Practical copper(I)-catalysed amidation of aldehydes†

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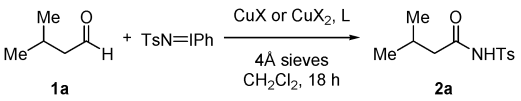
The direct synthesis of amides by insertion into the C–H bond of aldehydes is shown to be a practical procedure through application of cheap, readily available catalysts generated *in situ* from copper(I) halides and pyridine.

The synthesis of amides is of fundamental importance in the fields of biological, medicinal and materials chemistry.[1] In principle, the condensation of a carboxylic acid with an amine offers a near perfect synthesis of amides, since the only by-product is water. In practice, "activation" of the carboxylic acid is usually required, introducing an extra step, additional by-products and, in some cases, synthetic complications in the activated intermediates.[2] In this regard, the establishment of synthetically practical methods for amide bond synthesis that are conceptually different to the condensation approach continues to be actively pursued.[3,4]

Attracted by successes in C–H bond activation using metal–nitrenoid species,[4–9] we reasoned that it might be possible to develop the direct insertion of a nitrenoid into an aldehyde C–H bond. In an initial communication we demonstrated proof of principle.[4] We showed that a ruthenium(II) porphyrin catalyst chemoselectively mediated the reaction of a wide range of aldehydes with TsN=IPh to give *N*-acylsulfonamides. The second proof of concept stage of our programme has aimed to establish this new procedure as both synthetically useful and mechanistically well-defined. Our discovery that inexpensive and readily available simple pyridyl complexes of copper(I) halides formed *in situ* effect high yielding synthesis of amides from aldehydes by rate limiting insertion into the aldehyde C–H bond is reported herein.[10] It remains to extend the range of nitrene sources to permit structural variation not just in the acyl–carbon substituent, but also in the *N*-substitutent and this is the subject of ongoing studies.

Reports from our groups and others suggested that use of TsN=IPh or $TsNClNa{\cdot}3H_2O$ (chloramine-T trihydrate) as nitrene transfer agents and copper(I) salts as catalysts had promise in realising our goals.[5–9] We selected isovaleraldehyde **1a** and TsN=IPh as the model substrate and nitrene transfer agent, respectively.

Table 1 Screening of copper(I) and copper(II) salts and ligands[a]



1a **2a**

Entry	Catalyst	Ligand	Yield (%)
1	CuOTf	—	50
2	$Cu(OTf)_2$	—	36
3	CuI	—	87
4[b]	CuI	—	56
5	CuBr	—	43
6	CuCl	—	18
7	CuOAc	—	43
8	CuOTf	Pyridine	85
9	CuOTf	Bipyridine	60
10	CuOTf	Terpyridine	45
11	CuOTf	Phenylenediamine	39
12	CuOTf	Ethylenediamine	37
13	CuOTf	**A**	13
14	CuOTf	**B**	28
15	CuOTf	**C**	38
16	CuOTf	**D**	52
17	CuOTf	**E**	37
18	CuOTf	**F**	72
19	CuOTf	**G**	12
20	CuOTf	**H**	60
21	$Cu(OTf)_2$	Pyridine	54
22	CuI	Pyridine	97
23	CuBr	Pyridine	87
24	CuCl	Pyridine	80

[a] All reactions were carried out in the presence of powdered 4 Å MS in CH_2Cl_2 for 18 h. The catalyst:**1a**:TsN=IPh molar ratio was 1:10:20 for entries 1–3 and 5–7, and catalyst:ligand:**1a**:TsN=IPh molar ratio was 1:2:10:20 for entry 9; 1:1:10:20 for entries 10–20; and 1:4:10:20 for entries 8 and 21–24. [b] Reaction conducted with 1 equiv. of TsN=IPh.

Table 1 shows our initial evaluation of copper salts as catalysts. The comparison of copper(I) and copper(II) triflates led us to select a range of copper(I) salts (entries 1–2). We selected readily available copper(I) halides and copper(I) acetate at different loadings of TsN=IPh (entries 3–7), of which copper(I) iodide and 2 equiv. of TsN=IPh emerged as clearly superior (entry 3).

In view of recent work showing a pyridyl-copper(II) complex could efficiently mediate alkene aziridination with *N*-tosyloxycarbamates,[6d] we next proceeded to screen a range of *N*-based ligands shown in Fig. 1 in our test reaction with **1a**. Entries 8–24 in Table 1 summarises the results of this study. Pleasingly, with CuOTf as the copper salt, pyridine emerged as the best of the ligands examined (entries 8–20). Returning to the range of copper salts used in entries 1–7 in Table 1 confirmed that an increase in the yield of the product was

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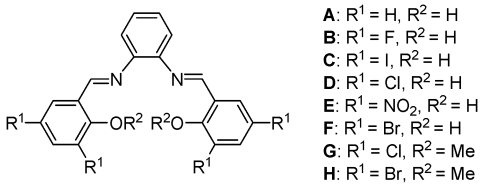


Fig. 1 *N*-Based ligands examined in this study.

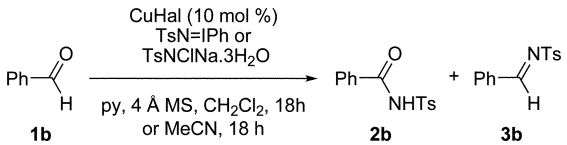
also found in all cases with the addition of 40 mol% of pyridine (entries 8 and 21–24). Once again, CuI was found to give the best result and afford **2a** in 97% yield (entry 22), comparable to that obtained for the analogous reaction of **1a** with TsN=IPh catalysed by ruthenium(II) porphyrin.[4]

We next sought to challenge our method with an aromatic aldehyde substrate and selected benzaldehyde **1b** (Table 2). Under our optimised conditions with 10 mol% of CuI and 40 mol% of pyridine, this was found to lead to a high conversion but also to significant formation of the imine byproduct **3b** (entry 1).[3f] Table 2 shows how this byproduct formation could be eliminated or minimised through two strategies. The first was by employing slow addition of aldehyde (entries 2–3). The second was by switching the nitrene transfer reagent to chloramine-T trihydrate (entries 4–5). In these latter reactions, CuCl was found to be more effective than CuI, giving **2b** in 93% yield, comparable to that obtained for analogous ruthenium(II) porphyrin-mediated reaction of **1b** with TsN=IPh.[4]

We were now ready to assess the substrate scope of our new procedure (Table 3). All the aldehydes in Table 3 were assessed with either TsN=IPh (2 equiv.), pyridine (40 mol%) and CuI (10 mol%) in CH_2Cl_2 or with $TsNClNa{\cdot}3H_2O$ (2 equiv.) and CuCl (10 mol%) in MeCN.

The results were very pleasing. For most alkyl aldehydes and electron-rich aromatic aldehydes, excellent yields of the *N*-acylsulfonamide were found (entries 1–6 and 11–13). Useful product yields were also observed with electron deficient aromatic aldehydes, furfuraldehyde and aldehydes where competing aziridination was a potential problem (entries 7–10 and 14). In addition, the product yields obtained for reactions of **1c–j**

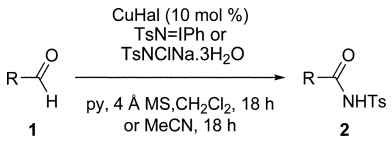
Table 2 Optimisation of the reaction conditions for **1b**[a]

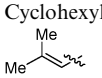
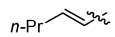


Entry	Nitrene source	Catalyst	Yield (%) 2b	Yield (%) 3b
1	TsN=IPh	CuI	75	25
2[b]	TsN=IPh	CuI	83	5
3[c]	TsN=IPh	CuI	60	8
4[d]	$TsNClNa{\cdot}3H_2O$	CuI	27	—[e]
5[d]	$TsNClNa{\cdot}3H_2O$	CuCl	93	—[e]

[a] All reactions were carried out in the presence of powdered 4 Å MS for 18 h with catalyst : pyridine : **1b** : TsN=IPh molar ratio = 1 : 4 : 10 : 20 in CH_2Cl_2. [b] Addition of **1b** over 2 h. [c] Addition of **1b** over 4 h. [d] Reaction conducted for 18 h with catalyst : **1b** : $TsNClNa{\cdot}3H_2O$ molar ratio = 1 : 10 : 20 in MeCN. [e] Not determined.

Table 3 Copper(I)-catalysed amidation of **1c–r**[a]



Entry	1, R	2, Product	Yield (%)
1	*n*-Hexyl	**2c**	95
2	Et	**2d**	81
3	*i*-Pr	**2e**	81
4	Cyclopropyl	**2f**	98
5	Cyclopentyl	**2g**	96
6	Cyclohexyl	**2h**	96
7		**2i**	65
8[b]		**2j**	62
9[b]	*p*-BrC_6H_4	**2k**	64[c]
10	*p*-ClC_6H_4	**2l**	47[c]
11	*p*-MeC_6H_4	**2m**	93[c]
12[b]	*p*-$MeOC_6H_4$	**2n**	99[c]
13[b]	1-Naphthyl	**2o**	99
14	2-Furyl	**2p**	64
15	2-Thienyl	**2q**	—[d]
16	2-Pyrrolyl	**2r**	—[d]

[a] All reactions were carried out in the presence of powdered 4 Å MS for 18 h with CuI : pyridine : **1** : TsN=IPh molar ratio = 1 : 4 : 10 : 20 in CH_2Cl_2 at rt. [b] Reaction conducted with CuCl, $TsNClNa{\cdot}3H_2O$ and MeCN in place of CuI, TsN=IPh, py, 4 Å MS and CH_2Cl_2. [c] Trace amounts of the corresponding imine also detected by ^1H NMR analysis of the crude mixture but not isolated. [d] No reaction with either CuI/TsN=IPh or CuCl/$TsNClNa{\cdot}3H_2O$ based on ^1H NMR and TLC analysis.

and **1m–p** were found to be comparable to those afforded (68–99%) in the analogous Ru-catalysed reactions.[4] The only substrates screened that failed in our procedure were the carbaldehydes of thiophene and pyrrole (entries 15–16).

We then moved on to the mechanistic component of our research; all the mechanistic studies reported here were carried out with the TsN=IPh/CuI system.

First, we investigated the possibility that the amidation reaction proceeded *via* an intermediate. Imines **3** were observed in some of our reactions (see Tables 2 and 3) and are plausible intermediates, as are oxaziridines **4**. However, no *N*-acylsulfonamide was formed when authentic samples of either **3b** or **4b**[11] (depicted in Fig. 2) were exposed to either PhI=O or $PhI(OAc)_2$ as oxidant under our standard reaction conditions. Additionally, when benzaldehyde labelled with ^{13}C at the aldehyde position was used as substrate, the progress of the reaction could be monitored by ^{13}C NMR spectroscopy. Two major signals were observed in aliquots taken from the reaction mixture, namely the labelled benzaldehyde starting material ^{13}C-**1b** decreasing in intensity and labelled amide product ^{13}C-**2b** increasing in intensity. All these data are consistent with direct conversion of aldehyde to amide.

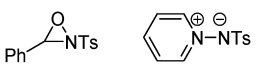


Fig. 2 Amidation intermediates **4b** and **5**.

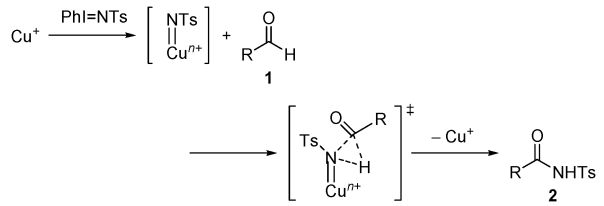


Fig. 3 Tentative mechanism for Cu(I)-catalysed amidation of aldehydes with TsN=IPh.

The beneficial effect of added pyridine led us to consider the possibility that *N*-tosyliminopyridine **5** shown in Fig. 2 was an intermediate nitrene transfer agent.[12] Once again, we were able to prepare an authentic sample of **5** and demonstrate that it was not competent as a nitrene source under our reaction conditions. Nor could **5** be observed when pyridine, TsN=IPh and CuI were combined in the absence of aldehyde. We therefore assume that the role of pyridine is as a ligand.

Given that direct reaction of an *in situ* formed copper nitrenoid species with the aldehyde appeared likely, we speculated that this occurred *via* rate determining insertion into the aldehyde C–H bond. This mechanism predicts deuterium incorporation into the amide product, that is formation of RCONDTs. Indeed, this was observed with the ruthenium-catalysed version of the reaction we communicated earlier.[4] Reaction of benzaldehyde-α-d_1 with TsN=IPh, copper(I) iodide and pyridine under standard conditions led to 56% deuterium incorporation (*cf.* 76% with ruthenium).[4] We therefore proceeded to measure the deuterium kinetic isotope effect for this reaction with **1b** and benzaldehyde-d_6 as the test substrates. Analysis by LCMS gave a k_H/k_D value of 3.8. This is clearly indicative of rate determining carbon–hydrogen bond cleavage. The value of 3.8 is similar to that we reported for copper catalysed nitrenoid insertion into dibenzyl ether,[7] which we explained by an asynchronous concerted mechanism[13] shown in Fig. 3. If this is the case, the transition state could resemble that depicted in Fig. 3 where N–H bond formation is further advanced than C–N bond formation.

In conclusion, we have developed a straightforward procedure for the amidation of a wide range of aldehydes. The catalysts are inexpensive and extremely simple to form *in situ* from copper(I) halides and pyridine. The reaction appears to proceed by rate determining insertion of a copper–nitrenoid species into the carbon–hydrogen bond of the aldehyde. For the synthesis of *N*-acylsulfonamides **2**, the new procedure should be considered as highly practical. Additionally, the free amide adduct can be accessed *via* a simple tosyl deprotection step, for example, with Mg powder in MeOH at room temperature. Extension of the method to other nitrogen substitutents is the subject of the next stage of our programme.

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Notes and references

1 (*a*) J. Fraxedas, *Molecular Organic Materials: From Molecules to Crystalline Solids*, Cambridge University Press, Cambridge, 2006; (*b*) A. Kleeman and J. Engel, *Pharmaceutical Substances: Syntheses, Patents, Applications*, Thieme, Stuttgart, 4th edn, 2001; (*c*) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243.

2 (*a*) C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827; (*b*) R. C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, Weinheim, 1999; (*c*) P. D. Bailey, I. D. Collier and K. M. Morgan, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon, Cambridge, 1995, ch. 6, vol. 5.

3 Selected recent examples: (*a*) J. Li, F. Xu, Y. Zhang and Q. Shen, *J. Org. Chem.*, 2009, **74**, 2575; (*b*) F. Wang, H. Liu, H. Fu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 246; (*c*) L. U. Nordstrøm, H. Vogt and R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672; (*d*) L. Wang, H. Fu, Y. Jiang and Y. Zhao, *Chem.–Eur. J.*, 2008, **14**, 10722; (*e*) K. R. Reddy, C. U. Maheswari, M. Venkateshwar and M. L. Kantam, *Eur. J. Org. Chem.*, 2008, 3619; (*f*) C. Fang, W. Qian and W. Bao, *Synlett*, 2008, 2529; (*g*) J. Chan, K. D. Baucom and J. A. Murry, *J. Am. Chem. Soc.*, 2007, **129**, 14106; (*h*) J. W. Bode and S. S. Sohn, *J. Am. Chem. Soc.*, 2007, **129**, 13798; (*i*) H. U. Vora and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 13796; (*j*) K. Ekoue-Kovi and C. Wolf, *Org. Lett.*, 2007, **9**, 3429; (*k*) C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790.

4 J. W. W. Chang and P. W. H. Chan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1138, and references therein.

5 (*a*) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061; (*b*) S. Fantauzzi, A. Caselli and E. Gallo, *Dalton Trans.*, 2009, 5434; (*c*) M. M. Díaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379; (*d*) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (*e*) H. M. L. Davies, *Angew. Chem., Int. Ed.*, 2006, **45**, 6422; (*f*) Z. Li and C. He, *Eur. J. Org. Chem.*, 2006, 4313; (*g*) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439; (*h*) H. Lebel, O. Leogane, K. Huard and S. Lectard, *Pure Appl. Chem.*, 2006, **78**, 363; (*i*) C. G. Espino and J. Du Bois, in *Modern Rhodium-Catalyzed Organic Reactions*, ed. P. A. Evans, Wiley-VCH, Weinheim, 2005, p. 379; (*j*) H. M. L. Davies and M. S. Long, *Angew. Chem., Int. Ed.*, 2005, **44**, 3518; (*k*) P. Müller and C. Fruit, *Chem. Rev.*, 2003, **103**, 2905.

6 Selected recent examples using TsN=IPh: (*a*) J. W. W. Chang, T. M. U. Ton, Z. Zhang, Y. Xu and P. W. H. Chan, *Tetrahedron Lett.*, 2009, **50**, 161, and references therein; (*b*) H. Han, S. B. Park, S. K. Kim and S. Chang, *J. Org. Chem.*, 2008, **73**, 2862; (*c*) Q. Xu and D. H. Appella, *Org. Lett.*, 2008, **10**, 1497; (*d*) H. Lebel, S. Lectard and M. Parmentier, *Org. Lett.*, 2007, **9**, 4797; (*e*) R. Liu, S. R. Herron and S. A. Fleming, *J. Org. Chem.*, 2007, **72**, 5587; (*f*) M. Fructos, S. Trofimenko, M. M. Díaz-Requejo and P. J. Pérez, *J. Am. Chem. Soc.*, 2006, **128**, 11784.

7 D. P. Albone, S. Challenger, A. M. Derrick, S. M. Fillery, J. L. Irwin, C. M. Parsons, H. Takada, P. C. Taylor and D. J. Wilson, *Org. Biomol. Chem.*, 2005, **3**, 107.

8 Selected examples using $TsNClNa{\cdot}3H_2O$: (*a*) R. Bhuyan and K. M. Nicholas, *Org. Lett.*, 2007, **9**, 3957; (*b*) I. Cano, M. C. Nicasio and P. J. Peréz, *Dalton Trans.*, 2009, 730; (*c*) H. Martínez-García, D. Morales, J. Pérez, D. J. Coady, C. W. Bielawski, D. E. Gross, L. Cuesta, M. Marquez and J. L. Sessler, *Organometallics*, 2007, **26**, 6511, and references therein.

9 A. Armstrong and D. P. G. Emmerson, *Org. Lett.*, 2009, **11**, 1547, and references therein.

10 In comparison, ruthenium(II) porphyrin catalysts are typically preformed prior to use. Additionally, for the analogous ruthenium(II) porphyrin-catalysed reactions of aromatic aldehydes with TsN=IPh, removal of the metal catalyst was found to be non-trivial and required careful separation by flash column chromatography. In this work, removal of the copper catalyst was readily achieved by filtration through Celite®. Please refer to ESI† for further details.

11 J. L. García-Ruano, J. Aleman, C. Fajardo and A. Parra, *Org. Lett.*, 2005, **7**, 5493.

12 Y. Jiang, G.-C. Zhou, G.-L. He, L. He, J.-L. Li and S.-L. Zheng, *Synthesis*, 2007, 1459.

13 See ref. 5 and K. W. Fiori, C. G. Espino, B. H. Brodsky and J. Du Bois, *Tetrahedron*, 2009, **65**, 3042, and references therein.

