Addition Reactions

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Alkylation of Aryl *N*-(2-Pyridylsulfonyl)aldimines with Organozinc Halides: Conciliation of Reactivity and Chemoselectivity**

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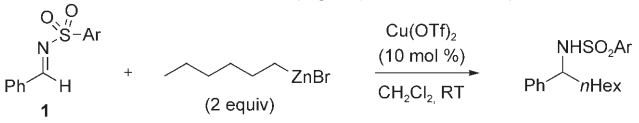
The direct addition of organometallic reagents to imines is a very convergent route to α-branched primary and secondary amines.[1] Consequently, a number of synthetically useful addition reactions for the formation of carbon–carbon bonds have been developed with organolithium,[2] Grignard,[3] dialkyl zinc,[4] alkenyl zirconium,[5] aryl tin,[6] aryl titanium,[7] and aryl boron[8] reagents as nucleophiles, including some very efficient catalytic enantioselective procedures.[9] Despite this great progress, limitations in the scope of this reaction remain, especially with regard to functional-group compatibility. Highly reactive organometallic species, such as organolithium or Grignard reagents, have typically been used for the alkylation of imines, as the reactions occur under mild conditions with such reagents. However, drawbacks associated with these organometallic reagents are the competitive formation of reduction products and difficulties in the reconciliation of reactivity and chemoselectivity when functional groups are present in either the nucleophile or the imine substrate. The use of softer boron, tin, or silicon reagents has been limited mainly to arylation reactions[6–8] and resonance-stabilized allyl metal species,[10] which are more reactive than ordinary alkyl organometallic reagents. Organozinc reagents show an optimal compromise in terms of reactivity and wide functional-group tolerance, but only a limited number of simple dialkyl zinc reagents (typically dimethylzinc or diethylzinc) have been used for the alkylation of imines.[4] Owing to their straightforward preparation[11] and commercial availability, alkyl zinc halides offer a unique opportunity to satisfy the need for a general method for the alkylation of imines that combines high reactivity and wide functional-group tolerance. Although an increasing number of methodologies benefit from the unique reactivity/selectivity profile of RZnX reagents,[12] alkyl zinc halides have been scarcely used as nucleophiles in 1,2-addition reactions to imines, [13] probably as a result of the poor electrophilicity of the imine group.

In recent years, we[14] and others[3f,15] have demonstrated that *N*-(heteroarylsulfonyl) imines show better reactivity and/or selectivity than other *N*-sulfonyl imines, such as *N*-tosylimines, in some addition and cycloaddition reactions. Furthermore, the *N*-(heteroarylsulfonyl) group facilitates the often problematic deprotection of the amine functionality. Herein, we report a novel procedure for the alkylation of aromatic *N*-sulfonyl imines with alkyl zinc bromides. Key features of this method, which relies on the presence of a heteroarylsulfonyl coordinating group on the imine nitrogen atom, are high reactivity and broad functional-group compatibility, as well as straightforward deprotection to generate the free amine.

To find a suitable sulfonyl substituent, we treated a representative set of imines, **1a–g**, with *N*-hexylzinc bromide (2 equiv) in CH_2Cl_2 at room temperature (Table 1). Substrates **1a** with a tosyl group, **1b** with a *p*-nosyl group, **1c** with an *o*-nosyl group, and **1d** with a 2-thienylsulfonyl group did not undergo the desired reaction in the presence of $Cu(OTf)_2$ (10 mol%; Table 1, entries 1–4).[16] Only products of imine hydrolysis were recovered following an aqueous workup. In contrast, the (8-quinolylsulfonyl)imine **1e**[14d] and (2-pyridylsulfonyl)imine **1f**[14a,b] underwent smooth addition reactions under the catalysis of $Cu(OTf)_2$[17] (10 mol%) to afford the corresponding adducts **2e** and **2f** in 80 and 97% yield, respectively, in 15 min or less (Table 1, entries 5 and 6). Imine **1f** underwent addition with *N*-hexylzinc bromide even in the absence of a copper salt, although the reaction became much slower (8 h at room temperature), and the yield of **2f**

Table 1: Influence of the N-sulfonyl group on the reactivity of the imine.



Entry	Ar	1	t	Product	Yield [%][a]
1	*p*-tolyl	**1a**	12 h	–[b]	–
2	*p*-$NO_2C_6H_4$	**1b**	12 h	–[b]	–
3	*o*-$NO_2C_6H_4$	**1c**	12 h	–[b]	–
4	2-thienyl	**1d**	12 h	–[b]	–
5	8-quinolyl	**1e**	15 min	**2e**	80
6	2-pyridyl	**1f**	5 min	**2f**	97
7	3-pyridyl	**1g**	12 h	–[b]	–

[a] After chromatographic purification. [b] Only the products of imine hydrolysis were recovered after aqueous workup. Tf = trifluoromethanesulfonyl.

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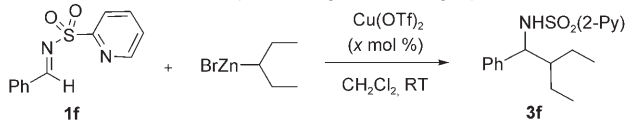
decreased to 64% as a result of partial hydrolysis of the imine. Interestingly, the (3-pyridylsulfonyl)imine **1g**, an isomer of **1f**, proved to be unreactive under the optimized reaction conditions (Table 1, entry 7), which suggests that a chelating interaction of the heteroaryl moiety with the metal center may be responsible for the dramatic increase in reactivity observed with imines **1e** and **1f**.

Next, the influence of catalyst loading was investigated for the addition of the secondary alkyl zinc reagent 2-pentylzinc bromide to **1f** (Table 2). The addition was equally effective with 5 mol% (Table 2, entry 1) and 1 mol% (entry 2) of

Table 2: Effect of the catalyst loading and scaling up on the reaction.



Entry	Quantity of **1f** [mmol]	*x*	*t* [min]	Yield [%][a]
1	0.2	5	5–10	92
2	2	1	15	90
3	4	0.1	75	77
4	0.2	0	270	66

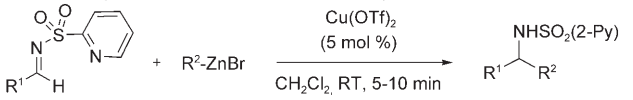
[a] After chromatographic purification.

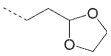
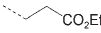
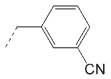
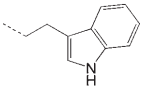
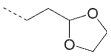
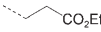
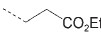
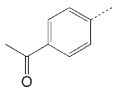
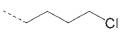
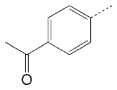
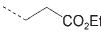
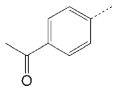
$Cu(OTf)_2$: In both cases the product **3f** was formed in over 90% yield in less than 15 min.[18] As a further demonstration of the potential of this method, the addition of 2-pentylzinc bromide to imine **1f** on a gram scale (4 mmol) in the presence of 0.1 mol% of $Cu(OTf)_2$ (molar ratio S/C = 1000) led to **3f** in 77% yield after 75 min at room temperature (Table 2, entry 3). In the absence of a copper catalyst, the reaction afforded **3f** in 66% yield after 4.5 h (Table 2, entry 4).

The scope of this Cu-catalyzed reaction was examined with a variety of aryl and heteroaryl *N*-(2-pyridylsulfonyl)aldimines (Table 3). Aliphatic imines were not investigated, as to date we have not succeeded in developing a general method for the isolation of this more labile type of imine.[19] For practical reasons, this study was undertaken with 5 mol% of $Cu(OTf)_2$, although we confirmed later that the catalyst is equally effective in a loading of 1 mol% (Table 3, entry 27). A wide variety of alkyl zinc bromide reagents of different substitution patterns and degrees of functionalization participated in the addition reaction to provide the corresponding protected amines in less than 10 min in yields typically in the range of 80–90%. Primary and secondary alkyl zinc bromide reagents with a broad variety of functional groups, including alkene, ether, acetal, chloride, ester, and nitrile groups, were used successfully in this procedure. Even an unprotected indole substituent with an acidic NH group proved to be compatible (Table 3, entry 13). Only the very bulky reagent *tert*-butylzinc bromide was unreactive under these conditions (Table 3, entry 5).

With respect to the imine substrate, aryl moieties with donor or acceptor substituents at the *ortho*, *meta*, or *para* position are tolerated well (Table 3, entries 14–21). Heteroaromatic 2-furyl, 2-thienyl, and 2-pyrryl imine derivatives also

Table 3: Scope of the direct addition of alkyl zinc bromides to imines.



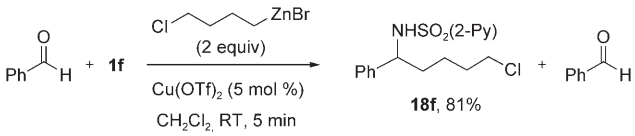
Entry	R^1	Imine	R^2	Product	Yield [%][a]
1	Ph	**1f**		**2f**	93
2	Ph	**1f**		**3f**	92
3	Ph	**1f**		**13f**	88
4	Ph	**1f**		**14f**	81
5	Ph	**1f**	*t*Bu	–	–[b]
6	Ph	**1f**		**15f**	90
7	Ph	**1f**		**16f**	84
8	Ph	**1f**		**17f**	92
9	Ph	**1f**		**18f**	95
10	Ph	**1f**		**19f**	88
11	Ph	**1f**		**20f**	90
12	Ph	**1f**		**21f**	90
13	Ph	**1f**		**22f**	82
14	4-$MeOC_6H_4$	**4f**		**23f**	80
15	4-$MeOC_6H_4$	**4f**		**24f**	83
16	4-FC_6H_4	**5f**		**25f**	88
17	4-FC_6H_4	**5f**		**26f**	85
18	2-BrC_6H_4	**6f**		**27f**	87
19	3-MeC_6H_4	**7f**		**28f**	84
20	2-naphthyl	**8f**		**29f**	91
21	2-naphthyl	**8f**		**30f**	89
22	2-furyl	**9f**		**31f**	92
23	2-furyl	**9f**		**32f**	90
24	2-thienyl	**10f**		**33f**	80
25		**11f**		**34f**	68[c]
26		**12f**		**35f**	77
27		**12f**		**36f**	83[d]
28		**12f**		**37f**	85

[a] After chromatographic purification. [b] The product was not observed after 16 h at room temperature. [c] Reaction time: 3 h. [d] $Cu(OTf)_2$: 1 mol%.

proved to be suitable (Table 3, entries 22–25). The more challenging substrate **12f**, with a potentially competitive ketone group, underwent imine alkylation with complete chemoselectivity (Table 3, entries 26–28).

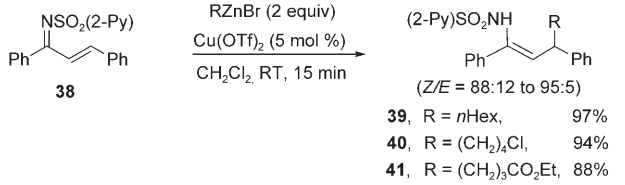
In a competition experiment that highlights the exceptional reactivity of the *N*-(2-pyridylsulfonyl)imines, an equimolar mixture of benzaldehyde and imine **1f** was treated with

4-chlorobutylzinc bromide (2.0 equiv) under the optimized reaction conditions. After a reaction time of 5 min, the sulfonamide adduct **18 f** was obtained as the only product. No trace of the product of addition to the aldehyde was detected by NMR spectroscopy, and benzaldehyde was recovered (Scheme 1).



Scheme 1. Chemoselectivity competition experiment between (2-pyridylsulfonyl)imine **1 f** and benzaldehyde. Py = pyridyl.

In connection with our studies on the conjugate addition of Et_2Zn to α,β-unsaturated *N*-(2-pyridylsulfonyl)ketimines,[14a] we examined the addition of alkyl zinc bromides to **38**, the (2-pyridylsulfonyl)imine of chalcone (Scheme 2).



Scheme 2. Conjugate addition of alkyl zinc bromides to the *N*-(2-pyridylsulfonyl)imine of chalcone.

Only conjugate addition was observed,[20] and the corresponding enamides **39**–**41** were obtained in high yields (88–97%) and with very good *Z* stereoselectivity.[21] In contrast, chalcone itself and its *N*-tosylimine were recovered unaltered after treatment under the same conditions, even after prolonged reaction times.

The exceptional reactivity of 2-pyridylsulfonylimines prompted us to study the mode of their coordination to copper. Initial attempts to isolate a copper complex of aldimine **1 f** failed as a result of its high propensity to undergo hydrolysis. However, the treatment of the more stable ketimine **38** with 1 equivalent of $[Cu(CH_3CN)_4]PF_6$[22] in CH_2Cl_2 at room temperature produced an instantaneous color change from colorless to deep red, accompanied by nearly quantitative formation of complex **42**, which was isolated as an air-stable red solid. X-ray diffraction analysis of suitable crystals[23] revealed a distorted trigonal-pyramidal N,N,N,N-tetracoordinated copper complex[24] in which the Cu^I atom coordinates to two molecules of **38** through the imino and pyridyl nitrogen atoms (Figure 1). The observation that the bonds between Cu^I and the imine nitrogen atoms (2.34 Å) are much longer than those between Cu^I and the pyridine nitrogen atoms (1.93 Å) reflects the higher affinity of the metal center to the more basic pyridine nitrogen atoms. The bidentate N,N chelation of *N*-(2-pyridylsulfonyl)imines through a favorable five-membered chelate ring[25] with the electrophilic copper salt provides a reasonable explanation for the much higher reactivity of 2-pyridylsulfonylimines over that of nonchelating *N*-sulfonyl imines.[26]

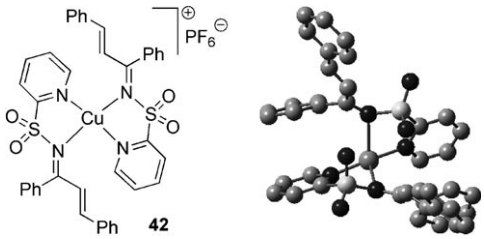
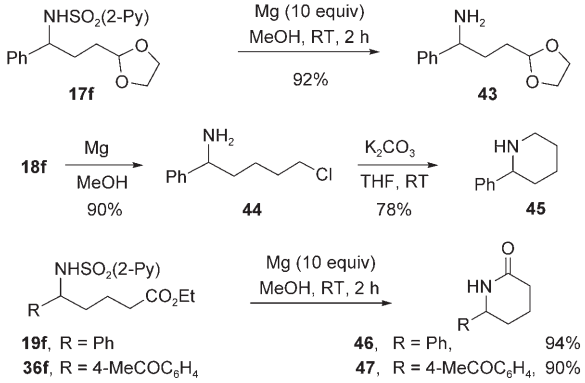


Figure 1. X-ray crystal structure of complex **42**. (The PF_6^- anion and the hydrogen atoms have been omitted).

The 2-pyridylsulfonyl group was removed by the simple treatment of the sulfonamide adducts with an excess of Mg in MeOH at room temperature for 2 h.[27] The corresponding primary amines were obtained in 90–94% yield (Scheme 3).



Scheme 3. Deprotection of the sulfonamide adducts and cyclization reactions.

This smooth deprotection reaction is compatible with sensitive functional groups, such as ketals, halides, and esters. The free chloroamine **44** was converted into the piperidine derivative **45** in 78% yield by subsequent treatment with K_2CO_3. The deprotection of the sulfonamide esters **19 f** and **36 f** led to the δ-lactams **46** and **47**, respectively, in excellent yields (> 90%) through the spontaneous cyclization of the corresponding free amines under the reaction conditions.

In conclusion, readily available alkyl zinc bromide reagents are excellent nucleophilic species for the alkylation of aromatic *N*-(2-pyridylsulfonyl)aldimines with unprecedented functional-group compatibility. Functionalized free amines can be accessed in very good yields upon facile deprotection under mild conditions. We attribute the exceptional reactivity of these imines to their N,N-bidentate character with respect to metal coordination, evidence for which was obtained from an X-ray crystallographic study of a Cu^I complex.

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[17] Cu^{I} salts, such as $[Cu(CH_3CN)_4]PF_6$ or CuTC, were also effective catalysts in a concentration of 10 mol% for the reaction of **1f**: Compound **2f** was formed in 93 or 94% yield within 15 min.

[18] In this model reaction, a similar high reactivity was observed in the presence of $Cu(OTf)_2$ (5 mol%) and a phosphine ligand (5 mol%), such as 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap). Unfortunately, however, the racemic product **3f** was obtained when (*R*)-binap was used as the ligand.

[19] Although aliphatic *N*-(2-pyridylsulfonyl)imines appear to be formed quantitatively in 2–3 h upon the direct condensation of an aldehyde with 2-pyridylsulfonamide in the presence of $Ti(OEt)_4$ (1 equiv) in CH_2Cl_2 at room temperature (TLC monitoring), all attempts to isolate the pure aldimine resulted in the recovery of the hydrolysis products.

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[22] $[Cu(CH_3CN)_4]PF_6$ was chosen as the stoichiometric copper source as a result of its much higher solubility in CH_2Cl_2 relative to that of $Cu(OTf)_2$.

[23] See the Supporting Information for experimental details and crystallographic data. CCDC-654016 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..

[24] For an N,N,N,N-tetracoordinated Cu^{II} complex of bis(2-pyridyl)sulfonamido ligands, see: A. Nanthakumar, J. Miura, S. Diltz, C.-K. Lee, G. Aguirre, F. Ortega, J. W. Ziller, P. J. Walsh, *Inorg. Chem.* **1999**, *38*, 3010.

[25] This N,N coordination the imine to copper contrasts with the N,O-type metal complexes of (2-pyridylsulfonyl)aldimines proposed by Toru and co-workers on the basis of theoretical calculations, whereby the pyridyl nitrogen atom and one of the sulfonyl oxygen atoms were proposed to form a five-membered chelate ring with the metal center; see refs. [3f, 14a].

[26] This mode of coordination could also facilitate pseudointramolecular delivery of the organocopper nucleophile following the Zn/Cu transmetalation; see, for example: P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.

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