

Oxidative Amination of Heteroaromatic
Zinc Reagents Mediated by $\text{PhI}(\text{OAc})_2$

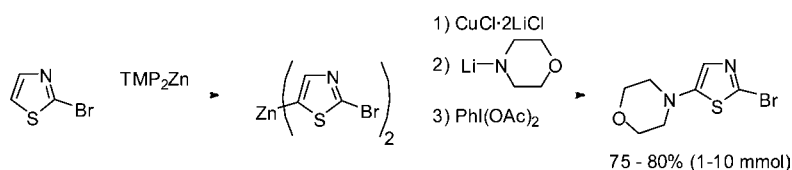
Marcel Kienle, Cora Dunst, and Paul Knochel*

Department Chemie & Biochemie, Ludwig-Maximilians-Universität, Butenandtstrasse
5-13, 81377, München (Germany)

paul.knochel@cup.uni-muenchen.de

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ABSTRACT



The oxidative amination of functionalized heterocycles has been achieved by using readily available heterocyclic zinc reagents and lithium amides. $\text{PhI}(\text{OAc})_2$ proved to be a suitable reagent for this oxidative amination.

Heteroaromatics belong to one of the most important classes of compounds in medicinal chemistry.¹ Especially amines containing five-membered heteroaryl groups such as furans, thiophenes, thiazoles, and pyrazoles are widely found in both natural products and drugs.² Whereas the direct amination of six-membered heterocyclic halides proceeds even uncatalyzed at high temperatures or high pressure,³ the amination of five-membered heteroaromatics has been hampered for a long time. However, due to the work of Buchwald and Hartwig and others on Pd-catalyzed aminations,^{4,5} many functional five- and six-membered heterocyclic amines are nowadays available.⁶ Nonetheless, these protocols still have some limitations, such as long reaction times and the use of strong bases. In addition, some functional groups such as iodides and bromides are

not compatible with this Pd-catalyzed amination procedure. Thus, the development of other mild and general methods for the amination of heteroaromatics is still an important goal.

Recently, we have described an oxidative amination of arylcopper reagents⁷ starting from organomagnesium reagents furnishing primary, secondary, and tertiary amines using chloranil as an oxidation reagent.⁸ For the oxidative

(1) (a) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley & Sons: Weinheim, 1997. (b) Wipf, P.; Wang, Z. *Org. Lett.* **2007**, 9, 1605.

(2) (a) Metzger, J. V. *Thiazole and its Derivatives*; John Wiley & Sons: New York, 1979. and references therein. (b) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, 1, 197. (c) Walcynski, K.; Gurn, R.; Zuiderveld, O. P.; Timmermann, H. *Il Farmaco* **1999**, 54, 684.

(3) Kosuki, H.; Sakai, H.; Shinohara, T. *Synlett* **2000**, 1, 116.

(4) For selected reviews see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, 37, 2046. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, 31, 852. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, 31, 805. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, 576, 125. (e) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, 219, 131. (f) Blaser, H.-U.; Indolese, A.; Naud, F.; Nettekoven, U.; Snyder, A. *Adv. Synth. Catal.* **2004**, 346, 1583. (g) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, 47, 6338. (h) Hartwig, J. F. *Acc. Chem. Res.* **2008**, 41, 1534.

(5) For recent reports: (a) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, 346, 1742. (b) Shekhar, S.; Ryberg, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, 128, 3584. (c) Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, 71, 430. (d) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altmann, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, 45, 6523. (e) Strieter, E. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, 45, 925. (f) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, 129, 10354. (g) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, 130, 13552. (h) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, 131, 5766. (i) Schulz, T.; Torborg, C.; Enthaler, S.; Schäffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Börner, A.; Beller, M. *Chem.—Eur. J.* **2009**, 15, 4528.

(6) (a) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, 68, 2861. (b) Hooper, M. W.; Hartwig, J. F. *Organometallics* **2003**, 22, 3394. (c) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, 7, 3965. (d) Reddy, C. V.; Kingston, J. V.; Verkade, J. G. *J. Org. Chem.* **2008**, 73, 3047. (e) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, 10, 4109. (f) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, 130, 6586.

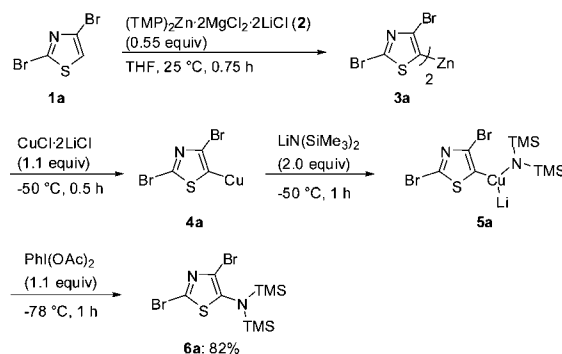
(7) (a) Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, 45, 2739. (b) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, 58, 5620. (c) Alberti, A.; Canè, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, 61, 1677. (d) Canè, F.; Brancaloni, D.; Dembech, P.; Ricci, A.; Seconi, G. *Synthesis* **1997**, 545. (e) Bernardi, P.; Dembech, P.; Fabbri, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1999**, 64, 641.

amination of heterocyclic copper derivatives obtained by transmetalation from zinc organometallics, the use of chloranil was unsatisfactory. Furthermore, the scale-up of such aminations was difficult with this oxidation reagent. Herein, we report an oxidative amination reaction starting from readily available zinc reagents mediated by $\text{PhI}(\text{OAc})_2$.^{9,10} We started our investigations on the amination of functionalized thiazoles. Thiazole derivatives containing an amino function in position 4 or 5 can be obtained either from α -thiocyanonitriles¹¹ or via the Cornforth rearrangement.¹²

Thus, 2,4-dibromothiazole (**1a**) was zincated using $(\text{TMP})_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$ (**2**, 0.55 equiv; TMP = 2,2,6,6-tetramethylpiperidyl)¹⁴ furnishing the diarylzinc compound **3a**. This zinc reagent was very stable and did not undergo halogen dance reactions as is usually the case for electron-poor heteroarylzinc compounds.¹⁵ After the addition of $\text{CuCl} \cdot 2\text{LiCl}$ (1.1 equiv) the corresponding copper derivative **4a** was obtained. Further addition of $\text{LiN}(\text{SiMe}_3)_2$ (2.0 equiv) afforded the amidocuprate **5a**. The subsequent oxidation of **5a** using $\text{PhI}(\text{OAc})_2$ (1.1 equiv) provided the thiazole amine derivative **6a** in 82% yield with only traces of the corresponding homocoupling product as byproduct (Scheme 1; Table 1, entry 1).

A range of thiazoles were aminated in 61–76% yield by this procedure (Table 1). Thus, the copper derivative **4a** was also reacted with *N*-lithium morpholide and *N*-lithium *N'*-methylpiperazide, leading to the tertiary amines **6b** and **6c** in 70% and 61% yield, respectively (Table 1, entries 2–3). 2-Bromothiazole (**1b**) was aminated with various cyclic and acyclic amines as well, furnishing the 2-bromothiazole amines **6d–6f** in 63–75% yield (Table 1, entries 4–6). Using this method, 4-amino thiazoles are also available. Thus, the zincation and subsequent transmetalation and amination of 2-bromo-5-trimethylsilylthiazole (**1c**) furnished the tertiary amines **6g** and **6h** in 73% and 75% yield and the triarylamine **6i** in 76% yield (Table 1, entries 7–9). 2-(Phenylthio)thiazole (**1d**) was also successfully aminated, provid-

Scheme 1. Zincation of 2,4-Dibromothiazole (**1a**) with $(\text{TMP})_2\text{Zn}$ (**2**) Followed by an Oxidative Amination Reaction



ing the amines **6j–6k** in 72–75% yield (Table 1, entries 10–11). These phenylthio thiazoles are useful intermediates since the phenylthio group can serve as a leaving group in cross-coupling reactions.¹⁶

We have also applied the method for the amination of other heteroaromatics, such as benzothiazole (**7a**), benzofuran (**7b**), and 2,5-dibromothiophene (**7c**). Benzothiazole (**7a**) was smoothly zincated at 25 °C using TMP_2Zn (**2**).¹³ Subsequent oxidative amination with *N*-lithium morpholide and LiTMP furnished the tertiary amines **8a,b** in 60–73% yield (Table 2, entries 1–2).

Benzofuran (**7b**) as well as 2,5-dibromothiophene (**7c**) were zincated using microwave irradiation (100 °C, 1 h)¹⁷ followed by an oxidative amination, yielding the corresponding amines **8c–e** in 60–70% yield (Table 2, entries 3–5).

Recently, we have reported a novel Mg insertion into aromatic and heterocyclic bromides and chlorides in the presence of LiCl and ZnCl_2 , leading to aromatic and heteroaromatic zinc organometallics.¹⁸ We have applied this method to the zincation of several heterocycles followed by an oxidative amination. Thus, 4-bromo-1,3,5-trimethyl-1*H*-pyrazole (**9a**) was treated with Mg turnings (2.5 equiv) in the presence of LiCl (2.5 equiv) and ZnCl_2 (1.0 equiv), furnishing the zinc species **10a**. After transmetalation with $\text{CuCl} \cdot 2\text{LiCl}$ (1.1 equiv) and the addition of lithium *N*-diphenylamide (2.0 equiv), the amidocuprate **11a** was obtained. Oxidation of **11a** using $\text{PhI}(\text{OAc})_2$ (1.1 equiv) led to the desired tertiary amine **12a** in 70% yield (Scheme 2; Table 3, entry 1).¹⁹

Other heterocycles such as **9b** and **9c** were also converted to the corresponding zinc compounds using the previously described Mg insertion in the presence of ZnCl_2 .¹⁸ These

(8) (a) del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7838. (b) Kienle, M.; Dubbaka, S. R.; del Amo, V.; Knochel, P. *Synthesis* **2007**, 1272.

(9) For an excellent overview of hypervalent iodine compounds, see: (a) Zhdarkin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. For recent reports, see: (b) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulisa, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (c) Kar, A.; Mangu, N.; Kaiser, H. M.; Tse, M. K. *J. Organomet. Chem.* **2009**, *694*, 524. (d) Zalatan, D. N.; Du Bois, J. J. *Am. Chem. Soc.* **2009**, *131*, 7558. For the synthesis and application of related hypervalent iodine compounds, see: (e) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. (f) Bielawski, M.; Olofsson, B. *Org. Synth.* **2009**, *86*, 308.

(10) After screening various benzoquinones as well as hypervalent iodine derivatives, $\text{PhI}(\text{OAc})_2$ proved to give the best results.

(11) (a) Obushak, N. D.; Matiichuk, V. S.; Ganushchak, N. I.; Martyak, R. L. *Chem. Heterocycl. Compd.* **1997**, *33*, 1000. (b) Obushak, N. D.; Matiichuk, V. S.; Martyak, R. L.; Ganushchak, N. I. *Chem. Heterocycl. Compd.* **1999**, *35*, 93.

(12) Corrao, S. L.; Macielag, M. J.; Turchi, I. J. *J. Org. Chem.* **1990**, *55*, 4484.

(13) (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685. (b) Wunderlich, S. H.; Knochel, P. *Chem. Commun.* **2008**, 6387.

(14) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

(15) (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon, 2002. (b) Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035. (c) Rocca, P.; Cochenec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832. (d) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1999**, *55*, 12149.

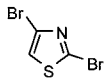
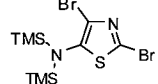

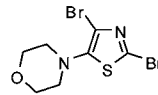

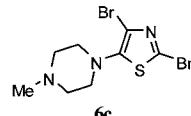


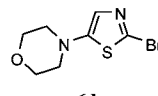

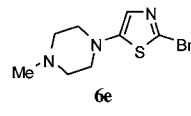

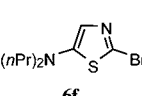
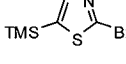

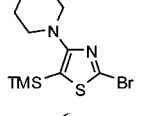

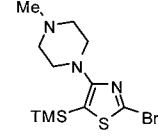
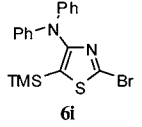


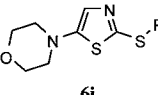

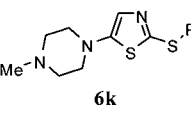
(16) (a) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (b) Metzger, A.; Melzig, L.; Despotopoulou, C.; Knochel, P. *Org. Lett.* **2009**, *11*, 4228.

(17) For microwave accelerated zincations, see: Wunderlich, S.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705.

(18) (a) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *48*, 6802. (b) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 7192.

(19) The amination sequence of the pyrazole **9a** with $\text{Li}(\text{SiMe}_3)_2$ yielded the desired TMS-protected amine. However, standard deprotection (TBAF) resulted in its decomposition.



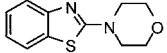

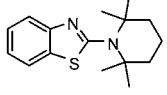


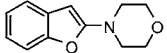
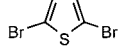

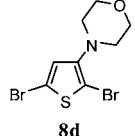
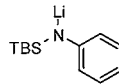
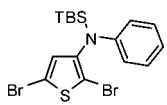
Table 1. Oxidative Amination of Various Functionalized Thiazoles after Zincation with TMP₂Zn (2)

entry	substrate ^a	amine	product	yield, % ^b
1	 1a (25, 0.75)	LiN(SiMe ₃) ₂	 6a	82
2	1a		 6b	70
3	1a		 6c	61
4	 1b (25, 2)		 6d	75
5	1b		 6e	71
6	1b		 6f	63
7	 1c (25, 8)		 6g	73
8	1c		 6h	75
9	1c	Ph ₂ NLi	 6i	76
10	 1d (25, 2)		 6j	75
11	1d		 6k	72

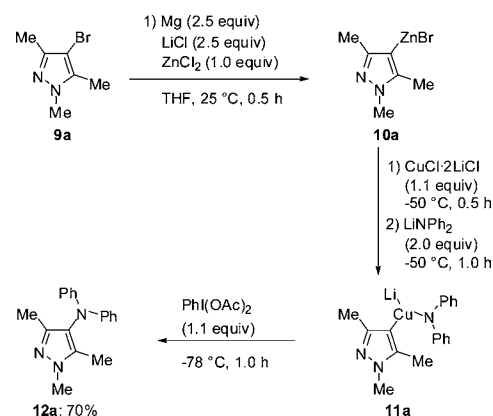
^a The reaction conditions for the metalation with TMP₂Zn (2) are given in parentheses (°C, h). ^b Isolated yield of analytically pure product.

zinc reagents were then aminated using the oxidative amination, yielding the tertiary amines **12b** and **12c** in 66%

Table 2. Oxidative Amination of Various Heterocycles Leading to Tertiary and Protected Secondary Amines

entry	substrate ^a	amide	product	yield, % ^b
1	 7a (25, 1)		 8a	73
2	7a		 8b	60
3	 7b (100, 1, MW)		 8c	60
4	 7c (100, 1, MW)		 8d	70
5	7c		 8e	67

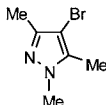
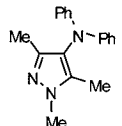
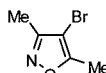

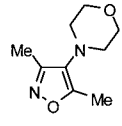
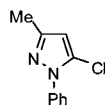

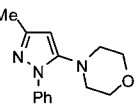
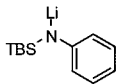
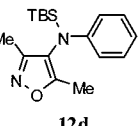
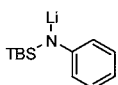
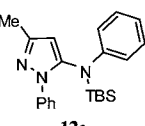
^a The reaction conditions for the metalation with TMP₂Zn (2) are given in parentheses (°C, h). ^b Isolated yield of analytically pure product.

Scheme 2. Mg Insertion in the Presence of LiCl and ZnCl₂ and Subsequent Oxidative Amination

and 67% yield (Table 3, entries 2–3). Using this protocol, we have also prepared various protected secondary amines: after zincation of the corresponding heteroaromatics **9b** and **9c** and subsequent oxidative amination, the TBDMS-protected diarylamines **12d–e** were obtained in 60% and 57% yield (Table 3, entries 4–5).

Furthermore, we have found that the previously described zinc reagents are suitable for large-scale oxidative amination

Table 3. Oxidative Amination of Zinc Reagents Obtained by Magnesium Insertion in the Presence of ZnCl₂ and LiCl

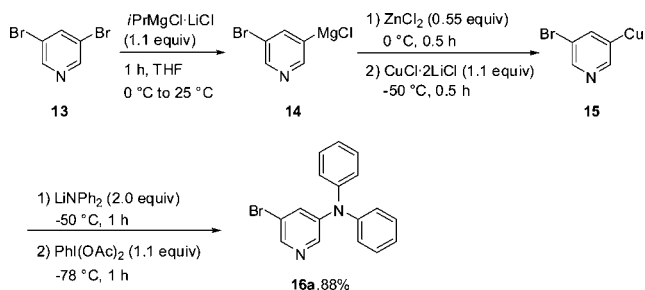
entry	substrate ^a	amide	product	yield, % ^b
1	 9a (25, 0.25)	LiNPh ₂	 12a	70
2	 9b (25, 0.25)		 12b	66
3	 9c (25, 1)		 12c	67
4	9b		 12d	60
5	9c		 12e	57

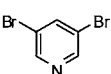

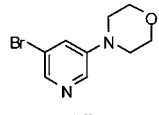

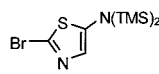

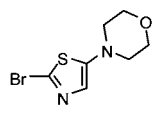
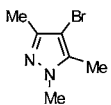
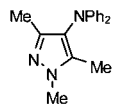
^a The reaction conditions for the metalation with TMP₂Zn (**2**) are given in parentheses (°C, h). ^b Isolated yield of analytically pure product.

reactions, regardless if the zinc reagent is formed by metalation using TMP₂Zn (**2**), by insertion or by addition of a ZnCl₂ solution to a preformed magnesium reagent. Thus, the treatment of 3,5-dibromopyridine (**13**, 10 mmol) with *i*PrMgCl·LiCl provided the corresponding magnesium reagent **14**. Subsequent addition of ZnCl₂ (0.55 equiv) and CuCl·2LiCl (1.1 equiv) furnished the copper species **15**. After the reaction with lithium *N*-diphenylamide and PhI(OAc)₂, the desired triarylamine **16a** is obtained in 88% yield (Scheme 3).

Similarly, the amination of 3,5-dibromopyridine (**13**) with lithium *N*-morpholide furnished the tertiary amine **16b** in 71% yield (Table 4, entry 1). In addition, after zincation of 2-bromothiazole (**1b**) with TMP₂Zn (**2**) the corresponding zinc species was also smoothly aminated on a 10 mmol scale, furnishing the desired amines **6l** and **6d** in 73% and 80% yield (Table 4, entries 2–3).

We found that the best results were obtained when only 0.55 equiv of ZnCl₂ was used. Nonetheless, zinc reagents obtained by magnesium insertion in the presence of ZnCl₂ and LiCl,¹⁸ therefore containing 1.0 equiv of ZnCl₂, are also well suited for these larger scale reactions. Thus, the previously described amination of **9a** on a 10 mmol scale furnished the tertiary amine **12a** in 66% yield (Table 4, entry 4; compared to 70% yield on a 1 mmol scale, Scheme 2).

Scheme 3. Oxidative Amination of 3,5-Dibromopyridine Mediated by PhI(OAc)₂ on a 10 mmol Scale**Table 4.** Oxidative Amination of Zinc Reagents on a 10 mmol Scale

entry	substrate	amide	product	yield, % ^a
1	 13		 16b	71
2	 1b	LiN(SiMe ₃) ₂	 6l	73
3	1b		 6d	80
4	 9a	LiNPh ₂	 12a	66

^a Isolated yield of analytically pure product.

In conclusion, we have developed a new general method for the amination of readily available heterocyclic zinc reagents. This procedure for the preparation of functional amines can be readily scaled up to 10 mmol scale.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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