ORGANIC LETTERS

2011
Vol. 13, No. 21
5792–5795

Copper(I) Catalyzed Regioselective Asymmetric Alkoxyamination of Aryl Enamide Derivatives

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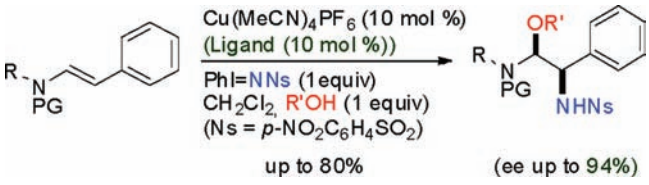
Received September 1, 2011

ABSTRACT



The copper(I) catalyzed reaction of an enamide with an iminoiodane, in the presence of an alcohol, triggers the direct alkoxyamination of the double bond. This transformation represents a straightforward access to α-amino aminals in a completely regio- and diastereoselective manner. Use of a chiral Box ligand allows this reaction to be carried out in an enantioselective fashion.

Since the seminal work of Breslow,[1] Mansuy,[2] and Evans,[3] iminoiodanes[4] have gained notoriety as highly versatile nitrenoid precursors, most notably to promote metal-catalyzed alkene aziridination and alkane amidation through C−H insertion. Over the past 25 years, research groups have striven to broaden the usefulness of these reagents by designing more practical and selective transformations.[5] This challenge was partly met by Evans who rapidly developed an enantioselective version[3b] of the copper-catalyzed aziridination reaction and extended the substrate scope from alkenes to silyl enol ethers.[3c] The latter are of particular interest since they allow the formal α-amination of a carbonyl compound (Scheme 1, eq 1).[3,6] Curiously, enamines have practically never been used as substrates for this type of reaction. We thus decided to probe the reactivity of enamine derivatives **1** toward iminoiodanes in the presence of copper catalysts. In particular, the question arose as to whether an amino-aziridine such as **2** could be generated and, if so, how it would evolve upon reaction with a nucleophile (Scheme 1, eq 2). Careful study of the literature only revealed a handful of examples of

(1) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400–1401.

(2) (a) Mansuy, D.; Mahy, J.-P.; Duréault, A.; Bédi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161–1163. (b) Mahy, J.-P.; Bédi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1517–1524.

(3) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744–6746. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753.

(4) (a) Abramovitch, R. A.; Bailey, T. D.; Takaya, T.; Uma, V. *J. Org. Chem.* **1974**, *39*, 340–345. (b) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361–362. For a review see:(c) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571–1586.

(5) For reviews, see ref 4c and (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619. (b) Li, A.-H.; Dai, L.-X. *Chem. Rev.* **1997**, *97*, 2341–2372. (c) McCoull, W.; Davies, F. A. *Synthesis* **2000**, 1347–1365. (d) Müller, C.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919. (e) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379–3394. (f) Padwa, A. In *Comprehensive Heterocyclic Chemistry*, Vol. III; Katritzky, A. R., Ed.; Elsevier: 2008; Vol. 18, pp 1−97. (g) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061–3394. (h) Karila, D.; Dodd, R. H. *Curr. Org. Chem.* **2011**, *15*, 1507–1538.

(6) (a) Nakanishi, M.; Salit, A.-F.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1835–1840. (b) Adam, W.; Roschmann, K. J.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **2000**, 557–561 and references therein.

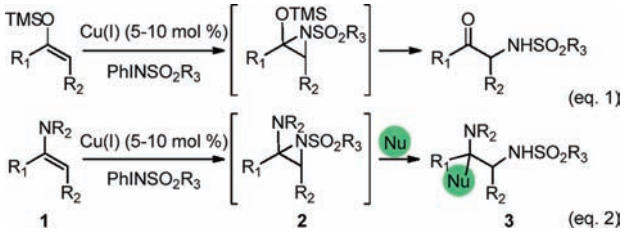
(7) (a) Warren, B. K.; Knaus, E. E. *J. Med. Chem.* **1981**, *24*, 462–464. (b) Ondrus, T. A.; Pednekar, P. P.; Knaus, E. E. *Can. J. Chem.* **1985**, *63*, 2362–2368. (c) Sunose, M. K.; Anderson, M.; Orpen, A. G.; Gallagher, T.; Macdonald, S. J. F. *Tetrahedron Lett.* **1998**, *39*, 8885–8888. (d) Katritzky, A. R.; Yao, J.; Bao, W.; Qi, M.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 346–350. (e) Kuznetsov, M. A.; Kuznetsova, L. M.; Schantl, J. G.; Wurst, K. *Eur. J. Org. Chem.* **2001**, 1309–1314.

(8) (a) Adam, W.; Reinhardt, D. *Tetrahedron* **1995**, *51*, 12257–12262. (b) Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 8885–8888. (c) Snider, B. B.; Zeng, H. *Org. Lett.* **2000**, *2*, 4103–4106. (d) Snider, B. B.; Zeng, H. *Org. Lett.* **2002**, *6*, 1087–1090. (e) Xiong, H.; Hsung, R. P.; Shen, L.; Hahn, J. M. *Tetrahedron Lett.* **2002**, *43*, 4449–4453.

10.1021/ol202367d
Published on Web 10/05/2011

amino-aziridines[7] and amino-epoxides,[8] which are invariably highly prone to nitrogen-assisted opening to generate a zwitterion that can then be trapped by a nucleophile.[7c−e,8] Similar intermediates have also been postulated in the case of the reaction of indoles with nitrenoids which, after reaction with an internal or external nucleophile, leads to oxyamination adducts.[9]

Scheme 1. Initial Endeavor

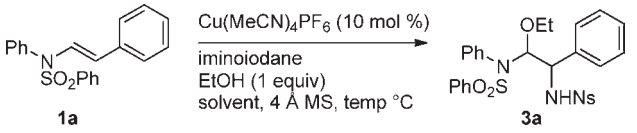


In our initial design, the sequence envisioned would lead to densely functionalized diamines such as **3** (Scheme 1) present in various bioactive natural products. For instance, marine indole derivatives trachycladindoles E and F possess a cyclic hydroxy-guanidine moiety which is crucial for cytotoxic activities.[10] Within the vast family of antitumor tetrahydroisoquinoline derivatives, many saframycins and congeners[11] display a cyclic α-amino hemiaminal or the corresponding α-aminonitrile.

The lack of practical procedures to easily prepare enamines, substrates reputed for their instability, may have curbed the study of their reactivity toward nitrenoid reagents. However, the recent development of efficient coupling reactions between amines and alkene halides or vinyl boron derivatives now provides rapid access to diversely substituted enamines.[12] In our hands, conditions developed by Buchwald using vinyl halides[12a] were successfully applied to a broad range of secondary amines and anilines, including sulfonamides which had not been previously utilized in this kind of cross-coupling reaction. In this study, sulfonamide based enamides appeared as choice substrates, due to their well-known robustness.[13]

Having several enamides in hand, our initial study began with styrylsulfonamide **1a** which was reacted with the nosylamine-derived iminoiodane (PhINNs) in the presence of a catalytic amount of copper(I) catalyst (Table 1, entry 1). Despite all our efforts, the expected aziridine **2a** could never be observed. Assuming the high reactivity of the latter was at play, we attempted to trap it in situ with a nucleophile. Thus, when the same reaction was run in the presence of 1 equiv of ethanol, the α-amino-aminal **3a** was isolated as a single diastereomer, albeit in low yield possibly due to competing solvolysis of the iminoiodane (entry 2).[14] Screening of reaction conditions quickly showed that dichloromethane was the most suitable solvent for this transformation and that running the reaction at a lower temperature (−10 °C) allowed the formation of **3a** with a 60% yield (entry 3). The presence of water proved detrimental as the reactants decomposed in the absence of molecular sieves (entry 4).

Table 1. Reaction Conditions Optimization



entry	reaction conditions	yield (%)[a]
1	PhINNs (1 equiv), **no EtOH**, MeCN, rt, 2 h	c. m.
2	PhINNs (1 equiv), MeCN, rt, 2 h	17
3	PhINNs (1 equiv), **DCM**, −10 °C, 2 h	60
4	PhINNs (1 equiv), **no MS**, DCM, −10 °C, 24 h	c. m.
5	PhINNs (1 equiv), DCM, **rt**, 12 h	c. m.
6	PhINNs (**1.5 equiv**), DCM, rt, 1 h	54[b]
7	**PhINTs** (1 equiv), DCM, −10 °C, 24 h	traces
8	**PhIO** + **$NsNH_2$** (1 equiv), DCM, −10 °C, 2 h	traces
9	PhINNs (1 equiv), **no Cu**, DCM, −10 °C, 24 h	NR

[a] Isolated yields; c. m.: complex mixture. [b] 1 mmol scale.

Running the reaction at higher temperature (rt) led to significant decomposition of both the starting material and the product (entry 5), a problem that could be overcome by using an excess of iminoiodane (entry 6). Other iminoiodanes such as PhINTs reacted sluggishly (entry 7) and attempts to generate the iminoiodane in situ[15] failed to promote the reaction (entry 8), probably because of the presence of ethanol in the reaction mixture. Finally, no reaction occurred in the absence of the catalyst (entry 9).

Using our optimized conditions, we next studied the scope of this reaction by first checking the influence of the nitrogen protecting group on the reaction (Table 2). Overall, the reaction was found to be quite general, with sulfonamides giving the best results (entries 1−5), as opposed to the Boc-protected substrate (entry 6). The reaction was also applicable to alkyl- and benzyl-protected enamines (entries 7−10), which in the case of **3i**, for instance, allowed the incorporation of three orthogonal protecting groups on the nitrogens.

(9) (a) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137–2139. (b) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377–6386. (c) Sato, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Chem. Commun.* **2009**, 6264–6266. (d) Beaumont, S.; Pons, V.; Retailleau, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 1634–1637.

(10) Capon, R. J.; Peng, C.; Dooms, C. *Org. Biomol. Chem.* **2008**, *6*, 2765–2771.

(11) (a) Avendaño, C.; de la Cuesta, E. *Chem.—Eur. J.* **2010**, *16*, 9722–9734. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730 and references therein.

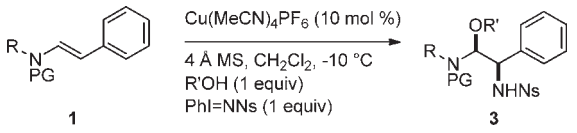
(12) (a) Jiang, L.; Job, G. E.; Klapars, A; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669. (b) See also: Dehli, J.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 239–242. (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418. (d) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927–4931.

(13) See Supporting Information for details.

(14) White, R. E. *Inorg. Chem.* **1987**, *26*, 3916–3919.

(15) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707–7708.

Table 2. Substrate Scope for the Alkoxyamination



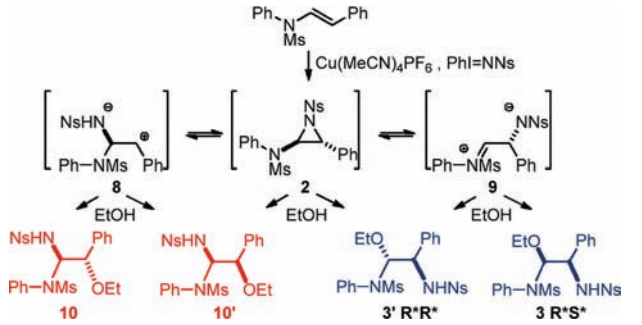
entry	R	PG	R′	product	yield (%)[a]
1	Ph	$PhSO_2$	Et	**3a**	60 (54)[b,c]
2	Ph	Ms	Et	**3b**	78
3	Ph	Ts	Et	**3c**	70 (80)[b]
4	Ph	PMPS	Et	**3d**	70
5	Ph	Ns	Et	**3e**	50
6	Ph	Boc	Et	**3f**	37
7	Me	$PhSO_2$	Et	**3g**	62
8	Bn	Ms	Et	**3h**	52
9	Bn	Ses	Et	**3i**	42
10	PMB	Ms	Et	**3j**	60[c]
11	Ph	Ms	Me	**4**	37
12	Ph	Ms	Bn	**5**	63
13	Ph	Ms	*i*Pr	**6**	58
14	Ph	Ms	*t*Bu	**7**	42

[a] Isolated yields. [b] reactions run at rt with 1.5 equiv of PhI = NNs. [c] 1 mmol scale.

We also explored whether other alcohols could be used for the alkoxyamination (entries 11−14). Methanol gave a rather low yield of product **4** (37%), probably due to the moderate stability of the final product. In contrast, benzyl and isopropyl alcohol provided acceptable yields of alkoxyamination products **5** (63%) and **6** (58%), respectively. However, product formation diminished as the steric bulk of the alcohol increased, *tert*-butanol affording only a 42% yield of product **7**.

Interestingly, this transformation is highly diastereoselective, the relative R*S* stereochemistry being assigned by X-ray crystallographic analysis of compound **3a**.[16] This observed relative configuration raises a few mechanistic issues. We assume that the iminoiodane first reacts with the copper catalyst to generate the active nitrenoid species which can then react with the enamide **1** stereoselectively to furnish aziridine **2** with a trans geometry (Scheme 2).[3] From there, two regioisomeric zwitterions could then be formed: generation of a benzylic cation would give **8** but, more probably,[7c−e,8] nitrogen assisted opening would lead to **9**. Depending on the reactive intermediate, addition of the nucleophile in an S_N2 or S_N1 fashion can give rise to four products, two being regioisomeric pairs of diastereomers. In our case, only compound **3** is formed,[17] thus pointing to the preeminence of zwitterionic iminium **9** as the reactive intermediate. However, the involvement of a planar iminium such as **9** would tend to disfavor a stereoselective process. Whether the observed stereoselectivity is due to purely steric effects or to more subtle interactions, the reactive intermediate apparently has a strong conformational bias which has yet to be clearly identified. It should also be pointed out that competition may exist between the ethanolysis of the hypervalent iodine reagent[14] and its reaction with the catalyst to form the nitrenoid species. The high reactivity of the latter, coupled with the nucleophilicity of the substrate, should ensure formation of the expected aziridine **2** first and then the zwitterionic iminium **9**. This highly reactive intermediate would then be immediately trapped by the nucleophile.[18,19]

Scheme 2. Possible Mechanistic Pathways



The next step was to take advantage of the high diastereoselectivity of this transformation to develop an enantioselective version starting from enamide **1b**. We first investigated the use of different types of chiral ligands which have already been proven to be efficient for copper-catalyzed asymmetric aziridinations.[20] Tetradentate ligand **11**, although more suitable for complexing copper(II), was tested but showed almost no reactivity (Table 3, entry 1). We therefore chose to focus on bidentate ligands, starting with diimine **12**, which proved quite efficient in terms of reactivity, affording **3b** in 88% yield with a significant enantioinduction (66% ee, entry 2). Turning then to bis-oxazolidine ligands (**13**−**17**), the reactivity dropped slightly using **13** (71% yield) but the selectivity was maintained (entry 3). Switching from a phenyl group to a *tert*-butyl on the Box framework (**14**) now induced an excellent enantioselectivity (91% ee) although with a slightly lower yield (58%, entry 4).

(16) CCDC 810284 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

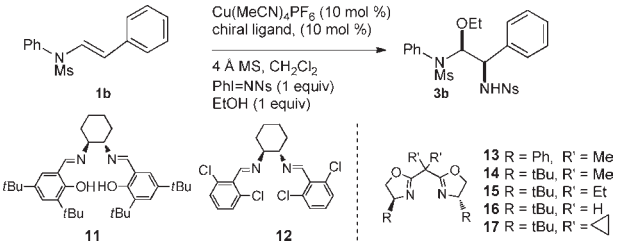
(17) Preliminary molecular calculations did show that **3-*R**S**** was the more stable of the four isomers.

(18) Indeed, addition of the ethanol after stirring the other reagents and reactants for 1 h only led to complex mixtures, demonstrating the necessity of intercepting the reactive intermediate as it forms.

(19) For examples of intermolecular trapping of an iminium, arising from an enamine functionalization, by an alcohol, see: (a) Norton Matos, M.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron* **2005**, *61*, 1221–1244. (b) Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814–3816. (c) Huang, X.; Shao, N.; Huryk, R.; Palani, A.; Aslanian, R.; Seidel-Dugan, C. *Org. Lett.* **2009**, *11*, 867–870. (d) Shao, N.; Huang, X.; Palani, A.; Aslanian, R.; Buevich, A.; Piwinski, J.; Huryk, R.; Seidel-Dugan, C. *Synthesis* **2009**, 2855–2872. (e) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553–2556. (f) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546–5549.

(20) (a) For Box ligands, see ref 3b. (b) Diimine ligands: Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326–5327.

Table 3. Screening of the Chiral Ligands for the Enantioselective Alkoxyamination



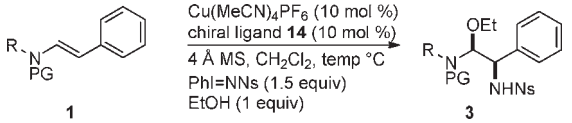
entry	ligand	time	temp (°C)	yield (%)[a]	ee (%)[b]
1	**11**	3 days	−10	traces	nd
2	**12**	5 h	−10	88	66
3	**13**	3 days	−10	71	66
4	**14**	3 days	−10	58	91
5	**14**	2 h[c]	−10	56	91
6	**15**	2 h[c]	−10	63	74
7	**16**	2 h[c]	−10	73	83
8	**17**	3 days	−10	58	78
9	**14**	0.5 h[c]	rt	60	87[c]

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Reactions run with 1.5 equiv of PhI=NNs.

From there, the R′ substituent was varied thus changing the dihedral angle of the ligand (entries 6−8),[21] but no real improvements in either yields or enantioselectivities were observed. Finally it should be noted that the reaction time can be decreased to 2 h by using an excess of iminoiodane (compare entries 4 and 5) and that running the reaction at rt is only slightly detrimental to the ee (87%), whereas both the reaction time (30 min) and the yield (60%) are improved (compare entries 9 and 5). Because ligand **14** provides the highest enantioselectivities for alkoxyamination and has the advantage of being commercially available, it was used for the subsequent studies.

These enantioselective reaction conditions were then applied to the other substrates **1a,c**−**f,h,j**. For compounds **1d** and **1e**, at −10 °C, slow conversion and lower yields were observed, although the ee's were satisfactory (90% and 93%, respectively, Table 4, entries 1,3). Taking advantage of our previous experience concerning the influence of the temperature (see Table 3), we ran the same experiments at rt (entries 2,4). The reaction times were greatly shortened (15 and 36 h instead of 3 days) and the yields were improved while the ee's remained in the same range. The other *N*-phenyl enamides (**1a**,**c**) behaved in a similar manner with good yields (74% and 71%) and ee's (85% and 87%) (entries 5−6). Overall, the electronic character of the sulfonyl group seems to only influence the yield, especially in the case of the strongly electron-withdrawing nosyl which provides only low yields of product because of either destabilization of the iminium intermediate or lowering of the nucleophilicity of the enamine (entries 3,4). The reactivity of Boc-protected **1f** is improved in the presence of the ligand (entry 7, compare with Table 2, entry 6), even if the enantioselectivity is moderate. Finally, both *N*-benzyl substrates **1h,j** exhibit analogous behavior, showcasing a moderate yield but a satisfying ee (entries 8,9).

Table 4. Substrate Scope for the Asymmetric Alkoxyamination



entry	SM	PG/R	time	temp (°C)	yield (%)[a]	ee (%)[b]
1	**1d**	PMPS/Ph	3 days	−10	50	90
2	**1d**	PMPS/Ph	15 h	rt	71	86
3	**1e**	Ns/Ph	3 days	−10	17	93
4	**1e**	Ns/Ph	36 h	rt	34	94
5	**1a**	SO_2Ph/Ph	24 h	rt	74	85
6	**1c**	Ts/Ph	1 h	rt	71	87
7	**1f**	Boc/Ph	24 h	rt	61	67
8	**1h**	Ms/Bn	6 h	rt	43	83
9	**1j**	Ms/PMB	24 h	rt	47	82

[a] Isolated yields. [b] Determined by chiral HPLC.

In conclusion, we disclose here a novel and efficient catalytic osmium-free direct asymmetric oxyamination[22] of enamine derivatives. Mediated by an iminoiodane, this oxidative difunctionalization allows the formation of α-amino aminals. The precise mechanism of this reaction, especially with respect to the actual involvement of an aziridine intermediate and of nitrenoid species, still remains to be explored, as are applications toward natural product total synthesis.

Acknowledgment. We wish to thank the Institut de Chimie des Substances Naturelles for financial support and fellowships (M.N., C.M.).

Supporting Information Available. Experimental procedures and characterization of all compounds and crystallographic data for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875–5878.

(22) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem.—Eur. J.* **2011**, *17*, 58–76.