuF. The CuF·3PPh_3·2EtOH complex is a well-characterized, stable CuF complex. See Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153.

(36) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147.

(37) Suto, Y.; Kanai, M.; Shibasaki, M. Unpublished result. In ref 36, a preliminary result using CuF−tol-BINAP as the catalyst was reported (48%, 49% ee, at −30 °C for 85 h).

(38) Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288.

(39) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225.

(40) For examples of catalytic asymmetric reductive aldol reactions of aldehydes, see (a) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (b) Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (c) Russell, A. E; Fuller, N. O; Taylor, S. J.; Aurriset, P.; Morken, J. P. *Org. Lett.* **2004**, *6*, 2309. (d) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972.

(41) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(42) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.

(43) For examples of Cu-catalyzed asymmetric conjugate reduction, see (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (b) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. See also the chapter written by Krause and Lipshutz in this issue.

(44) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292.

(45) (a) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440. (b) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403.

(46) Recent examples of catalytic asymmetric alkylative aldol reactions to aldehydes (a) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984. (b) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874. (c) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306. (d) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977.

(47) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439.

(48) Jeulin, S.; de Paule, S. D.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320.

(49) For reviews of asymmetric Mannich reactions, see (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10. (c) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348.

(50) Tetrasubstituted carbon-forming catalytic enantioselective Mannich reactions of special ketoiminoesters have been reported by Jørgensen, see (a) Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jørgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 6145. (Zn catalysis). (b) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed* **2004**, *43*, 4476. (organocatalysis). For a general diastereoselective synthesis of β,β-disubstituted amino acids, see (c) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846. (d) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376.

(51) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500.

(52) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Vittanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019.

(53) Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536.

(54) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895.

(55) For other examples of catalytic enantioselective addition of zinc acetylide to ketones not using a copper catalyst, see (a) Wang, Q.; Zhang, B.; Hu, G.; Chen, C.; Zhao, Q.; Wang, R. *Org. Biomol. Chem.* **2007**, *5*, 1161, and references cited thereinFor a review of catalytic enantioselective alkynylation of ketones, see (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873.

(56) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057.

(57) Motoki, R.; Tomita, D.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 8083.

(58) (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (b) Fässler, C. S.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843.

(59) For other selected examples of catalytic enantioselective alkynylation of aldehydes, see (a) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (b) Yamashita, M.; Yamada, K.-i.; Tomioka, K. *Adv. Synth. Catal.* **2005**, *347*, 1649. (c) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207. Selected

examples of catalytic enantioselective alkynylation of aldimines: (d) Wei, C.; Li, C. J. J. *Am. Chem. Soc.* **2002**, *124*, 5638. (e) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (f) Bisai, A.; Singh, V. K *Org. Lett.* **2006**, *8*, 2405. Catalytic enantioselective alkynylation of ketimines has yet to be developed.
(60) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.
(61) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658.
(62) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757.
(63) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.
(64) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997.
(65) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967.
(66) For examples of catalytic enantioselective carbonyl-ene reactions of glyoxylates, see (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (b) Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5478.
(67) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936.
(68) Yang, D.; Yang, M.; Zhu, N.-Y. *Org. Lett.* **2003**, *5*, 3749.
(69) Langner, M.; Rémy, P.; Bolm, C. *Synlett* **2005**, 781.
(70) For representative reviews, see (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.
(71) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Rochi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.
(72) For examples of catalytic enantioselective allylation of ketones using allyltin reagents, see (a) Tagliavini, E.; Casolari, S.; D'Addario, D. *Org. Lett.* **1999**, *1*, 1061. (b) Cunningham, A.; Woodward, S. *Synthesis* **2002**, 43. (c) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697. (d) Kii, S.; Maruoka, K. *Chirality* **2003**, *15*, 67. (e) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743. (f) Wooten, A. J.; Kim, J. G.; Walsh, P. J. *Org. Lett.* **2007**, *9*, 381. (g) Zhang, X.; Chen, D.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 5227.
(73) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536.
(74) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.
(75) For a recent paper discussing the metallotropic equilibrium of allyllic metal compounds, see Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642.
(76) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556.
(77) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3701.
(78) Lou, S.; Moquist, P.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.
(79) For examples of enhancing the reactivity of allylboronate by increasing the Lewis acidity of the boron via coordination of the alkoxy ligand to catalytic Lewis acid metals, see (a) Kennedy, J. W.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518.
(80) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752.
(81) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
(82) For a general asymmetric allylation of ketone-derived *N*-acyl hydrazones using a chiral allylsilane, see Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.
(83) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192.
(84) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *80*, 1055.
(85) Catalytic enantioselective addition of aryl and alkenyl groups to simple ketones requires organozinc reagents as nucleophiles. For examples, see (a) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239. (b) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651. (c) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (d) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355. Review (e) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284. Review (f) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749.
(86) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009.
(87) Corma, A.; García, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. *Chem. Commun.* **2002**, 1058.
(88) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901.
(89) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127.
(90) (a) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138. (b) Tomita, D.; Kanai, M.; Shibasaki, M. *Chem. Asian J.* **2006**, *1*, 161.
(91) For example Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 985.
(92) (a) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055. (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (d) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940. (e) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692. (f) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260. (g) See also Tomioka's chapter in this thematic issue.
(93) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743.
(94) (a) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651. (b) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (c) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416. (d) Forrat, V. J.; Pieto, O.; Ramón, D. J.; Yus, M. *Chem.—Eur. J.* **2006**, *12*, 4431. (e) Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4535.
(95) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(96) (a) Johannsen, M.; Yao, S.; Jørgensen, K. A. *Chem. Commun.* **1997**, 2169. (b) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599. For a review of catalytic asymmetric hetero-Diels−Alder-type reaction of ketones, see. (c) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093.
(97) Ghosh, A. K.; Shirai, M. *Tetrahedron Lett.* **2001**, *42*, 6231.
(98) Dalko, P. I.; Moisan, L.; Cossy, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 625.
(99) For other examples of catalytic asymmetric hetero-Diels−Alder-type reaction of activated ketones (pyruvates), see (a) Furuno, H.; Kambara, T.; Tanaka, Y.; Hanamoto, T.; Kagawa, T.; Inanaga, J. *Tetrahedron Lett.* **2003**, *44*, 6129. (rare earth metal catalyst). (b) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284. (organocatalyst)
(100) Landa, A.; Richter, B.; Johansen, R. L.; Minkkilä, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 240.
(101) For examples, see (a) Cabrera, S.; Gómez-Arrayás, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (c) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043. (d) Carrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587. (e) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Synthesis* **2007**, 950. (f) Review Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272.
(102) For examples of asymmetric [3 + 2] cycloadditions other than using Cu catalyst, see (a) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. (Zn). (b) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (Ag). (c) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (Ag). (d) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (Ag)
(103) Cross-coupling reactions and olefin metathesis are typical examples.
(104) Three reports relevant to this chapter appeared during the review. See Sedelmeier, J.; Hammerer, T.; Bolm, C. *Org. Lett.* **2008**, *10*, 817. (b) Doherty, S.; Goodrich, P.; Hardacre, C.; Pârvulescu, V.; Paun, C. *Adv. Synth. Catal.* **2008**, *350*, 295. (c) Mandoli, A.; Lessi, M.; Pini, D.; Evangelisti, C.; Salvadori, P. *Adv. Synth. Catal.* **2008**, *350*, 375.

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