

ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

COMMUNICATION

(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a Chiral Diamine Ligand for Copper(II)-Catalysed Henry Reactions with Superb Enantiocontrol[†]

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Dagmar Scharnagel,^{‡a} Felix Prause,^{‡a} Johannes Kaldun,^{‡a} Robert G. Haase^a and Matthias Breuning^{*a}

A *cis*-2-aminomethyl-5-phenylpyrrolidine, which is easily available from methyl Boc-L-pyrroglutamate, was found to be a highly efficient chiral ligand for Cu(II)-catalysed Henry reactions. Excellent yields (>90%) and superb levels of enantiocontrol (98.5–99.6% ee) were reached with aromatic, heteroaromatic, vinylic, and aliphatic aldehydes (36 examples).

The Henry (or nitroaldol) reaction is a powerful tool for C-C bond formation, because it permits rapid access to valuable synthetic intermediates such as 1,2-amino alcohols and α -hydroxy acids.¹ Tremendous advances had been made over the last two decades in the development of enantioselective versions of this reaction.² Among the many highly efficient systems based on heterobimetal,³ transition metal,^{4–6} organo⁷ and enzyme⁸ catalysis, chirally modified copper complexes have received particular attention due to the wide structural variability of the ligands (diamines, amino alcohols, amino imines, amino pyridines, imino pyridines, Schiff bases, box-type ligands, salen-type ligands, and others),^{5,6} the ease of preparation and the, in part, high levels of stereocontrol reached. Several of these catalysts permit 99% ee in the addition of nitromethane to some of the aldehydes tested,⁵ but none is capable of providing 99% ee for the majority of substrates. Herein we present the first copper catalyst that fulfils this demand, giving, for the addition of nitromethane to a broad range of aldehydes, the corresponding β -nitro alcohols in high yield and excellent 99% ee.

In the course of our studies on bicyclic diamines⁹ we became interested in 2-aminomethylpyrrolidines of general type **1** (Fig. 1), which carry an additional *cis*-aryl group in 5-position, as compared to proline derived diamines. Chelation of a metal with **1** will lead to a rigid bicyclic system, in which the aryl substituent is forced into an *endo*-position directly on top of the active metal site. As illustrated by complex **2**, such a shielding might be of particular importance in asymmetric transition metal catalysts preferring Jahn-Teller distorted octahedral geometries, because it selectively blocks one apical position and thereby reduces the number of possible transition states. The equatorial coordination sites L¹_{eq} and L²_{eq} are still differentiated by the intrinsic steric and electronic properties of the C₁-

symmetric diamine **1**, which might offer another advantage over C₂-symmetric ligands.

Copper(II)-catalysed Henry reactions, which are supposed to proceed via such a pentacoordinate intermediate,¹⁰ might provide an ideal test system to probe the potential of the diamines **1**.¹¹ After investigating some derivatives, we quickly identified the simple compound **3** as the ligand of choice for these reactions.¹²

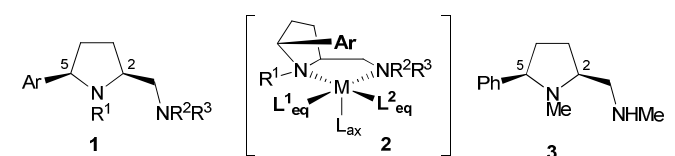
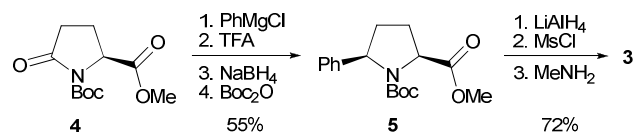


Fig. 1 *Cis*-2-aminomethyl-5-arylpiperidines **1** and **3** and a square-pyramidal metal complex of **1**, **2**

Diamine **3** is easily accessible from commercially available methyl Boc-L-pyrroglutamate (**4**, Scheme 1). Treatment of **4** with phenylmagnesium chloride and re-cyclisation of the resulting, ring-opened ketone delivered the diastereomerically pure pyrrolidine **5** after crystallization.¹³ Exhaustive reduction followed by OH/NHMe exchange afforded the target molecule **3** in overall seven simple steps and 40% yield.



Scheme 1 Synthesis of diamine **3** from pyrroglutamate **4**

The enantioselective Henry reactions between the aromatic aldehydes **6a-u** and nitromethane (11 equivalents) were performed on a 1 mmol scale in THF at -25 °C (Table 1, entries 1–21). The copper(II) complex [3•CuBr₂], prepared prior to use by stirring CuBr₂ with a slight excess of pyrrolidine **3** in THF, was used as the chiral catalyst and NEt₃ (1.5 mol%) as the base. Under these conditions¹² and in the presence of just 2 mol% [3•CuBr₂], the Henry products **7a-u** were formed within 18 to

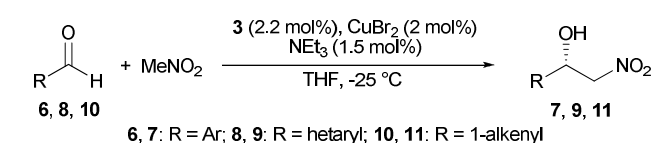
67 h in excellent 92-99% yield. Outstanding 99% ee, in several cases even more than 99.5% ee, were obtained with electronically more or less neutral (**6a-g**), electron-deficient (**6h-o**) and electron-rich (**6p-u**) aromatic aldehydes, carrying substituents in *ortho*-, *meta*-, or *para*-position.

Hetarylic aldehydes **8a-f** were also treated with nitromethane under these conditions (Table 1, entries 22-27). And again, the Henry products **9a-f** were obtained in excellent yields (90-99%) and superb >99.0% ee, irrespective of the heterocycle (furyl, thiophenyl, or NBoc-pyrryl) and the substitution pattern.

The α,β -unsaturated aldehydes **10a** and **10b** solely afforded the 1,2-addition products **11a** and **11b**. The latter one is the only compound tested within this context that delivered less than 99.0% ee, namely 98.7%.

In all cases, the *re*-face of the aldehyde was attacked by the nitronate; the, in part, opposite absolute stereo descriptors in the products are a formal consequence of the CIP-notation.

Table 1 Aromatic, heteroaromatic and vinylic aldehyde scope^a



Entry	Com-pounds	R	Time (h)	Yield (%) ^b	ee (%) ^c (Config.)
1	6a, 7a	Ph	24	92	99.3 (S)
2	6b, 7b	2-Me-Ph	18	99	99.2 (S)
3	6c, 7c	3-Me-Ph	20	99	99.5 (S)
4	6d, 7d	4-Me-Ph	22	93	99.4 (S)
5	6e, 7e	4-Ph-Ph	38	99	99.6 (S)
6	6f, 7f	1-naphthyl	65	99	99.4 (S)
7	6g, 7g	2-naphthyl	42	99	99.0 (S)
8	6h, 7h	2-O ₂ N-Ph	20	97	99.0 (S)
9	6i, 7i	3-O ₂ N-Ph	22	95	99.4 (S)
10	6j, 7j	4-O ₂ N-Ph	21	94	99.4 (S)
11	6k, 7k	2-Cl-Ph	18	99	99.6 (S)
12	6l, 7l	3-Cl-Ph	19	96	99.5 (S)
13	6m, 7m	4-Cl-Ph	42	95	99.5 (S)
14	6n, 7n	4-F-Ph	20	99	99.6 (S)
15	6o, 7o	4-NC-Ph	21	94	99.6 (S)
16	6p, 7p	2-MeO-Ph	42	97	99.5 (S)
17	6q, 7q	3-MeO-Ph	48	99	99.3 (S)
18	6r, 7r	4-MeO-Ph	67	99	99.2 (S)
19	6s, 7s	2,4-(MeO) ₂ -Ph	48	98	99.3 (S)
20	6t, 7t	2,5-(MeO) ₂ -Ph	39	99	99.6 (S)
21	6u, 7u	3,4-(MeO) ₂ -Ph	40	93	99.1 (S)
22	8a, 9a	2-furyl	40	91	99.6 (R)
23	8b, 9b	5-Me-2-furyl	112	96	99.5 (R) ^d
24	8c, 9c	3-furyl	72	99	99.4 (S)
25	8d, 9d	2-thiophenyl	86	95	99.2 (R)
26	8e, 9e	NBoc-2-pyrryl	21	99	99.5 (R)
27	8f, 9f	NBoc-3-indolyl	160	90	99.4 (S)
28	10a, 11a	(E)-PhCH=CH	120	90	99.3 (S)
29	10b, 11b	(E)-1-penten-1-yl	90	97	98.7 (S) ^d

^a Performed on a 1 mmol scale in THF (600 μ L) and MeNO₂ (600 μ L \approx 11 eq.). ^b Isolated yield. ^c Determined by HPLC analysis on a chiral phase; absolute configurations were established by comparison with literature data. ^d Absolute configuration was assigned based on a *re*-face attack on the aldehyde.

Aliphatic aldehydes **12** provided significantly lower enantioselectivities and yields under these conditions. Nonanal (**12b**), for example, delivered the Henry product **13b** in unsatisfying 53% yield and 94.5 % ee after 40 h. In order to compensate the lower reactivity, we raised the amount of catalyst to 8 mol% and the temperature to -20 °C, which afforded **13b** in good 86%

yield, but low 92.1% ee. Finally, a significant increase in the level of chirality transfer was observed by changing the copper salt from CuBr₂ to CuCl₂.¹⁴ Under these modified conditions, both, linear (**12a-c**) and α -branched (**12d-g**) aliphatic aldehydes provided the Henry products **13a-g** in excellent 98.5-99.5% ee and >95% yield (Table 2).

Table 2 Aliphatic aldehyde scope^a

Entry	Com-pounds	R	Time (h)	Yield (%) ^b	ee (%) (Config.) ^c
1	12a, 13a	<i>n</i> Bu	40	95	98.5 (S)
2	12b, 13b	<i>n</i> Oct	60	97	98.6 (S)
3	12c, 13c	PhCH ₂ CH ₂	40	95	99.5 (S)
4	12d, 13d	<i>i</i> Pr	44	96	99.1 (S)
5	12e, 13e	<i>c</i> Pent	44	99	98.9 (S)
6	12f, 13f	<i>c</i> Hex	44	99	99.4 (S)
7	12g, 13g	<i>t</i> Bu	44	99	98.6 (S)

^a Performed on a 1 mmol scale in THF (600 μ L) and MeNO₂ (600 μ L \approx 11 eq.). ^b Isolated yield. ^c Determined by HPLC analysis on a chiral phase; absolute configurations were established by comparison with literature data.

The stereochemical outcome of the Henry reactions can be explained via the transition state **14** (Fig. 2). As mentioned earlier, the aryl group of the chiral ligand **3** blocks the upper apical position at the Cu(II) ion, thus leaving three open coordination sites, two equatorial ones and one apical one. Based on the known model,¹⁰ the nitronate should bind apically for maximum activation, since its negative charge is less stabilised in this position by the copper ion. Of the two higher Lewis-acidic equatorial sites, the aldehyde should coordinate to the one next to the pyrrolidine moiety for two reasons: (i) This allows the sterically more demanding counter ion X to occupy the less congested position next to the aminomethyl group^{9b} and (ii), with the weaker electron donating secondary amine opposite, the electrophilicity of the carbonyl group is increased thus facilitating a nucleophilic attack. Furthermore, the aldehyde must be oriented inwards in order to avoid severe steric repulsions with the chiral backbone. The C-C bond formation will presumably proceed via a six-membered, chair-shaped transition state, thus obviating repulsions between the nitronate-oxygen and the pyrrolidine *N*-methyl group.¹⁵ It might be possible that this arrangement receives some further stabilisation and rigidity by an intramolecular hydrogen bridge between the nitronate oxygen and the NH-proton of the chiral ligand. Thus, the steric and electronic properties of the diamine ligand apparently create close to perfect preconditions for the experimentally observed, almost exclusive *re*-face attack of the nitronate on the aldehyde carbonyl group.

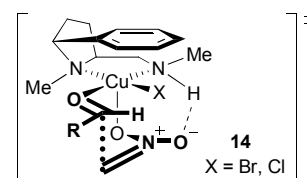


Fig. 2 Proposed transition state **14**

In summary, the *cis*-5-phenyl substituted 2-aminomethylpyrrolidine **3**, which is accessible in just a few steps from methyl Boc-L-pyrroglutamate (**4**), was successfully utilized as the chiral ligand in CuBr₂- and CuCl₂-catalysed Henry reactions. Excellent isolated yields (>90%) and superb enantioselectivities (98.5–99.6% ee) were obtained with a wide variety of aromatic, heteroaromatic, vinylic and aliphatic aldehydes (36 examples). Further studies are ongoing.¹⁶

Financial support of the German research foundation (DFG) is gratefully acknowledged.

Notes and references

^a Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany. E-mail: matthias.breuning@uni-bayreuth.de

† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, HPLC- and NMR spectra. See DOI: 10.1039/c000000x/

‡ These authors contributed equally to this work.

- Reviews: (a) F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915; (b) *The Nitro Group in Organic Synthesis*, ed. N. Ono, Wiley-VCH, New York, 2001.
- Reviews: (a) J. Boruwa, N. Gogoi, P. P. Saikia and N. C. Barua, *Tetrahedron: Asymmetry*, 2006, **17**, 3315; (b) C. Palomo, M. Oiarbide and A. Laso, *Eur. J. Org. Chem.*, 2007, 2561; (c) Y. Alvarez-Casao, E. Marques-Lopez and R. P. Herrera, *Symmetry*, 2011, **3**, 220; (d) G. Blay, V. Hernández-Olmos and J. R. Pedro, *Synlett*, 2011, 1195; (e) C. Chelucci, *Coord. Chem. Rev.*, 2013, **257**, 1887; (f) N. Ananthi and S. Velmathi, *Ind. J. Chem.*, 2013, **52B**, 87.
- Selected examples: (a) H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418; (b) T. Nitabar, A. Nojiri, M. Kobayashi, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 13860; (c) T. Nitabar, N. Kumagai and M. Shibasaki, *Angew. Chem. Int. Ed.*, 2012, **51**, 1644; (d) D. Sureshkumar, K. Hashimoto, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2013, **78**, 11494.
- Selected examples (except Cu-catalysis): (a) B. M. Trost and V. S. C. Yeh, *Angew. Chem. Int. Ed.*, 2002, **41**, 861; (b) C. Palomo, M. Oiarbide and A. Laso, *Angew. Chem. Int. Ed.*, 2005, **44**, 3881; (c) J. Park, K. Lang, K. A. Abboud and S. Hong, *J. Am. Chem. Soc.*, 2008, **130**, 16484; (d) S. Liu and C. Wolf, *Org. Lett.*, 2008, **10**, 1831; (e) R. Kowalczyk, P. Kwiatkowski, J. Skarzewski and J. Jurczak, *J. Org. Chem.*, 2009, **74**, 753; (f) K. Lang, J. Park and S. Hong, *Angew. Chem. Int. Ed.*, 2012, **51**, 1620.
- Cu-catalysed Henry reactions of nitromethane giving 99% ee with at least one aldehyde: (a) M. Bandini, F. Piccinelli, S. Tommasi, A. Umami-Ronchi and C. Ventrici, *Chem. Commun.*, 2007, 616; (b) T. Arai, M. Watanabe and A. Yanagisawa, *Org. Lett.*, 2007, **9**, 3595; (c) G. Zhang, E. Yashima and W.-D. Woggon, *Adv. Synth. Catal.*, 2009, **351**, 1255; (d) W. Jin, X. Li, Y. Huang, F. Wu and B. Wan, *Chem.–Eur. J.*, 2010, **16**, 8259; (e) G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha and Z. Wang, *Chem.–Eur. J.*, 2011, **17**, 1114; (f) A. T. Herrmann, S. R. Martinez and A. Zakarian, *Org. Lett.*, 2011, **13**, 3636; (g) B. V. Subba Reddy and J. George, *Tetrahedron: Asymmetry*, 2011, **22**, 1169; (h) Y. Zhou, J. Dong, F. Zhang and Y. Gong, *J. Org. Chem.*, 2011, **76**, 588; (i) W. Jin, X. Li and B. Wan, *J. Org. Chem.*, 2011, **76**, 484; (j) R. I. Kureshy, A. Das, N. H. Khan, S. H. R. Abdi and H. C. Bajaj, *ACS Catal.*, 2011, **1**, 1529; (k) Y. Wei, L. Yao, B. Zhang, W. He and S. Zhang, *Tetrahedron*, 2011, **67**, 8552; (l) L. Yao, Y. Wei, P. Wang, W. He, and S. Zhang, *Tetrahedron*, 2012, **68**, 9119; (m) D.-D. Qin, W.-H. Lai, D. Hu, Z. Chen, A.-A. Wu, Y.-P. Ruan, Z.-H. Zhou and H.-B. Chen, *Chem.–Eur. J.*, 2012, **18**, 10515; (n) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen and Z. Wang, *Chem.–Eur. J.*, 2012, **18**, 12357; (o) A. Das, R. I. Kureshy, K. J. Prathap, M. K. Choudhary, G. V. S. Rao, N. H. Khan, S. H. R. Abdi and H. C. Bajaj, *Appl. Catal. A*, 2013, **459**, 97; (p) T. Deng and C. Cai, *J. Fluorine Chem.*, 2013, **156**, 183; (q) R. Ćwiek, P. Niedziejko and Z. Kałuża, *J. Org. Chem.*, 2014, **79**, 1222.
- Selected recent examples of enantioselective Cu-catalysed Henry reactions: (a) G. Blay, V. Hernández-Olmos and J. R. Pedro, *Org. Lett.*, 2010, **12**, 3058; (b) T. Arai, Y. Taneda and Y. Endo, *Chem. Commun.*, 2010, **46**, 7936; (c) L. Cheng, J. Dong, J. You, G. Gao and J. Lan, *Chem.–Eur. J.*, 2010, **16**, 6761; (d) A. Chougnet, G. Zhang, K. Liu, D. Häussinger, A. Kägi, T. Allmendinger and W.-D. Woggon, *Adv. Synth. Catal.*, 2011, **353**, 1797; (e) M. W. Leighty, B. Shen, and J. N. Johnston, *J. Am. Chem. Soc.*, 2012, **134**, 15233; (f) J. D. White and S. Shaw, *Org. Lett.*, 2012, **14**, 6270; (g) Q. Dai, N. K. Rana and J. C.-G. Zhao, *Org. Lett.*, 2013, **15**, 2922; (h) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou and H.-B. Chen, *Chem.–Eur. J.*, 2013, **19**, 16541.
- Selected recent examples: (a) D. Uruguchi, S. Nakamura and T. Ooi, *Angew. Chem. Int. Ed.*, 2010, **49**, 7562; (b) K. Kanagaraj, P. Suresh and K. Pitchumani, *Org. Lett.*, 2010, **12**, 4070; (c) Q. Dai, H. Huang and J. C.-G. Zhao, *J. Org. Chem.*, 2013, **78**, 4153; (d) A. Quintavalla, M. Lombardo, S. P. Sanap and C. Trombini, *Adv. Synth. Catal.*, 2013, **355**, 938; (e) S. Kitagaki, T. Ueda and C. Mukai, *Chem. Commun.*, 2013, **49**, 4030; (f) M. T. Corbett and J. S. Johnson, *Angew. Chem. Int. Ed.*, 2014, **53**, 255.
- M. Gruber-Khadjawi, T. Purkharthofer, W. Skranc and H. Griengl, *Adv. Synth. Catal.*, 2007, **349**, 1445.
- (a) M. Breuning, D. Hein, M. Steiner, V. H. Gessner and C. Strohmann, *Chem.–Eur. J.*, 2009, **15**, 12764; (b) M. Breuning, M. Steiner, C. Mehler, A. Paasche and D. Hein, *J. Org. Chem.*, 2009, **74**, 1407; (c) M. Breuning and D. Hein, *Eur. J. Org. Chem.*, 2013, 7575.
- D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692.
- Enantioselective, Cu-catalysed Henry reactions using proline-derived ligands: (a) B. V. Subba Reddy, S. Madhusudana Reddy, S. Manisha and C. Madan, *Tetrahedron: Asymmetry*, 2011, **22**, 530; (b) D. Lu, Y. Zhou, Y. Li, S. Yan and Y. Gong, *J. Org. Chem.*, 2011, **76**, 8869; (c) B. Ni and J. He, *Tetrahedron Lett.*, 2013, **54**, 462; (d) Y. Zhou, Y. Zhu, S. Yan and Y. Gong, *Angew. Chem. Int. Ed.*, 2013, **52**, 10265; (e) H. Yuan, J. Hu and Y. Gong, *Tetrahedron: Asymmetry*, 2013, **24**, 699; (f) H. A. Sema, G. Bez and S. Karmakar, *Appl. Organometal. Chem.*, 2014, **28**, 290; (g) Refs. 5e,h,n.
- Details about the diamine screening and the optimization of the reactions conditions as well as further mechanistic investigations will be reported elsewhere.
- Synthesis of related compounds: (a) M.-C. Fournie-Zaluski, R. Coric, V. Thery, W. Gonzalez, H. Meudal, S. Turcaud, J.-B. Michel and B. P. Roques, *J. Med. Chem.*, 1996, **39**, 2594; (b) Momotake, H. Togo

and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1193; (c) A. C. Rudolph, R. Machauer and S. F. Martin, *Tetrahedron Lett.*, 2004, **45**, 4895.

- 14 A similar effect on the ee was not observed with aromatic aldehydes.
- 15 A boat-type transition state cannot fully be excluded, but seems less likely.
- 16 Initial studies on Henry reactions with other nitroalkanes revealed acceptable to good diastereoselectivities and excellent enantioselectivities in the major *syn*-diastereomer. The reaction of benzaldehyde (**6a**) with nitropropane, for example, afforded the corresponding β -nitro alcohol in 99% yield with a *syn/anti* ratio of 79:21 and 98% ee in the major diastereomer.