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Copper(I)-catalyzed diastereoselective formation of oxazolines and *N*-sulfonyl-2-imidazolines

David Benito-Garagorri, Vladica Bocokić and Karl Kirchner*

Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria

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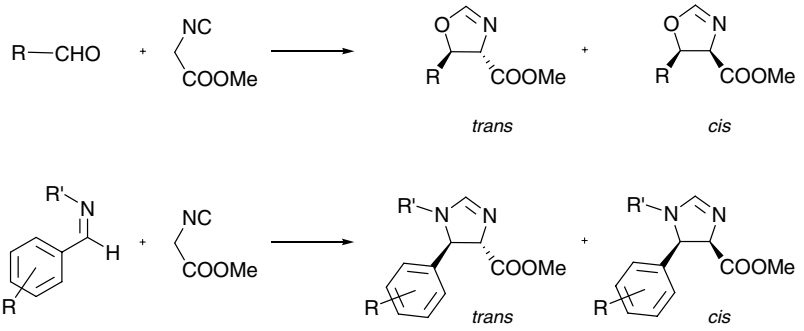
Abstract—A simple and short method for the reaction of methyl isocyanoacetate with aldehydes and *N*-sulfonylimines is presented. The reaction is catalyzed by copper(I) complexes and proceeds with excellent yields and high diastereoselectivities.

The construction of five-membered nitrogen-containing heterocycles such as oxazolines and imidazolines has received considerable attention because of the wide applicability of these compounds to the synthesis of biologically active compounds (e.g., β-hydroxy-α-amino acids, α,β-diamino acids[1a–e] and β-substituted serines[1f–h]) and their presence in the structure of several biologically active natural products, such as marine cyclopeptides[2] (e.g., bistratamides C and D).[3] The reaction of aldehydes and imines with isocyanocarboxylates is one of the methods for the preparation of oxazolines and imidazolines bearing a 1,3-*O*,*N*- and 1,3-*N*,*N*-ring system in the heterocycle, respectively (Scheme 1).[4] The mechanism of this reaction can be seen as an aldol mechanism; however, other mechanisms have been proposed.[5] Whereas there are several examples covering the synthesis of oxazolines using strong proazaphosphatrane bases[6] and transition metal complexes such as Au(I),[7] Ag(I),[8] Pd(II),[9] and Pt(II)[5] complexes, there have been few reports on the catalytic reaction of imines with isocyanocarboxylates due to the low reactivity of imines. These include the use of Au(I)[10] and Ru(II)[11] complexes. It has to be noted that imidazolines have also been prepared via a multicomponent reaction (MCR) between amines, aldehydes and isocyanides using AgOAc as the catalyst.[5b,c] However, such methods require the use of relatively expensive transition metals and long reaction times are needed in order to achieve reasonable yields. Here, we wish to report that using simple Cu(I) catalysts, *trans*-oxazolines and *N*-sulfonylimidazolines can be smoothly obtained in 2 h in quantitative yields with high diastereoselectivity



Scheme 1.

Keywords: Catalysis; Copper; Aldol reaction; Diastereoselective; Oxazolines; Imidazolines.
* Corresponding author. Tel.: +43 1 58801 15401; fax: +43 1 58801 15499; e-mail: kkirch@mail.zserv.tuwien.ac.at

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by the reaction of methyl isocyanoacetate with aromatic aldehydes and *N*-sulfonylimines. Due to the fact that the trans products are easily accessible with this method, it can be regarded as a useful complement to other already published procedures, in which the cis products are usually obtained.[10]

Although the reaction of isocyanocarboxylates with aldehydes catalyzed by Cu_2O was reported over 30 years ago,[12] 1:1 mixtures of *cis*- and *trans*-imidazolines were obtained. We discovered that by using a different copper(I) salt, CuCl, the reaction between benzaldehyde and methyl isocyanoacetate proceeded in 80% yield in 2 h with the selective formation of the trans product (Table 1, entry 1). The yield of the reaction could be improved to quantitative by adding PPh_3 in a 1:2 ratio in respect to CuCl (entry 2). The same procedure was then applied to other aldehydes (entries 3–7). In all cases, the reaction proceeded quantitatively to give *trans* oxazolines with over 85% diastereoselectivity both with electron withdrawing and electron donating groups in the aromatic ring. In the absence of copper salt, the reaction does not take place under otherwise the same reaction conditions.

For the synthesis of imidazolines, when the *N*-aryl-substituted benzaldehyde-*N*-phenylimine was used, only traces of the coupling product were observed; given the low reactivity of imines towards nucleophilic addition, a strong electron withdrawing group, that is, tosyl, was introduced on the nitrogen atom of the imines in order to activate the C=N bond. If the reaction is performed solely with CuCl, a nearly 50:50 trans:cis ratio was observed for the imines **3a** and **3b** (Table 2, entries 1 and 2). Contrary to the synthesis of oxazolines, where PPh_3 only seemed to influence the yield of the reaction, the use of an additive proved to be crucial for the diastereoselective preparation of imidazolines. It is known that, depending on the metal salt/ligand ratio, CuCl can form several complexes with different stoichiometries and geometries with triphenylphosphine.[13] The trigonal planar complex $[(PPh_3)_2CuCl]$, formed in situ in the course of the reaction, seems to offer the best steric and electronic properties in the reaction between **3a** and methyl isocyanoacetate: when CuCl and PPh_3 were used in a 1:2 ratio, the reaction proceeded selectively to give exclusively *trans*-**4a** (Table 2, entry 4). Other CuCl:PPh_3 ratios by using equimolar amounts of metal salt and phosphine or larger excesses of phosphine resulted either in decreased yields or in decreased diastereoselectivities presumably due to the formation of copper complexes with different geometries (entries 3–7). When these conditions were applied to imine **3b**, however, the diastereoselectivity decreased (entry 5). Thus, an optimization of the catalyst was performed by screening the activity of several CuCl/ligand systems (Table 2).

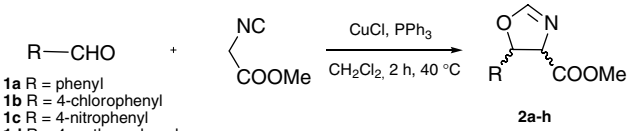
The best catalyst turned out to be the *N*-heterocyclic carbene complex **H**,[14] which gave good yields and selectivities both for imines **3a** and **3b**. With these conditions in hand, several other *N*-sulfonylimines were tested, all of which gave the corresponding imidazolines in a quantitative yield and over 85% diastereoselectivity (Table 3). Only in the case of imine **3d**, a slightly lower diastereomeric ratio was observed, which may be attributed to the electron donating methoxy group (Table 3, entry 4). Like for the oxazolines, no reaction took place if the reaction was performed in the absence of copper catalyst.

In summary, we have shown that the coupling of aldehydes and *N*-sulfonylimines with methyl isocyanoacetate can be achieved in short reaction times (2 h) with good diastereoselectivities and in high yields using simple Cu(I) catalysts. The simplicity of the procedure, the mildness of the reaction conditions and the inexpensive nature of the metal make this method an attractive alternative to similar reactions catalyzed by other transition metals. The use of different isocyanides as well as the expansion of this method in the enantioselective synthesis of oxazolines using chiral phosphines is currently under investigation.

Typical procedures: *Oxazolines*: Methyl isocyanoacetate (1 equiv) was added to a mixture of the catalyst, *i*Pr_2EtN (10 mol %) and aldehyde (1 equiv) in CH_2Cl_2 under an argon atmosphere. The reaction mixture was stirred for 2 h at 40 °C after which it was allowed to cool down to room temperature. The products were isolated from the crude reaction mixture by flash chromatography with ethyl acetate/hexanes (1:1) as eluent. *Imidazolines:* The reaction procedure was identical to that for oxazolines, with the exception that no *i*Pr_2EtN was used.

trans-**2e**: ^{1}H NMR (δ, $CDCl_3$, 20 °C): 3.84 (s, 3H, $COOCH_3$), 4.54 (d, $J = 6.3$ Hz, 1H, C*H*), 6.10 (d, $J = 6.3$ Hz, 1H, C*H*), 7.20 (s, 1H, C*H*), 7.59 (d, $J = 8.5$ Hz, 1H, Ph), 8.20–8.13 (m, 2H, Ph). *trans*-**2f**: ^{1}H NMR (δ, $CDCl_3$, 20 °C): 3.78 (s, 3H, $COOCH_3$), 4.77 (dd, $J = 8.7$ Hz, $J = 1.7$ Hz, 1H, C*H*), 6.17 (d, $J = 8.7$ Hz, 1H, C*H*), 7.04–6.98 (m, 2H, C*H* and Ph),

Table 1. Synthesis of oxazolines[a]



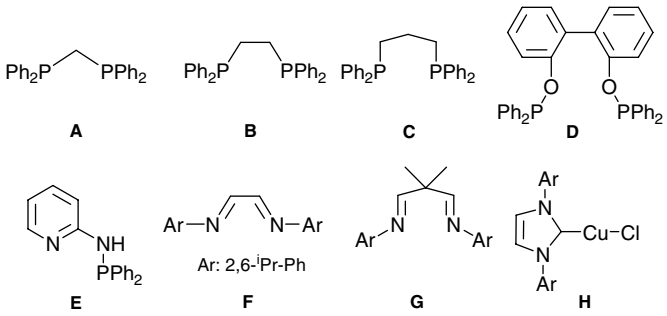
1a R = phenyl
1b R = 4-chlorophenyl
1c R = 4-nitrophenyl
1d R = 4-methoxyphenyl
1e R = 2-chloro-5-nitrophenyl
1f R = 2-chloro-6-fluorophenyl
1g R = 2-methylphenyl
1h R = *iso*propyl

2a-h

Entry	Aldehyde	Yield[b] of **2** (%)	Ratio[c] of trans/cis
1	**1a**	>99	>99/<1
2	**1b**	>99	86/14
3	**1c**	>99	90/10
4	**1d**	>99	91/9
5	**1e**	>99	86/14
6	**1f**	>99	96/4
7	**1g**	>99	88/12
8	**1h**	>99	>99/<1

[a] Conditions: 1 equiv aldehyde, 1 equiv methyl isocyanoacetate, 10 mol % *i*Pr_2EtN, 5 mol % CuCl, 10 mol % PPh_3, CH_2Cl_2, 40 °C, 2 h.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by ^{1}H NMR spectroscopy.

Table 2. Optimization of the catalyst for the synthesis of imidazolines[a]

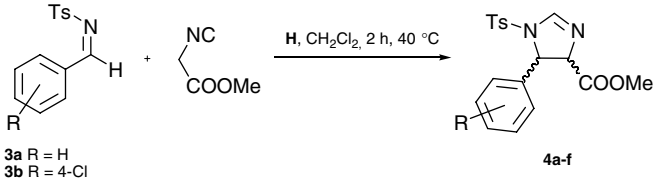


Entry	Imine	Catalyst	Yield[b] of **4** (%)	Ratio[c] of trans/cis
1	**3a**	CuCl (5 mol %)	>99	52/48
2	**3b**	CuCl (5 mol %)	>99	40/60
3	**3a**	CuCl (5 mol %) + PPh_3 (5 mol %)	54	84/16
4	**3a**	CuCl (5 mol %) + PPh_3 (10 mol %)	>99	>99/<1
5	**3b**	CuCl (5 mol %) + PPh_3 (10 mol %)	96	64/36
6	**3a**	CuCl (5 mol %) + PPh_3 (15 mol %)	97	90/10
7	**3a**	CuCl (5 mol %) + PPh_3 (20 mol %)	75	84/16
8	**3a**	CuCl (5 mol %) + $P(OPh)_3$ (10 mol %)	>99	83/17
9	**3a**	CuCl (5 mol %) + **A** (5 mol %)	31	98/2
10	**3a**	CuCl (5 mol %) + **B** (5 mol %)	76	97/3
11	**3a**	CuCl (5 mol %) + **C** (5 mol %)	92	86/14
12	**3a**	CuCl (5 mol %) + **D** (5 mol %)	57	67/33
13	**3a**	CuCl (5 mol %) + **E** (5 mol %)	14	98/2
14	**3a**	CuCl (5 mol %) + **F** (5 mol %)	Traces	—
15	**3a**	CuCl (5 mol %) + **G** (5 mol %)	Traces	—
16	**3a**	**H** (5 mol %)	>99	96/4
17	**3b**	**H** (5 mol %)	>99	95/5

[a] Conditions: 1 equiv imine, 1 equiv methyl isocyanoacetate, catalyst (5–20 mol%), CH_2Cl_2, 40 °C, 2 h.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by ^1H NMR spectrospcopy.

7.32–7.18 (m, 2H, Ph). *trans*-**4e**: ^1H NMR (δ, $CDCl_3$, 20 °C): 2.34 (s, 3H, C*H*$_3$), 3.62 (s, 3H, COOC*H*$_3$), 4.59 (d, $J = 6.3$ Hz, 1H, C*H*), 5.48 (d, $J = 6.3$ Hz, 1H, C*H*), 7.23–7.19 (m, 3H, Ph), 7.37–7.32 (m, 1H, Ph), 7.48–7.42 (m, 1H, Ph), 7.56–7.52 (m, 1H, Ph), 7.67 (d, $J = 2.1$ Hz, 1H, C*H*), 7.99 (s, 1H, Ph). *trans*-**4f**: ^1H NMR (δ, $CDCl_3$, 20 °C): 2.32 (s, 3H, C*H*$_3$), 3.62 (s, 3H, COOC*H*$_3$), 4.71 (dd, $J = 7.5$ Hz, $J = 1.8$ Hz, 1H, C*H*), 5.64 (d, $J = 7.5$ Hz, 1H, C*H*), 7.17–7.06 (m, 4H, Ph and C*H*), 7.55–7.43 (m, 4H, Ph).

Table 3. Synthesis of imidazolines[a]



3a R = H
3b R = 4-Cl
3c R = 4-NO_2
3d R = 4-OMe
3e R = 2-Cl, 5-NO_2
3f R = 2-Cl, 6-F

Entry	Imine	Yield[b] of **4** (%)	Ratio[c] of trans/cis
1	**3a**	>99	96/4
2	**3b**	>99	95/5
3	**3c**	>99	85/15
4	**3d**	>99	83/17
5	**3e**	>99	89/11
6	**3f**	>99	85/15

[a] Conditions: 1 equiv imine, 1 equiv methyl isocyanoacetate, 5 mol % **H**, CH_2Cl_2, 40 °C, 2 h.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by ^1H NMR spectroscopy.

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References and notes

1. (a) Potts, K. T. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, p 457; (b) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27*, 241–326; (c) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 355; (d) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 789–804; (e) Matsumoto, K.; Moriya, T.; Suzuki, M. *Synth. Org. Chem. Jpn.* **1985**, *43*, 764–776; (f) Hining, H.; Seufer-Waserthal, P.; Weber, H. *Tetrahedron* **1990**, *46*, 3841–3850; (g) Gaparski, C. M.; Miller, M. J. *Tetrahedron* **1991**,

47, 5367–5378; (h) Togni, A.; Pastor, S. D.; Ribs, G. *J. Organomet. Chem.* **1990**, *381*, C21–C25.
2. For reviews, see: (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115–2134; (b) Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1–23, and references cited therein.
3. (a) Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671–6675; (b) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2477–2480; (c) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826–831.
4. (a) Gerhart, F.; Schöllkopf, U. *Tetrahedron Lett.* **1968**, *59*, 6231–6234; (b) Hoppe, D.; Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 300–301; (c) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333; (d) Hoppe, D.; Schöllkopf, U. *Liebigs. Ann. Chem.* **1972**, *763*, 1–16; (e) Schröder, R.; Schöllkopf, U.; Blume, E.; Hoppe, I. *Liebigs. Ann. Chem.* **1975**, *3*, 533–546; (f) Hantke, K.; Schöllkopf, U.; Hausberg, H. H. *Liebigs. Ann. Chem.* **1975**, *7–8*, 1531–1537; (g) Schöllkopf, U.; Gerhart, F.; Hoppe, I.; Harns, R.; Hantke, H.; Scheunemann, K. D.; Eilers, E.; Blume, E. *Liebigs. Ann. Chem.* **1976**, *1*, 183–202; (h) Meyer, R.; Schöllkopf, U.; Böhme, P. *Liebigs. Ann. Chem.* **1977**, *7*, 1183–1193.
5. (a) Horne, D. A.; Yakusijin, K.; Büchi, G. *Heterocycles* **1994**, *39*, 139–153; (b) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759–3762; (c) Bon, R. S.; van Vliet, B.; Sprenkels, N. E.; Schmitz, R. F.; de Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2005**, *70*, 3542–3553.
6. Kisanga, P.; Ilankumaran, P.; Verkade, J. G. *Tetrahedron Lett.* **2001**, *42*, 6263–6266.
7. (a) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7–12; (b) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6646; (c) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215–6218; (d) Pastor, S. D.; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333–2334; (e) Yoshihiko, I.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253–5262; (f) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649–1664; (g) Pastor, S. D.; Togni, A. *Tetrahedron Lett.* **1990**, *31*, 839–840; (h) Hayashi, T.; Sawamura, M.; Yoshihiko, I. *Tetrahedron* **1992**, *48*, 1999–2012.
8. (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 5935–5936; (b) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, *32*, 2799–2802.
9. (a) Gorla, F.; Togni, A.; Venanzi, L. M.; Albinati, A.; Lianza, F. *Organometallics* **1994**, *13*, 1607–1616; (b) Longmire, J. M.; Zhang, X.; Shang, M. *Organometallics* **1998**, *17*, 4374–4379; (c) Motoyama, Y.; Kawakami, H.; Shimozono, K.; Aoki, K.; Nishiyama, H. *Organometallics* **2002**, *21*, 3408–3416; (d) Fossey, J. S.; Richards, C. J. *Organometallics* **2002**, *21*, 5259–5264; (e) Gosiewska, S.; Veld, M. H.; De Pater, J. M.; Bruijnincx, P. C. A.; Lutz, M.; Spek, A. L.; Van Koten, G.; Gebbink, K.; Robertus, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 674–686; (f) Giménez, R.; Swager, T. M. *J. Mol. Catal. A* **2001**, *166*, 265–273.
10. (a) Hayashi, T.; Kishi, E.; Soloshonok, V.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969–4972; (b) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331–1334; (c) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Assymetry* **1999**, *10*, 855–862.
11. Lin, Y.-R.; Zhou, X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799–1803.
12. Saegusa, T.; Ito, Y.; Kinoshita, H.; Tomita, S. *J. Org. Chem.* **1971**, *36*, 3316–3323.
13. Kräuter, T.; Neumüller, B. *Polyhedron* **1996**, *15*, 2851–2857.
14. Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157–1160.