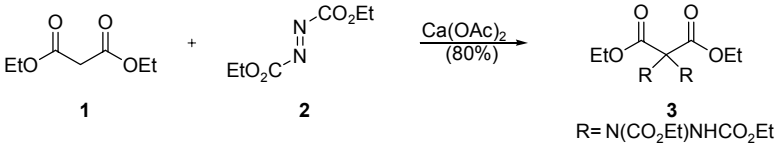
CATALYTIC ASYMMETRIC α-AMINATION OF CARBONYL COMPOUNDS USING AZODICARBOXYLATE ESTERS

Reported by Jeremy Cobb September 5, 2002

INTRODUCTION

The biological importance of enantiomerically pure natural and non-natural α-amino acids, α-amino hydrazides, α-amino carbonyls, α-amino alcohols, as well as *syn*-β-amino-α-hydroxyesters has stimulated considerable synthetic interest.[1] In particular, construction of these compounds by way of asymmetric catalysis has focused on both C-C and C-N bond forming reactions. Notable C-C bond forming reactions include catalytic asymmetric variants of the Strecker[2] and Mannich[3,4] reactions. Development of a catalytic asymmetric C-N bond forming reaction to access this class of compounds represents a major advancement in synthetic methodology.[5] Diels and Behncke first observed the reaction between diethyl malonate and diethyl azodicarboxylate (DEAD) (Scheme 1) to afford the adduct **3** in 1924.[6] Subsequently, other methods of amination using sources of electrophilic nitrogen including sulfonyl-azides,[7] sulfonyloxycarbamates,[8] 1-chloro-1-nitroso reagents,[9] and oxaziridines[10] have been developed. In the course of creating a diastereoselective variant of electrophilic amination β-hydroxyesters,[11] chiral imine modified carbonyl compounds,[12] as well as auxiliary based methods[5,7,13] have been developed. This review focuses on the development of metal- and proline-catalyzed asymmetric α-amination of enolate equivalents to azodicarboxylate esters.

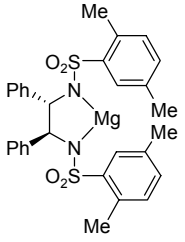
Scheme 1. Electrophilic Amination Reaction



1 **2** **3**

METAL-CATALYZED α-AMINATION

Magnesium Bis(sulfonamide)-Catalyzed Asymmetric Amination



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Attempts to promote a direct catalytic asymmetric α-amination of aryl-substituted carboximides was first undertaken by Evans and Nelson, using a chiral magnesium bis(sulfonamide) complex **4**.[14] The general reaction (Table 1) involves an aryl-substituted carboximide reacting with an azodicarboxylate ester of in the presence of catalyst **4** and 20 mol % of *N*-methyl-*p*-toluenesulfonamide. Aryl-substituted carboximides were chosen based upon their relative ease of enolization and propensity toward formation of well-defined Z-enolates. Under these conditions, amination was achieved using a variety of aryl-substituted carbox-imides in high yield with excellent enantio-selectivity. While the role

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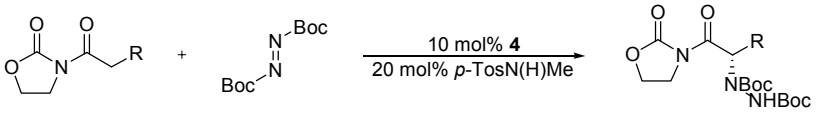
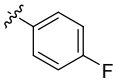
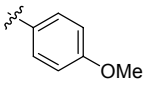
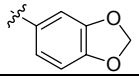
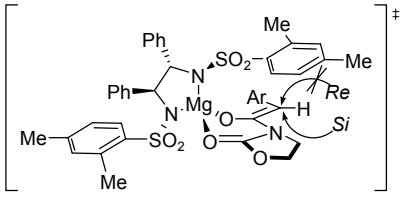
Table 1. Amination using a Chiral Magnesium Bis(sulfonamide) Catalyst



5 6 7

entry	R	T (°C)	time	% yield	er
1		-75	48h	92	93:7
2		-65	48h	97	95:5
3		-65	48h	93	93:7
4		-75	72h	85	91:9



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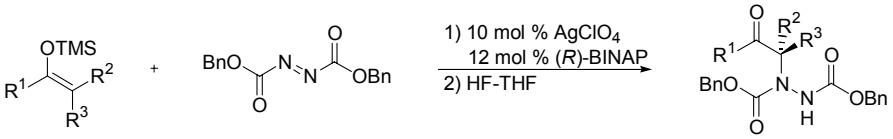
of *N*-methyl-*p*-toluene-sul-fonamide is not fully understood, it was proposed through kinetic studies that this additive accelerates the rate of protonation of the conjugate hydrazide, thereby accelerating catalyst turnover, which is the rate determining step. The proposed transition state leading to asymmetric induction follows a similar rationale to that proposed by Corey and coworkers for enantioselective Diels-Alder and aldol reactions using chiral bis-sulfonamides.[15] Corey proposes that the phenyl groups of the (1*S*,2*S*)-diphenylethylenediamine force the vicinal aryl substituents on the *N*-sulfonyl to the opposite face of the five-membered metallocycle. This would cause the *Re* face of the aryl-substituted carboxymide enolate to be blocked, favoring amination to occur from the less encumbered *Si* face (see transition structure **8**). This methodology, while providing high yield and excellent enantioenrichment, suffers by being limited only to aryl-substituted carboximides as viable precursors to amination.

Silver-Catalyzed Asymmetric Amination

Kobayashi and coworkers reported the first catalytic amination of silyl enol ethers[16] and subsequently reported a catalytic asymmetric variant using $AgClO_4$-BINAP.[17] The reaction (Table 2) involves either an aryl-enolsilane or silyl ketene acetal reacting with dibenzyl azo-dicarboxylate in the presence of a catalytic amount of $AgClO_4$ and BINAP. This affords enantioenriched hydrazides in high yield for both aryl-enolsilanes and silyl ketene acetals with moderate to excellent enantioselectivities. A marked increase in enantiomeric ratio (entries 1 and 2) is seen when mixtures of THF and aromatic solvents are used, although no explanation for this phenomenon is

Table 2. Amination using a $AgClO_4$-BINAP catalyst



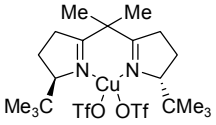
9 10 11

entry	R^1	R^2	R^3	Solvent	% yield	er
1	Ph	Me	H	A	99	84:16
2	Ph	Me	H	B	97	93:7
3	Ph	H	Et	A	93	79:21
4	OPh	Me	H	A	92	62:38
5	OPh	Me	H	C	73	75:25

A = THF
B = Mesitylene-THF (5:1)
C = Toluene-THF(5:1)

given. This method lacks general applicability due to limited substrate scope and variable enantioselectivity. Unlike the direct amination of the magnesium-catalyzed system, this method requires a separate step in which enolates are preformed; it is not a direct amination method in which enolate formation and subsequent amination occur in one pot.

Amination of Enolsilanes Using Chiral Copper (II) Complexes



12

In an attempt to further extend the utility of chiral copper (II) Lewis acid catalysts, Evans and Johnson sought to develop an enantioselective amination using copper-box **12**.[18] During the development of this reaction, it was observed that a catalyst loading of 25 mol % was required for complete conversion. Upon reduction of catalyst loading from 25 mol % to 10 mol %, incomplete conversion and diminished enantiomeric enrichment was observed. Evans postulated this inefficiency was due to competitive binding of the product to the catalyst. Addition of $Cu(OTf)_2$ (50 mol %) led to complete conversion with little effect on enantioselectivity, in some cases. However, this did not prove to be of general use, because highly reactive enolsilanes underwent amination via a racemic pathway catalyzed by $Cu(OTf)_2$. A substantial rate enhancement was observed upon addition of alcohol solvents, in particular trifluoroethanol. To probe the general mechanism and reason for rate acceleration by trifluoroethanol, *in situ* spectroscopic studies were carried out. An initial product (**16**) with a stretch of 1687 cm^{-1}, characteristic of the C=N stretch common to 5,6-dihydrooxadiazene, was observed (Scheme 2). This product, presumably the result of a formal hetero-Diels-Alder (HDA) reaction, is rapidly transformed to the hydrazide upon addition of triflouroethanol, as demonstrated by the disappearance of the stretch at 1687 cm^{-1} and appearance of a stretch at 1764 cm^{-1}. Evans proposes that this HDA goes through the standard transition state (**21**) proposed for similar copper-catalyzed HDA's, in which the geometry about the copper species is square planar.[19] The optimized conditions (Table 3) involves reaction of an enolsilane with an azodicarboxylate ester in the presence of a catalytic quantity of **12** and trifluoroethanol in order to facilitate catalyst turnover. Excellent enantiomeric ratios as well as high yields were obtained using arylketone enolsilanes, thioester silylketene acetals, and

Scheme 2. Mechanistic IR Spectroscopy Studies

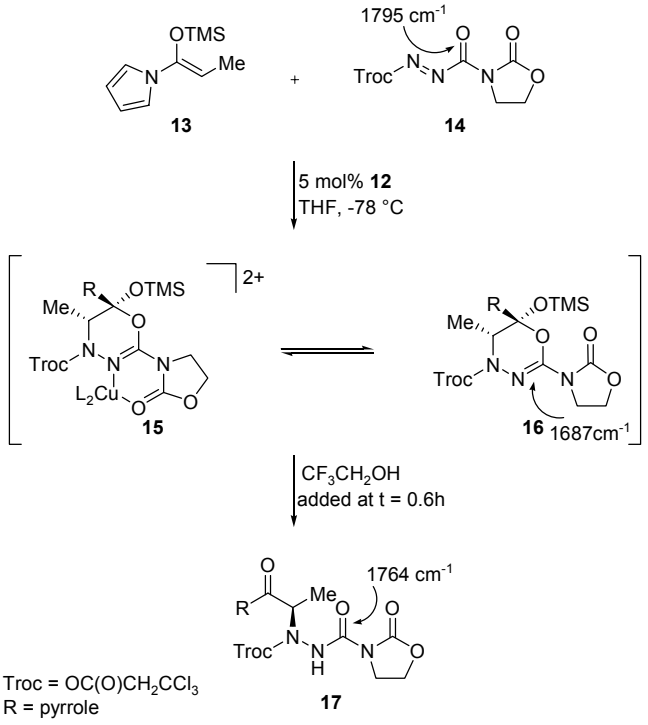
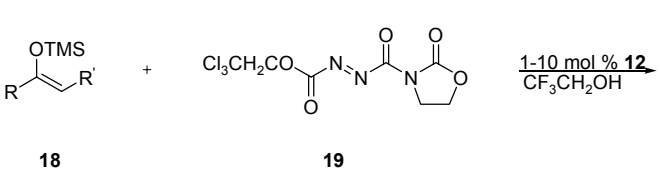
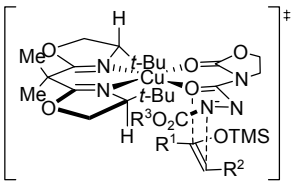


Table 3. Amination Using Copper (II) Complexes with Enolsilanes



18 19 20

entry	R	R'	T (°C)	time	% yield	er
1	Ph	Me	-20	2 min	95	99:1
2	Ph	*i*-Pr	-20	3h	86	99:1
3	*t*-BuS	Me	-20	2h	85	98:2
4		Me	-20	1 min	96	99:1
5		*i*-Pr	-20	5 min	65	99:1



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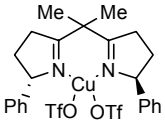
acylpyrrole enolsilanes. While this method gives both high yield and excellent enantiomeric enrichment it is limited to arylketones. Furthermore, increasing the size of R' causes competitive amination of the pyrrole ring resulting in diminished yield, (see entry 5). In comparison to the Kobayashi method described previously, this method also relies on the formation of the enolate prior the introduction of the azodicarboxylate ester rather than a direct amination protocol.

Amination of 2-Keto Esters using Chiral Copper (II) Complexes



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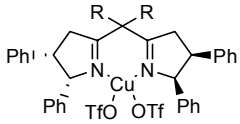
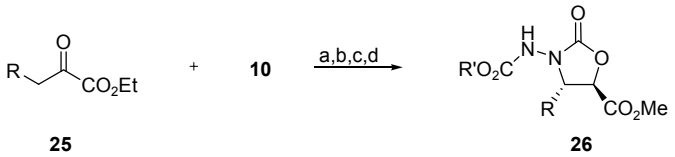


23R = H
24R = Me

Jørgensen and Juhl recently reported an alternative use of chiral copper (II) box-complexes in which the copper acts as a bi-functional catalyst in the complexation and enolization of an α-keto ester, with subsequent electrophilic attack of a suitable azodicarboxylate ester.[20] Jørgensen and coworkers had previously demonstrated the bi-functional nature of these chiral copper complexes in early studies involving catalytic asymmetric Mannich reactions.[21] In this Jørgensen system, the copper catalyst, complexed with the enolate nucleophile directs the attack of the azodicarboxylate ester elect-rophile. This is in contrast to the Evans system, where the catalyst plays the opposite role, complexation of the electrophile and guiding attack of the enolate. This asymmetric amination reaction, unlike the previously discussed amination methods, provides access to *syn*-β-amino-α-hydroxy esters, which are common moieties found in taxol analogues, as well as other biologically active natural products.[22] The procedure (Table 4) involves a one-pot, four-step reaction sequence, with the first step being reaction of an α-keto ester with a dibenzyl azodicarboxylate in the presence of a catalytic amount of copper-box **22**-**24**. It is noteworthy that reaction of α-keto ester **25** in the presence of the related catalyst **12** resulted in low yield and with nearly no enantiomeric enrichment. Ensuing reduction of the ketone functionality with *L*-Selectride in order to prevent racemization of the newly formed stereogenic center, followed by treatment with sodium hydroxide and trimethyl-silyl diazo-methane, affords oxazolidinone **26**. These products can be subsequently exposed to standard

hydrogenolysis conditions to remove the CBz group and treated with zinc to furnish the fully protected *syn*-β-amino-α-hydroxy esters. While good to excellent enantiomeric enrichment can be achieved, only moderate yields have been obtained. Catalyst **23** proved to be superior in yield and enantiomeric enrichment, especially with more sterically bulky R groups, which can be explained in part by the postulated transition state. Jørgensen proposed a transition state **27** in which both the enol and azodicarboxylate ester are coordinated to copper, with the enol coordinating in either a mono- or bi-dentate manner. Once chelated, the enol and azodicarboxylate ester are presumed to adopt a six-membered chairlike transition state in which the R group is placed in the less sterically encumbered pseudoequatorial position. While excellent enantiomeric ratios can be achieved, this method lacks applicability to general α-amination because of the requirement of the α-keto ester functionality. Thus, this methodology is not applicable to the synthesis of α-amino acids.

Table 4. Amination Using Copper (II) Complexes with 2-Keto Esters

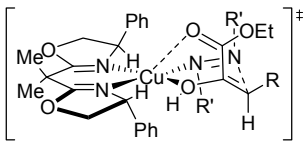


25 **26**

Key: (a) 10 mol % **22**-**24** (c) 0.5 N NaOH, 2h
(b) *L*-Selectride, -78 °C (d) $TMSCHN_2$

entry	R	Catalyst	Solvent	% yield	er
1	Me	**22**	A	33	89:11
2	Me	**23**	A	45	95:5
3	Me	**24**	A	36	89:11
4	Bn	**23**	B	57	95:5
5	*i*-Bu	**23**	B	51	97:3

A = CH_2Cl_2
B = THF



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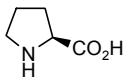
PROLINE CATALYZED α-AMINATION

Asymmetric α-Amination of Aldehydes Using Proline Catalysis

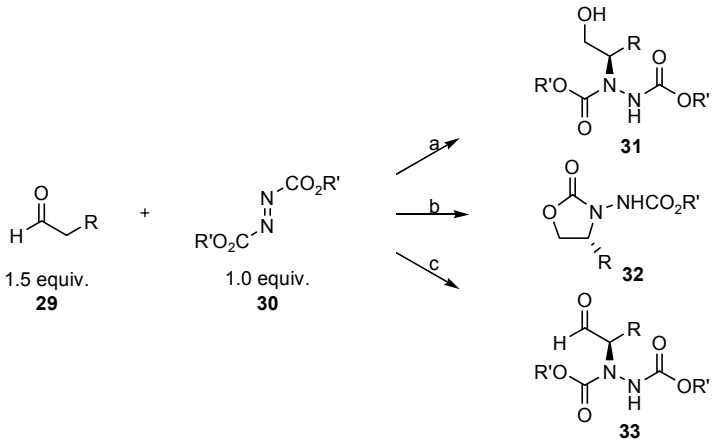
Proline (**28**) catalyzed reactions represent a burgeoning field of synthetic research as it has been used to effect such asymmetric transformations as direct aldol additions, Mannich reactions, and conjugate addition reactions, to name only a few.[23] The use of organocatalysis, in particular proline (**28**), represents a drastic change in approach to asymmetric α-amination. Recently, both List and Jørgensen disclosed the asymmetric α-amination of aldehydes using catalytic quantities of proline (**28**).[24,25] While these approaches (Table 5) parallel each other in many ways, minor variations in reaction conditions result in different products, as well as differences in yields and enantiomeric ratios. The reaction involves the addition of (*L*)-Proline (**28**) (10 mol %) to a solution of aldehyde and azodicarboxylate ester. List found that optimal enantiomeric enrichment of alcohol product **31**, was obtained when the reaction temperature of 0 °C and *in situ* reduction with sodium borohydride was employed (path a). Alternatively, Jørgensen found that aldehydes could be isolated directly, with diminished enantiomeric enrichment as reaction times increased, if the reaction was carried out in



28

methylene chloride at room temperature. This procedure furnishes aldehyde products of type **33**, as demonstrated by entries 2 and 5, and these could be converted to the fully protected α-amino acids via a multi-step protocol of oxidation, deprotection, protection, and hydrogenolysis. To access *N*-amino oxazolidinones, precursors to α-amino alcohols, Jørgensen's standard proline protocol was used, followed by addition of sodium borohydride and subsequent treatment with sodium hydroxide to facilitate cyclization to the desired product **32** (path b). These additional steps resulted in significantly diminished yields compared to List's route to α-amino alcohol precursors. As shown by entries 7 and 8, both List and Jørgensen were able to achieve high yields and excellent enatiomeric ratios using sterically hindered substrates. This method is easily performed on gram scale using inexpensive chiral catalyst and can be performed in the absence of solvent. The key shortcoming of this method is that excess aldehyde **29** is required, a serious disadvantage when using valuable aldehydes. Both List and Jørgensen proposed transition states that rationalize the observed stereochemical outcome. While these transition structures (Figure 1) involve the anticipated enamine intermediate, they differ substantially in the prediction of the lowest energy conformation of the transition state. Jørgensen proposed a boatlike transition state **34**, whereas List a chairlike transition state **35**, analogous to that proposed for proline- catalyzed intramolecular aldol reaction.[3] It is worth mentioning that transtion structure **35** lacks the hydrogen bond to the proline nitrogen, as Houk and coworkers have recently shown through a series of calculations that the N-H hydrogen bond does not lower the transition state energy in the corresponding aldol reaction.[26] While both transition structures

Table 5. Amination of Aldehydes Using Proline



Key: (a) **28** 10 mol %, CH_3CN, 0°C, 3h; $NaBH_4$, EtOH
(b) **28** 10 mol %, CH_2Cl_2, RT; $NaBH_4$, MeOH; 0.5 N NaOH
(c) **28** 10 mol %, CH_2Cl_2, RT; H_2O

entry	R	R'	method	% yield	er
1	Me	Bn	A	97	98:2
2	Me	*t*-Bu	C	99	95:5
3	Me	Et	B	67	97:3
4	*n*-Pr	Bn	A	93	98:2
5	Et	Et	C	77	98:2
6	Et	Et	B	77	95:5
7	*i*-Pr	Bn	A	99	98:2
8	*i*-Pr	Et	B	83	97:3
9	Bn	Bn	A	95	98:2
10	Bn	Et	B	68	95:5

A = List
B, C = Jørgensen

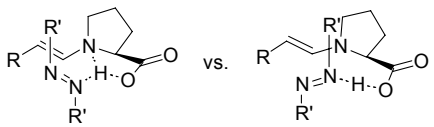


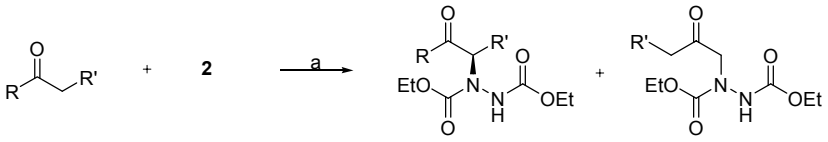
Figure 1. Proline Transition State

lead to identical products directed by the hydrogen bond from the carboxcylic acid of proline, they presumably possess unique energies, so one transition state should be the favored. However, the operative transition state has yet to be established.

Asymmetric α-Amination of Ketones Using Proline Catalysis

In conjunction with studies on asymmetric α-amination of aldehydes, Jørgensen and coworkers reported the formation of α-amino hydrazine ketones by way of amination using proline catalysis.[27] The optimized reaction (Table 6) involves the addition of proline (**28**) (10 mol %) to a solution of ketone and DEAD. Ensuing reduction with either sodium borohydride or titanium tetrachloride/triethylsilane and treatment with sodium hydroxide provides *syn* or *anti*-α-amino alcohol, respectively, as the *N*-amino oxazolidinone. As shown by entries 1-3, competitive amination at the two enolizable positions results when non-symmetrical ketones are employed, with competitive formation of the undesired constitutional isomer **38** increasing as the steric bulk of R' increases. Jørgensen proposed a similar transition state to that previously proposed for aldehyde **29**. Formation of the *E*-enamine was anticipated to be favored in order to prevent steric interactions with the trisubstituted nitrogen. In addition, the smaller substituent is proximal to proline to avoid steric repulsion. This preferred enolization leads to the observed products **37**. While this method achieves moderate to good yields with excellent enantioselectives, it suffers by requiring 1.5 equivalents of ketone. Moreover, unselective enolization leading to products **38** reveals that further development is needed.

Table 6. Amination Ketones Using Proline



Key: (a) **25** 10 mol %, CH_3CN, RT; H_2O

entry	R	R'	ratio (**37**:**38**)	% yield **37**	er
1	Me	Me	91:9	73	98:2
2	Me	Bn	82:18	75	99:1
3	Me	*i*-Pr	76:24	52	99:1
4	Me	Me	-	79	97:3

CONCLUSION

Significant advances in the development of efficient methods for creating C-N bonds by way of catalytic asymmetric α-amination to produce α-amino acids, α-amino hydrazides, α-amino aldehydes/ketones, α-amino alcohols, as well as *syn*-β-amino-α-hydroxyesters have been made. Metal catalyzed α-amination using magnesium, silver, and copper species paired with various asymmetric ligands offer powerful catalytic methods for the construction of these desired adducts. The recent introduction of proline as a viable catalyst for asymmetric α-amination offers a method in which an

inexpensive organocatalyst can be used to furnish the aforementioned products. While these methods offer many advantages, significant advances in the realm of catalytic asymmetric α-amination are still necessary. Future studies should focus on the further elucidation of transition states of the proline-catalyzed methodologies. In addition, the development of catalytic methodologies that utilize alternate sources of electrophilic nitrogen would facilitate the introduction of nitrogen electrophiles that could be transformed in a more facile manner to highly desirable protected or free amines.

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