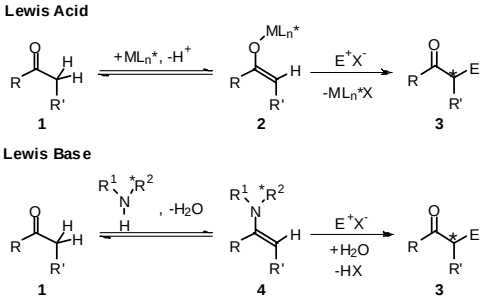
CATALYTIC, ENANTIOSELECTIVE, ELECTROPHILIC α-FUNCTIONALIZATION OF CARBONYL COMPOUNDS

Reported by Nathan Werner September 28, 2006

INTRODUCTION

Carbonyl compounds occupy a central role in synthetic chemistry because of the broad range of carbon subunits and functional groups that can be derived from them.[1] Enantiomerically pure, α-heteroatom-substituted carbonyl compounds represent a family of derivatives important in nearly all fields of organic chemistry.[2] Access to this class can be obtained through attack of nucleophilic enolates or enamines on electrophilic heteroatom sources (Scheme 1).

Scheme 1. General Catalytic Carbonyl Activation



Although this transformation seems straightforward there are two major challenges for enantioselective, α-heteroatom functionalization of carbonyl compounds. The first is to identify chiral catalysts able to discriminate the enantiotopic faces of the carbonyl functionality while favoring the kinetic, enantioselective process. The second is to tune electrophilic reagents to allow for catalytic processes without significant background reaction. Chiral modification of carbonyl compounds is well understood, due in part, to the extensive studies of the enantioselective aldol reaction, but developing suitably electrophilic sources of heteroatoms has proven to be a difficult challenge. This can be attributed to the fact that most heteroatom sources are either unreactive with metalloenolates or enamine nucleophiles, or far too reactive for enantioselective processes. Recently, new reagents have been introduced that meet the challenge of providing the reactivity needed to make enantioselective α-heteroatom functionalization a reality.

α-AMINATIONS

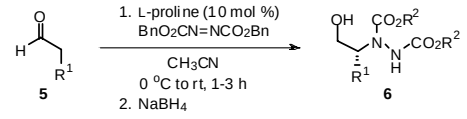
Azodicarboxylates as the Electrophilic Source of Nitrogen

The two commonly used sources of electrophilic nitrogen are azodicarboxylates and nitrosobenzene. Azodicarboxylates can serve as electrophiles for reactions of metalloenolates, enamines

Copyright © 2006 by Nathan Werner

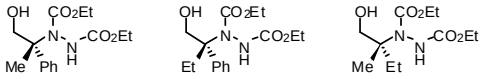
and enol derivatives. Jørgensen and List have independently reported the use of proline and azodicarboxylate to afford α-hydrazino aldehydes.[3,4] These reactions proceed with excellent yields and high enantioselectivities with a variety of aldehydes (Table 1). α,α-Disubstituted aldehydes are also competent substrates, although yields are moderate and selectivities are variable.[5] The stereocenter produced is prone to epimerization upon purification, therefore the products are reduced *in situ* with $NaBH_4$ to primary alcohols. These chiral β-hydroxycarbazides can then be further elaborated to the corresponding oxazolidinones in greater than 60% yield by hydrogenation over Raney nickel followed by treatment with phosgene.[4]

Table 1. α-Amination with Azodicarboxylate



5 **6**

entry	R^1	R^2	yield, %	er
1	Me	Bn	97	98:2
2	*i*-Pr	Bn	99	98:2
3	Bn	Bn	95	98:2



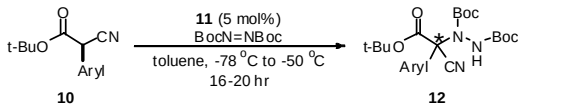
7 62% yield 90:10 er

8 59% yield 90:10 er

9 52% yield 64:36 er

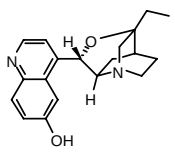
Jørgensen and co-workers have also described the catalytic, enantioselective amination of α-cyanoacetates and β-dicarbonyl compounds with β-isocupreidine (β-ICD **11**) to form tetrasubstituted stereocenters.[6] This highly efficient reaction proceeds with 5 mol % of β-ICD to give the desired product with excellent levels of enantioselectivity for a variety of aryl-substituted α-cyanoacetates as well as a few β-dicarbonyl compounds (Table 2). Cleavage of the N–N bond without loss of enantiomeric purity is achieved by exposure to trifluoroacetic acid and pyridine, followed by treatment with SmI_2.

Table 2. α-Amination Catalyzed by β-Isocupreidine

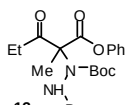


10 **12**

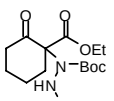
entry	Aryl	yield, %	er
1	Ph	99	>99:1
2	2-F-C_6H_4	99	99:1
3	3-Me-C_6H_4	99	98:2
4	4-NO_2-C_6H_4	99	96:4
5	4-MeO-C_6H_4	95	94:6



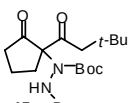
11



13 99% yield 95:5 er



14 86% yield 92:8 er

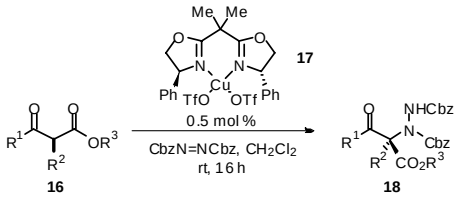


15 90% yield 92:8 er

Copyright © 2006 by Nathan Werner

Azodicarboxylates can also serve as electrophiles for the α-amination reaction of 1,3-dicarbonyl compounds via metalloenolates. Jørgensen has described the use of C_2-symmetric Cu(II) bis(oxazoline) complexes to catalyze the amination reaction of α-substituted β-ketoesters (Table 3).[7] The reaction generally affords high yields and enantioselectivities although the substrate scope is limited to 1,3-dicarbonyl compounds because two-point binding of the Cu(II) catalyst is required for good stereocontrol.

Table 3. α-Amination Using a Copper(II)-Bis(oxazoline) Catalyst



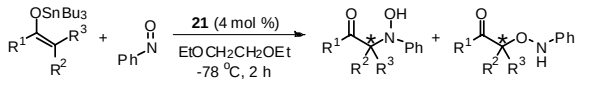
entry	R^1	R^2	yield, %	er
1	Me	Me	91	98:2
2	Et	Me	98	99:1
3	Ph	Me	81	94:6
4	-$(CH_2)_3$-		96	>99:1
5	-$(CH_2)_4$-		96	>99:1
6	-$(CH_2)_5$-		70	>99:1

Nitrosobenzene as the Electrophilic Source of Nitrogen

The use of nitrosobenzene as a nitrogen equivalent in catalytic reactions has only recently been described, even though the reagent has been known for more than 100 years.[8,9] Although nitrosobenzene is an attractive electrophilic source of nitrogen, predicting the siteselectivity is difficult because of an equilibrium between monomer and azodioxy dimer. Nevertheless, in 2004, Yamamoto described the addition of trialkyltin enolates to nitrosobenzene using a catalytic amount of (*R*)-BINAP·$(AgOTf)_2$ complex to afford α-oxyamines.[10] Cyclic tin enolates give excellent yields and enantioselectivities (Table 4). Jiang *et al.* recently reported the N-selective α-amination reaction of α-branched aldehydes with nitrosobenzene catalyzed by L-prolinamide.[11] This group proposes that hydrogen bonding between either the alcohol or amide, and the oxygen of the nitroso group leads to a more electrophilic nitrogen favoring N-selective attack of the enamine. Although only moderate yields and enantioselectivities are seen using this method, this catalyst provides valuable insight into the nitroso electrophile.

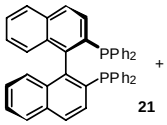
Copyright © 2006 by Nathan Werner

Table 4. N-Selective Tin Enolate/Nitrosobenzene Amination



19 20 22 23

entry	enolate		yield, %	N-/O-	er of N-adduct
1		n = 1	90	97/3	93:7
2		n = 2	95	96/4	>99:1
3		n = 3	96	>99/1	98:2
4			94	>99/1	94:6



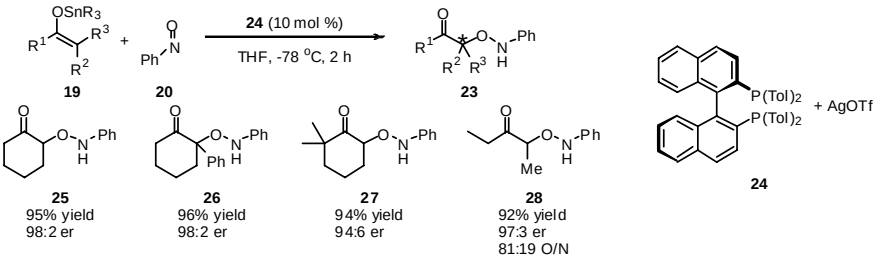
21 + 2 AgOTf

α-CHALCOGENATION

α-Oxygenation

Nitrosobenzene as the electrophilic source of oxygen. The first catalytic, enantioselective oxygenation reaction using nitrosobenzene was reported by Yamamoto and co-workers in 2003. The use of a catalyst with 1:1 AgOTf:(*R*)-Tol-BINAP stoichiometry afforded the corresponding α-hydroxy ketones in excellent yields with excellent enantiomeric purity (Scheme 2).[12] No explanation for the change in O/N-selectivity is offered and poor O/N-selectivity is seen with acyclic tin enolates. This seminal report stimulated interest in the use of nitrosobenzene as an electrophilic source of oxygen.

Scheme 2. O-Selective Tin Enolate/Nitrosobenzene Oxygenation



19 20 23

25 95% yield 98:2 er

26 96% yield 98:2 er

27 94% yield 94:6 er

28 92% yield 97:3 er 81:19 O/N

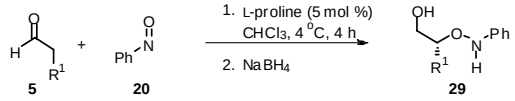
24

Soon after this initial report, Zhong, MacMillan, and Hayashi independently reported the O-selective proline-catalyzed reaction of aldehydes with nitrosobenzene using different solvents and substrates.[13,14,15] In contrast to the previously mentioned report by Jiang, the difference in O/N-selectivity observed between the L-proline- and L-prolinamide-catalyzed reaction is thought to result from activation of the oxygen through protonation of the nitrogen of nitrosobenzene by the carboxylic acid function of L-proline. Aldehydes undergo the transformation with good yield and excellent enantioselectivity (Table 5). Ketones are more challenging substrates because of their diminished ability to reversibly form enamines and the presence of two enolizable reactive sites. These difficulties were diminished using a slow addition of nitrosobenzene along with symmetrical ketones. Problems with acyclic ketones still exist in this system as a 10-fold excess of ketone must be employed to achieve

Copyright © 2006 by Nathan Werner

similar yields to that of cyclic ketones.[16,17] Cleavage of the O–N bond of the resulting α-aminooxy aldehyde or ketone can be accomplished by catalytic hydrogenation using Adams' catalyst in greater than 95% yield without loss in enantiomeric purity.[13]

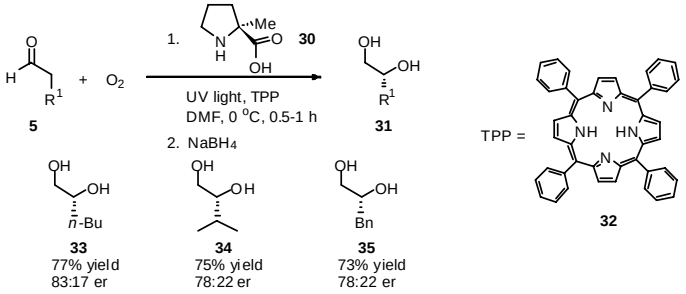
Table 5. α-Oxygenation Catalyzed by L-Proline



entry	R^1	yield, %	er
1	*n*-Bu	79	99:1
2	*i*-Pr	85	>99:1
3	Ph	60	>99:1
4	$(CH_2)_2OTIPS$	76	99:1

Singlet oxygen as the electrophilic source of oxygen. The amino acid catalyzed α-hydroxylation of aldehydes with molecular oxygen to afford diols and α-hydroxy aldehydes was reported by Cordova *et al.* in 2004.[18,19] Aldehydes of different structure are exposed to singlet oxygen and an amino acid catalyst. The reactive electrophile is generated using UV light and the photosensitizer tetraphenylporphyrin **32**. The empirically optimized catalyst, L-α-methyl proline **30**, provides increased stereoselectivity relative to natural amino acid catalysts. Although the modest yields and enantioselectivities reported to date will limit general application, the strength of this reaction lies in the excellent atom economy of the electrophile (Scheme 3).

Scheme 3. α-Oxygenation Using Singlet Oxygen



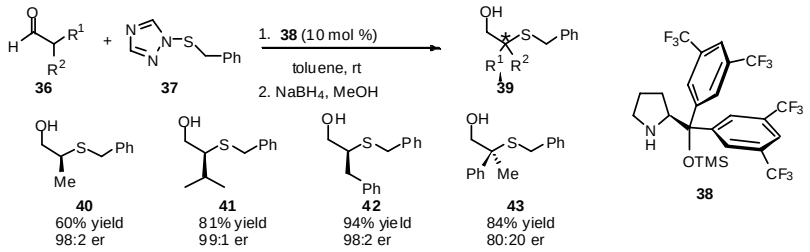
α–Sulfenylation and α-Selenenylation

Despite the synthetic potential of α-sulfenylated aldehydes and the merits of organocatalytic processes, only one report of the catalytic enantioselective α-sulfenylation of aldehydes exists in the literature.[20,21] Other methods for the preparation of chiral α-sulfenylated compounds are known but these are multiple step sequences that require the use of chiral auxiliaries.[22] A survey of various sulfenylating reagents and multiple secondary amine catalysts identified a *N*-sulfenyltriazole and a modified prolinol, **38**, as the optimal electrophile and catalyst respectively.[21] The enantioselective, α-

Copyright © 2006 by Nathan Werner

sulfenylation of aldehydes proceeds with variable yield and enantioselectivity (Scheme 4). A single report of catalytic, enantioselective α-selenenylation has also been published.[23]

Scheme 4. α-Sulfenylation with *N*-Sulfenyltriazole

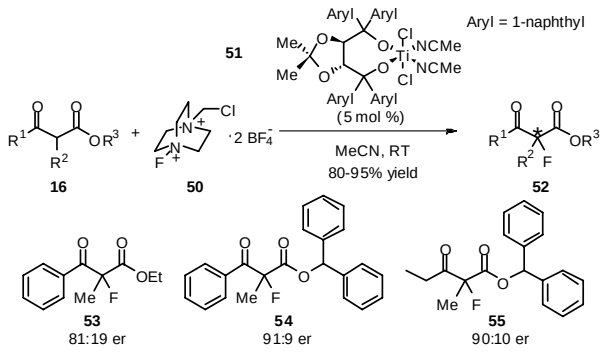


α–HALOGENATION

α-Fluorination

Selectfluor® as the electrophilic source of fluorine. The catalytic, enantioselective α-fluorination reaction is the most actively studied halogenation reaction because of the importance of fluorinated compounds in medicinal chemistry.[24] The first example of a catalytic, enantioselective α-fluorination was reported by Togni and Hintermann in 2000.[25] In this report a TADDOL-titanium complex, **51**, catalyzes the α-fluorination of β-ketoesters with using Selectfluor®, **50**, as the source of electrophilic fluorine (Scheme 5).

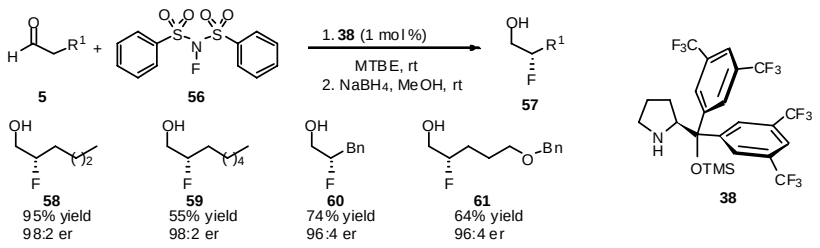
Scheme 5. α-Fluorination of β-Ketoesters



N-Fluorobenzenesulfonimide (NFSI) as the electrophilic source of fluorine. Jørgensen, Barbas, and MacMillan have all described the use of NFSI as the electrophilic source of fluorine. Jørgensen developed a bulky, silylated prolinol derivative, **38**, whereas Barbas and MacMillan developed very similar imidazolidinone catalysts for this process (Scheme 6).[26,27,28] Jørgensen and Barbas both reported the α-fluorination of not only linear but also α-branched aldehydes that resulted in the formation of tetrasubstituted stereogenic centers.

Copyright © 2006 by Nathan Werner

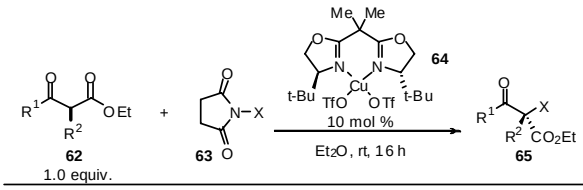
Scheme 6. α-Fluorination of Aldehydes



α-Chlorination and Bromination

A variety of methods using *N*-halosuccinimide reagents as the electrophilic source of heteroatom have been developed. Employing inexpensive *N*-chlorosuccinimide as the electrophilic chlorine source and a (2*R*,5*R*)-diphenylpyrrolidine catalyst, Jørgensen reports high yields (90-99%) and good enantioselectivities (85:15 to 98:2 er) with a variety of aldehydes.[29] A 4,5-diphenylimidazolidine catalyst was later reported for the α-chlorination of ketones providing moderate yields (40-83%), yet high enantioselectivities (93:7 to 99:1 er).[30] Jørgensen has also developed a method of α-chlorinating and α-brominating β-ketoesters in good yield and moderate enantioselectivity using Cu(II) bis(oxazoline) catalyst (Table 6).[31]

Table 6. α-Chlorination and α-Bromination of β-Ketoesters



entry	R^1	R^2	X	equiv.	yield, %	er
1	Me	Me	Cl	1.2	98	88:12
2	*i*-Pr	Me	Cl	1.2	88	74:26
3	Ph	Me	Cl	1.2	98	76:24
4		$-(CH_2)_4-$	Cl	1.2	99	88:12
5	Me	Me	Br	1.1	98	90:10
6	*i*-Pr	Me	Br	1.1	70	73:27
7	Ph	Me	Br	1.1	95	70:30
8		$-(CH_2)_4-$	Br	1.1	85	91:9

CONCLUSIONS AND OUTLOOK

α-Heteroatom functionalization of carbonyl compounds can now be achieved in a catalytic enantioselective fashion. Both metalloenolate and enamine nucleophiles have been utilized in these transformations. The use of enamine nucleophiles has expanded the scope of α-heteroatom functionalization to include aldehydes, although acyclic ketones remain problematic. Metalloenolate nucleophiles are useful within a limited substrate scope, but require two-point binding of the catalyst or cyclic trialkyltin enolates. Further development of methods for the α-functionalization of acyclic

Copyright © 2006 by Nathan Werner

ketones is needed, as these substrates pose problems in the systems known to date. Despite these limitations, significant progress toward this transformation has been made, and a variety of heteroatoms can be directly installed with high degrees of enantiomeric selectivity.

REFERENCES

1. Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Transformations*; Wiley: New York, 1999.
2. Marigo, M.; Jørgensen, K. *Chem. Comm.* **2006**, 2001-2011.
3. Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, 41, 1790-1793.
4. List, B. *J. Am. Chem. Soc.* **2002**, 5656-5657.
5. Vogt, H.; Vanderheiden, S.; Brase, S. *Chem Commun.* **2003**, 2448-2449.
6. Saaby, S.; Bella, M.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2004**, 126, 8120-8121.
7. Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, 124, 2420-2421.
8. Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514-3525.
9. Baeyer, A. *Chem. Ber.* **1874**, 7, 1638-1640.
10. Yamamoto, H.; Momiyama, N. *J. Am. Chem. Soc.* **2004**, 126, 5360-5361.
11. Guo, H.; Cheng, L.; Cun, L.; Gong, L.; Mi, A.; Jiang, Y. *Chem. Commun.* **2006**, 429-431.
12. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, 125, 6038-6039.
13. Zhong, G. *Angew. Chem. Int Ed.* **2003**, 42, 4247-4250
14. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, W. C. *J. Am. Chem. Soc.* **2003**, 125, 10808-10809.
15. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, 44, 8293-8296.
16. Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem. Int. Ed.* **2004**, 43, 1109-1112.
17. Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, 43, 1112-1115.
18. Cordova, A.; Sunden, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, 126, 8914-8915.
19. Sunden, H.; Engqvist, M.; Casas, J.; Ibrahem, I.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, 43, 6532-6535.
20. Wang, W.; Li, H.; Wang, J.; Liao, L. *Tetrahedron Lett.* **2004**, 45, 8229-8231.
21. Marigo, M.; Wabnitz, T.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, 44, 794-797.
22. Evans, D.; Campos, K.; Tedrow, J.; Michael, F.; Gagne, M. *J. Am. Chem. Soc.* **2000**, 122, 7905-7935.
23. Wang, J.; Li, J.; Mei, Y.; Lou, B.; Xu, D.; Xie, D.; Guo, H.; Wang, W. *J. Org. Chem.* **2005**, 70, 5678-5687.
24. Smart, B. *J. Fluorine Chem.* **2001**, 109, 3-11.
25. Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, 39,4359-4362.
26. Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, 44, 3703-3706
27. Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, 44, 3706-3710
28. Beeson, T.D. MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, 127, 8826-8828.
29. Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2004**, 126, 4790-4791.
30. Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2004**, 43, 5507-5510.
31. Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, 10, 2133-2137.

Copyright © 2006 by Nathan Werner