Domino Reactions

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Zinc Bromide Promoted Coupling of Isonitriles with Carboxylic Acids To Form 2,4,5-Trisubstituted Oxazoles**

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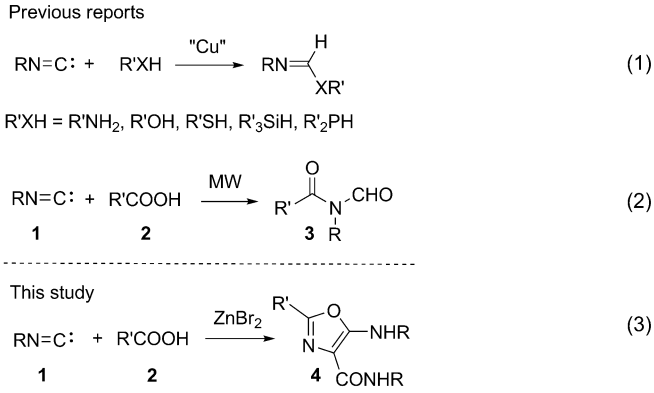
Dedicated to Professor Pierre Vogel on the occasion of his 70th birthday

The carbene-like reactivity of the divalent carbon atom of isonitriles makes these compounds ideal starting materials for the development of multicomponent reactions,[1] insertion reactions,[2] and oligo-/polymerization processes.[3] Saegusa, Ito, and co-workers pioneered the field of transition-metal-catalyzed reactions of isonitriles and demonstrated that a copper salt is able to catalyze the insertion of isonitriles into amines, alcohols, thiols, silanes, and phosphines [Eq. (1), Scheme 1].[4] Formally, these reactions correspond to the α-addition of the heteroatom–hydrogen bond to the carbon atom of the isonitrile functional group. In 2008, Danishefsky and co-workers reported that in the absence of an external reagent (catalyst), the reaction of an isonitrile **1** with a carboxylic acid **2** under microwave irradiation (MW) afforded an *N*-formylamide **3**[5] through a sequence involving α-addition followed by a 1,3-acyl shift [Eq. (2), Scheme 1].[6,7]



Scheme 1. Insertion reactions of isonitriles.

The divalent carbon atom of isonitriles has pronounced nucleophilicity and readily undergoes nucleophilic addition to electrophiles.[8,9] On the contrary, reactions initiated by its electrophilicity are rare.[10,11] As a continuation of our studies on the development of isonitrile-based novel transformations,[12] we became interested in Lewis acid mediated reactions between isonitriles and nucleophiles.[13] We report herein that in the presence of $ZnBr_2$, the reaction between isonitriles **1** and carboxylic acids **2** deviated completely from the α-addition/1,3-acyl-shift sequence [Eq. (2)] to a complex but ordered reaction manifold that led to 2,4,5-trisubstituted oxazoles **4** in good to excellent yields [Eq. (3), Scheme 1].

We began our studies by using *tert*-butyl isocyanide (**1a**) and *p*-toluic acid (**2a**) as test substrates. The heating of an equimolar amount of **1a** and **2a** in toluene in the presence of $ZnBr_2$ (0.2 equiv) afforded *N*-(*tert*-butyl)-*N*-formyl-4-methylbenzamide (**3a**) together with a small amount of an unknown compound whose structure was determined by X-ray crystal-structure analysis to be the 5-aminooxazole **4a** (see the Supporting Information). Constitutionally, **4a** is composed of one molecule of **2a** and three molecules of **1a** with the loss of a *tert*-butyl group. Intrigued by the mechanism of this unprecedented reaction and further motivated by the importance of oxazoles in natural products and medicinal chemistry,[14] we set out to investigate this reaction in detail. To channel the reaction towards the formation of **4a**, we carried out a systematic survey of the reaction conditions by varying the Lewis acid (LA), the solvent, the temperature, and the reaction time, and investigating various additives. Some representative results are summarized in Table 1. Of the Lewis acids examined [$ZnBr_2$, $Zn(OTf)_2$, $Yb(OTf)_3$, $Cu(OTf)_2$, $Ga(OTf)_3$], only $Yb(OTf)_3$ displayed discernable catalytic activity (Table 1, entry 7). However, the yield of **4a** was low, and the reaction was accompanied by the formation of the *N*-formylamide **3a**. Furthermore, the yield of **4a** decreased with an increased loading of $Yb(OTf)_3$, probably as a result of concurrent decomposition of the product (Table 1, entry 8). Although $ZnBr_2$ was incapable of catalyzing the desired reaction, the yield of **4a** increased significantly when a stoichiometric amount of this Lewis acid was used (Table 1, entry 10) and reached 81% with 1.5 equivalents of $ZnBr_2$ (entry 11). The addition of an extra proton source (*t*BuOH) had no impact on the reaction efficiency (Table 1, entry 12),[15] whereas the addition of molecular sieves led to a lower yield of **4a** (entry 13). Overall, the optimum conditions found consisted of heating a solution of **1a** (1.7 equiv) and **2a**

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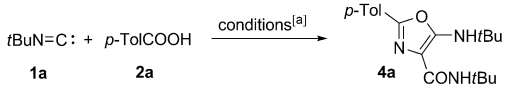
Table 1: Lewis acid catalyzed reaction between *tert*-butyl isocyanide (**1a**) and *p*-toluic acid (**2a**).



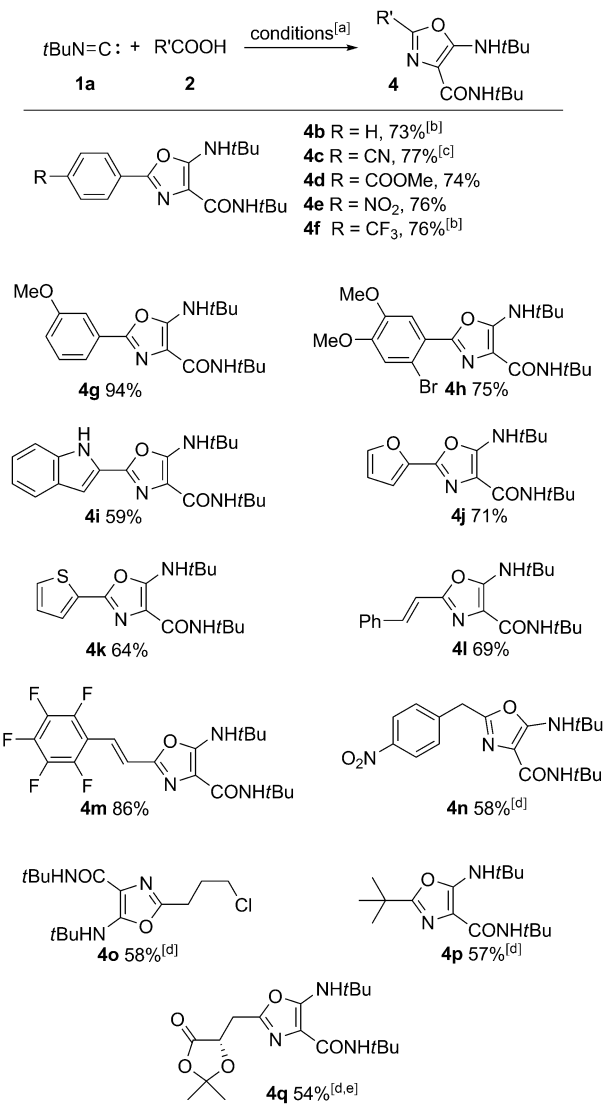
1a **2a** **4a**

Entry	LA (mol%)	Solvent	*T* [°C]	Additive	**4a** [%]
1	$ZnBr_2$ (20)	toluene	100	–	trace[b]
2	$ZnBr_2$ (20)	toluene	100	Et_3N	trace[b]
3	$Zn(OTf)_2$ (20)	toluene	100	–	trace[b]
4	$Yb(OTf)_3$ (20)	toluene	100	–	10
5	$ZnBr_2$ (10)	CH_2Cl_2	RT	–	trace
6	$Cu(OTf)_2$ (10)	CH_2Cl_2	RT	–	< 5[c]
7	$Yb(OTf)_3$ (10)	CH_2Cl_2	RT	–	34[d]
8	$Yb(OTf)_3$ (50)	CH_2Cl_2	RT		17[d]
9	$Ga(OTf)_3$ (10)	CH_2Cl_2	RT	–	trace
10	$ZnBr_2$ (100)	toluene	100	–	65[d]
11	$ZnBr_2$ (150)	toluene	100	–	81[d]
12	$ZnBr_2$ (150)	toluene	100	*t*BuOH	80
13	$ZnBr_2$ (150)	toluene	100	4 Å MS	73[d]

[a] Reaction conditions: **1a** (1.7 equiv), **2a** (1.0 equiv), solvent (solution concentration: 0.1 M), argon atmosphere, 30 min. [b] The *N*-formylamide **3a** was the major product. [c] The yield was determined by NMR spectroscopy. [d] Yield of the isolated product. Tf = trifluoromethanesulfonyl.

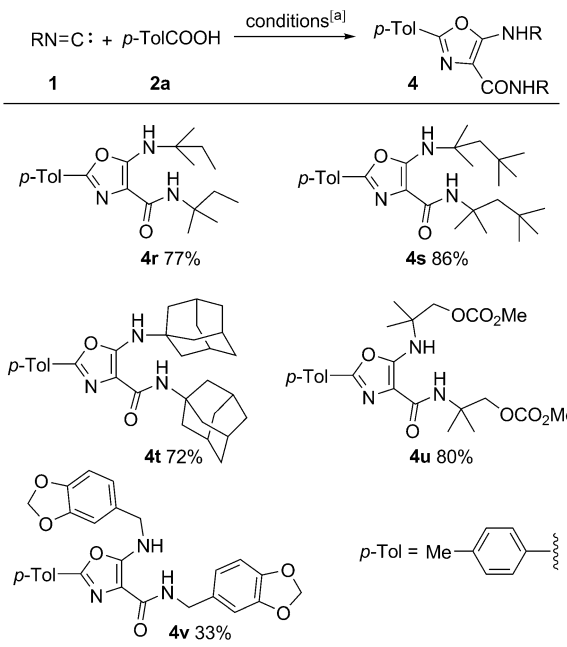
(1.0 equiv, 0.1 M) in toluene in the presence of $ZnBr_2$ (1.5 equiv relative to **2a**) for 30 min. Under these conditions, compound **4a** was isolated in 81% yield.

The scope of the reaction was examined under these optimum conditions (Scheme 2). Aromatic acids regardless of their electronic nature participated in the reaction efficiently to afford biaryls **4a**–**h** in good to excellent yields. Cyano (in **4c**), ester (in **4d**), nitro (in **4e**), trifluoromethyl (in **4f**), and bromine functional groups (in **4h**) at positions *ortho*, *meta*, and *para* to the carboxylic acid functionality were tolerated well. The heteroaromatic compounds 1*H*-indole-2-carboxylic acid, furan-2-carboxylic acid, and thiophene-2-carboxylic acid underwent co-trimerization with **1a** to furnish the bis(heteroarenes) **4i**–**k** in good yields. Our method thus provides a useful alternative for the construction of biaryl compounds from aryl carboxylic acids.[16] Cinnamic acids were also accepted as substrates to afford the 2-vinyl-substituted oxazoles **4l** and **4m**. Finally, aliphatic acids, including benzylic, functionalized, and sterically demanding substrates, reacted equally well with **1a** to furnish the 2-alkyl-substituted oxazoles **4n**–**q**. The oxazoles derived from aliphatic acids (**4n**–**q**) are acid-labile and should be purified on an alumina support. Besides *t*BuNC, other tertiary alkyl isocyanides, including functionalized substrates, participated in this reaction to afford the corresponding oxazoles in good to excellent yields (Scheme 3). Use of the primary isocyanide 5-(isocyanomethyl)benzo[*d*][1,3]dioxole led to the corresponding oxazole **4v** in moderate yield (33%; Scheme 3). However, reactions involving other primary and secondary alkyl isocyanides ($PhCH_2NC$, *p*-$MeOC_6H_4CH_2NC$, *i*PrNC, *c*-$C_6H_{11}NC$) and phenyl isocyanide (PhNC) afforded a complex reaction mixture, whereas 2,2-bis(4′-methoxyphenyl)methylisocyanide underwent clean isomerization to furnish 2,2-bis(4′-methoxyphenyl)acetonitrile.

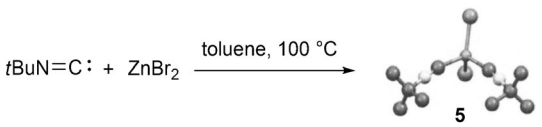


Scheme 2. Scope of the reaction with respect to the carboxylic acid substrate. [a] Reaction conditions: **1a** (1.7 equiv), **2** (1.0 equiv, 0.1 M), $ZnBr_2$ (1.5 equiv), toluene, 60°C, 30 min. The products were purified on silica gel unless otherwise specified. [b] The reaction was performed at 100°C. [c] The reaction was finished in 5 min. [d] The product was purified on an alumina support (Brockmann type IV). [e] The *ee* value was not determined owing to the instability of **4q** under HPLC conditions.

The reaction of authentic *N*-(*tert*-butyl)-*N*-formyl-4-methylbenzamide (**3a**) with **1a** under standard conditions failed to produce even a trace amount of oxazole **4a**, thus indicating that **3a** is not an intermediate in the formation of **4a**. To gain insight into the reaction mechanism, we synthesized the complex $(tBuNC)_2ZnBr_2$ (**5**) by heating a solution of *t*BuNC (3.0 equiv) and $ZnBr_2$ in toluene at 100°C. This complex was fully characterized for the first time, including by X-ray crystal-structure analysis (Scheme 4).[17] It is monomeric with a distorted tetrahedral coordination geometry around the zinc atom. The isonitrile–zinc moiety is linear (N-C-Zn 170.11°, C-N-C 174.87°), which indicates that both the carbon atom and the nitrogen center are sp-hybridized. The



Scheme 3. Scope of the reaction with respect to the isocyanide substrate. [a] Reaction conditions: **1** (1.7 equiv), **2a** (1.0 equiv, 0.1 M), $ZnBr_2$ (1.5 equiv), toluene, 100 °C, 2 h.

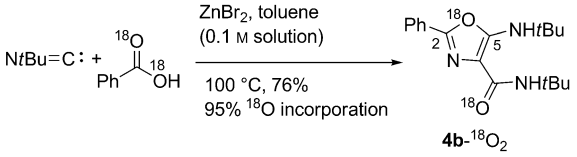


Scheme 4. Synthesis and X-ray crystal structure of $(t\text{BuNC})_2ZnBr_2$ (**5**).

N≡C bond length of the coordinated isonitrile ligand is 1.136 Å, which is shorter than that of the uncoordinated isonitrile,[18] whereas the Zn–C bond length is 2.072 Å and thus longer than that in the dimethyl terpyridine zinc complex (2.028 Å).[19] The shortened N≡C bond length is also evident from the increased N≡C vibrational frequency of this bond [$\tilde{\nu}(\text{N}\equiv\text{C})_{\text{coord}} = 2230\ \text{cm}^{-1}$, $\tilde{\nu}(\text{N}\equiv\text{C})_{\text{free}} = 2134\ \text{cm}^{-1}$: $\Delta\tilde{\nu} = 96\ \text{cm}^{-1}$]. These spectroscopic data indicate that, unlike most other RNC–transition-metal complexes,[13] **5** is a σ complex with very weak back-donation from the metal, and that the ligated isonitrile is activated towards nucleophilic addition.

Mixing of equimolar amounts of 1,1,3,3-tetramethylbutyl isocyanide (the Walborsky reagent) and **5** provided a mixture of several zinc bromide complexes, as evidenced by ^{13}C NMR spectra. Mixing of the Walborsky reagent with **5** and **2a** afforded a complex mixture, from which three different aminooxazoles corresponding to the statistical distribution of the four possible constitutional isomers (two of which have the same molecular weight) were detected by LC/MS analysis (see the Supporting information).[15] On the other hand, heating of a solution of *p*-toluic acid (**2a**) with $(t\text{BuNC})_2ZnBr_2$ (**5**) in toluene at 60 °C for 2 h afforded the oxazole **4a** in 56% yield. The results of all these control experiments indicate that complex formation between the isocyanide and zinc bromide is a dynamic process, and that the reaction most probably takes place in the ligand sphere of the complex.

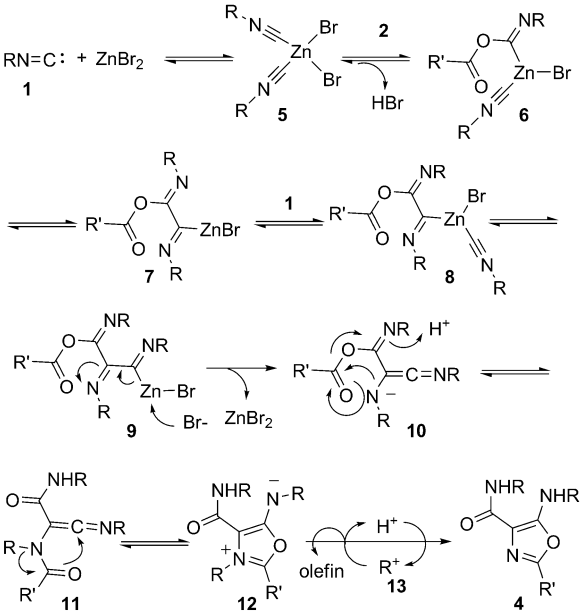
The formation of an oxazole **4** from an isonitrile **1** and a carboxylic acid **2** implies a complex reaction manifold. To determine the source of the two oxygen atoms in **4**, we carried out an isotopic-labeling experiment. The treatment of $PhC^{18}O^{18}OH$[20] with *tert*-butyl isocyanide (**1a**) under standard conditions afforded a double-^{18}O-labeled oxazole **4b**-$^{18}O_2$, as evidenced by mass spectrometry (Scheme 5). The upfield shift



Scheme 5. Isotopic-labeling experiment.

of the ^{13}C NMR signal of the amide carbonyl group in **4b**-$^{18}O_2$ relative to that for **4b** ($\delta_{C=^{18}O} - \delta_{C=^{16}O} = -2.9$ Hz) is in agreement with previous reports.[21] The same shielding effect of ^{18}O was observed for carbon atoms C2 and C5 in accordance with the oxazole structure of **4b**-$^{18}O_2$ ($\delta_{C2-^{18}O} - \delta_{C2-^{16}O} = -2.9$ Hz, $\delta_{C5-^{18}O} - \delta_{C5-^{16}O} = -2.5$ Hz). These results indicate clearly that both oxygen atoms in oxazole **4** come from the carboxylic acid, and that adventitious water or dioxygen are not involved in the formation of **4**.

On the basis of the aforementioned structural analysis and the results of control experiments, a possible reaction pathway leading to **4** is depicted in Scheme 6. Nucleophilic addition of the carboxylic acid to the ligated isonitrile affords **6**, which upon migratory insertion provides intermediate **7**.[22] Coordination of another molecule of the isonitrile to **7**,[23]



Scheme 6. Possible reaction mechanism.

followed by a second migratory insertion, furnishes **9** via **8**. The elimination of $ZnBr_2$ delivers ketenimine **10**, which is predisposed for the subsequent Mumm rearrangement to afford **11**. Intramolecular nucleophilic addition of the amide oxygen atom to the ketenimine affords **12**, which upon dealkylation provides the observed 2,4,5-trisubstituted oxazole **4**. The reaction should be catalytic in $ZnBr_2$ according to the proposed reaction pathway. The need for a stoichiometric amount of $ZnBr_2$ is probably due to product inhibition, as oxazole **4** might chelate strongly to the Zn^{2+} ion.[24] We stress that cationic isomerization/oligomerization is completely suppressed under our reaction conditions.[25,26]

In summary, we have developed an unprecedented zinc bromide mediated co-trimerization of isonitriles with carboxylic acids as an efficient synthesis of 2,4,5-trisubstituted oxazoles.[27] A broad range of carboxylic acids, including aromatic, heteroaromatic, aliphatic, and α,β-unsaturated substrates, participated readily in this reaction. The structure of $(t\text{BuNC})_2ZnBr_2$ was fully characterized and provided useful hints regarding the reaction mechanism. Experimental results indicated that the reaction might be initiated by nucleophilic addition of the carboxylic acid to the ligated isonitrile, followed by a double-migratory-insertion/metal-salt-elimination/acyl-migration/cyclization/dealkylation sequence.

Experimental Section

Typical procedure: A suspension of a carboxylic acid (1.0 equiv, 0.1M), an isonitrile (1.7 equiv), and zinc bromide (1.5 equiv) in toluene was heated to 100°C under argon until complete consumption of the carboxylic acid was observed. A saturated aqueous K_2CO_3 solution was then added to the mixture, and the resulting solution was stirred for 30 min. The reaction mixture was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was then purified by flash chromatography to give the desired oxazole. Compound **4a** (isolated by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) as colorless crystals in 81% yield): m.p.: 81–85°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (d, $J = 8.1$ Hz, 2H), 7.22 (d, $J = 8.1$ Hz, 2H), 6.51 (s, 1H), 6.36 (s, 1H), 2.39 (s, 3H), 1.47 ppm (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.0$, 156.9, 149.6, 139.4, 129.5, 125.1, 124.6, 108.1, 52.7, 50.8, 30.0, 29.4, 21.5 ppm; IR: $\tilde{\nu} = 3413$, 3351, 2983, 2872, 1647, 1623, 1526, 1365, 1246, 1205, 1109, 1046, 874 cm^{-1}; HRMS (ESI): m/z calcd for $C_{19}H_{28}N_3O_2^+$: 330.2176 $[M+H]^+$; found: 330.2173.

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[1] *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**.

[2] For reviews, see: a) A. V. Lygin, A. de Meijere, *Angew. Chem.* **2010**, *122*, 9280–9311; *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124; b) M. Tobisu, N. Chatani, *Chem. Lett.* **2011**, *40*, 330–340; c) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257–5269.

[3] M. Suginome, Y. Ito, *Adv. Polym. Sci.* **2004**, *171*, 77–136.

[4] a) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, H. Yoshioka, *Tetrahedron Lett.* **1966**, *7*, 6121–6124; b) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, *J. Am. Chem. Soc.* **1967**, *89*, 2240–2241; c) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, *Tetrahedron Lett.* **1967**, *8*, 521–524; d) T. Saegusa, S. Kobayashi, K. Hirota, Y. Okumura, Y. Ito, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1638–1642; e) T. Saegusa, Y. Ito, S. Kobayashi, *Tetrahedron Lett.* **1968**, *9*, 935–936.

[5] a) X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448; b) X. Li, Y. Yuan, W. F. Berkowitz, L. J. Todaro, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 13222–13224; c) X. Li, Y. Yuan, C. Kan, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 13225–13227; see also: d) A. Basso, L. Banfi, A. Galatini, G. Guanti, F. Rastrelli, R. Riva, *Org. Lett.* **2009**, *11*, 4068–4071.

[6] a) G. O. Jones, X. C. Li, A. E. Hayden, K. N. Houk, S. J. Danishefsky, *Org. Lett.* **2008**, *10*, 4093–4096; b) J.-L. Hou, D. Ajami, J. Rebek, Jr., *J. Am. Chem. Soc.* **2008**, *130*, 7810–7811.

[7] R. M. Wilson, J. L. Stockdill, X. Wu, X. Li, P. A. Vadola, P. K. Park, P. Wang, S. J. Danishefsky, *Angew. Chem.* **2012**, *124*, 2888–2902; *Angew. Chem. Int. Ed.* **2012**, *51*, 2834–2848.

[8] a) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; b) N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444–8454; c) L. El Kaim, L. Grimaud, *Tetrahedron* **2009**, *65*, 2153–2171; d) L. A. Wessjohann, D. G. Rivera, O. E. Vercillo, *Chem. Rev.* **2009**, *109*, 796–814; e) L. Banfi, R. Riva, A. Basso, *Synlett* **2010**, 23–41; f) A. V. Gulevich, A. G. Zhdanko, R. V. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331.

[9] For selected examples of Lewis acid catalyzed reactions, see: a) N. Chatani, M. Oshita, M. Tobisu, Y. Ishii, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 7812–7813; b) G. Bez, C.-G. Zhao, *Org. Lett.* **2003**, *5*, 4991–4993; c) T. Godet, Y. Bonvin, G. Vincent, D. Merle, A. Thozet, M. Ciufolini, *Org. Lett.* **2004**, *6*, 3281–3284; d) S. Yoshioka, M. Oshita, M. Tobisu, N. Chatani, *Org. Lett.* **2005**, *7*, 3697–3699; e) J. D. Winkler, S. M. Asselin, *Org. Lett.* **2006**, *8*, 3975–3977; f) M. Tobisu, A. Kitajima, S. Yoshioka, I. Hyodo, M. Oshita, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 11431–11437; g) C.-F. Lei, D. X. Wang, L. Zhao, J. Zhu, M.-X. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 4708–4711; for Lewis acid catalyzed enantioselective processes, see: h) U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Dömling, *Org. Lett.* **2003**, *5*, 4021–4024; i) P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2004**, *6*, 4231–4233; j) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Eur. J. Org. Chem.* **2007**, 4076–4080; k) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Org. Lett.* **2007**, *9*, 3615–3618; l) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 394–397; *Angew. Chem. Int. Ed.* **2008**, *47*, 388–391; m) T. Yue, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 9596–9599; *Angew. Chem. Int. Ed.* **2008**, *47*, 9454–9457; n) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson, J. Zhu, *J. Org. Chem.* **2009**, *74*, 8396–8399; o) H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 8384–8385.

[10] Only strong nucleophiles, such as organolithium, organomagnesium, and organozinc reagents, can undergo nucleophilic addition to isonitriles: a) H. M. Walborsky, G. E. Niznik, *J. Am. Chem. Soc.* **1969**, *91*, 7778; b) H. M. Walborsky, W. H. Morrison III, G. E. Niznik, *J. Am. Chem. Soc.* **1970**, *92*, 6675–6676; c) M. Murakami, H. Ito, Y. Ito, *J. Org. Chem.* **1988**, *53*, 4158–4159.

[11] a) M. Tobisu, S. Yamaguchi, N. Chatani, *Org. Lett.* **2007**, *9*, 3351–3353; see also: b) M. Suginome, T. Fukuda, Y. Ito, *Org. Lett.* **1999**, *1*, 1977–1979.

[12] a) D. Bonne, M. Dehkane, J. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 6926–6927; b) J. M. Grassot, G. Masson, J. Zhu, *Angew. Chem.* **2008**, *120*, 961–964; *Angew. Chem. Int. Ed.* **2008**, *47*, 947–950. For an earlier account, see: c) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144.

[13] Nucleophilic addition to isonitriles ligated to high-valent electron-poor metal centers to give aminocarbene complexes is well-known; for a review, see: a) R. A. Michelin, A. J. L. Pombeiro, A. F. Guedes da Silva, *Coord. Chem. Rev.* **2001**, *218*, 75 – 112; for recent examples, see: b) A. S. K. Hashmi, C. Lothschütz, C. Böhling, T. Hengst, C. Hubbert, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 3001 – 3012; c) A. S. K. Hashmi, Y. Yu, F. Rominger, *Organometallics* **2012**, *31*, 895 – 904.

[14] a) P. Wipf, *Chem. Rev.* **1995**, *95*, 2115 – 2134; b) V. S. C. Yeh, *Tetrahedron* **2004**, *60*, 11995 – 12042; c) Z. Jin, *Nat. Prod. Rep.* **2011**, *28*, 1143 – 1191; d) J. Zhang, P.-Y. Coqueron, M. A. Ciufolini, *Heterocycles* **2011**, *82*, 949 – 980.

[15] We thank one of the referees for proposing this control experiment.

[16] For direct cross-coupling reactions, see: a) X. Bugaut, F. Glorius, *Angew. Chem.* **2011**, *123*, 7618 – 7620; *Angew. Chem. Int. Ed.* **2011**, *50*, 7479 – 7481; b) D. Zhao, J. You, C. Hu, *Chem. Eur. J.* **2011**, *17*, 5466 – 5492; for the direct C–H functionalization of oxazoles, see: c) C. Verrier, P. Lassalas, L. Théveau, G. Quéguiner, F. Trécourt, F. Marsais, C. Hoarau, *Beilstein J. Org. Chem.* **2011**, *7*, 1584 – 1601.

[17] $(t\text{BuNC})_2ZnBr_2$ has been reported previously without full characterization: B. L. Holman, A. G. Jones, J. Lister-James, A. Davison, M. J. Abrams, J. M. Kirshenbaum, S. S. Tumeh, R. J. English, *J. Nucl. Med.* **1984**, *25*, 1350 – 1354.

[18] The estimated N≡C bond length in MeNC is 1.167 Å: M. Kessler, H. Ring, R. Trambarulo, W. Gordy, *Phys. Rev.* **1950**, *79*, 54 – 56.

[19] T. Shalumova, J. M. Tanski, *Acta. Crystallogr. Sect. E* **2009**, *65*, m1325.

[20] $PhC^{18}O^{18}OH$ was synthesized from $PhCCl_3$ and $H_2{}^{18}O$ by slight modification of a previously reported procedure: M. Kobayashi, R. Kiritani, *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1782 – 1784.

[21] For the ^{18}O-induced shift of ^{13}C NMR signals, see: a) J. C. Vederas, *J. Am. Chem. Soc.* **1980**, *102*, 374 – 376; b) J. M. Risley, R. L. Van Etten, *J. Am. Chem. Soc.* **1980**, *102*, 4609 – 4614.

[22] The formation of *p*-toluic acid–$ZnBr_2$ with concurrent liberation of HBr was not observed in an NMR spectroscopic titration experiment (see the Supporting Information).

[23] The reaction may also start from the polycoordinated $(RNC)_n$–$ZnBr_2$ complex. Indeed, the mixing of $(t\text{BuNC})_2ZnBr_2$ (δ_{NC} = 130.7 ppm, s) with different amounts of *t*BuNC (1.0–5.0 equiv; δ_{NC} = 153.6 ppm, t, J = 4.5 Hz] in CD_2Cl_2 led rapidly to the formation of a new species (see the Supporting Information).

[24] a) R. C. Jones, M. W. Chojnacka, J. W. Quail, M. G. Gardiner, A. Decken, B. F. Yates, R. A. Gossage, *Dalton Trans.* **2011**, *40*, 1594 – 1600; b) M.-T. Chen, C.-T. Chen, *Dalton Trans.* **2011**, *40*, 12886 – 12894.

[25] T. Saegusa, N. Takaishi, Y. Ito, *J. Org. Chem.* **1969**, *34*, 4040 – 4046.

[26] For the trimerization of benzoyl isocyanide, see: a) H. Dounchis, *J. Org. Chem.* **1972**, *37*, 2583 – 2587; see also: b) H. Uno, K. Oka, H. Tani, Y. Kawada, N. Ono, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1763 – 1767.

[27] For recent examples of oxazole syntheses, see: a) N. Elders, E. Ruijter, F. J. J. de Kanter, R. V. A. Orru, *Chem. Eur. J.* **2008**, *14*, 4961 – 4973; b) J. Zhang, P.-Y. Coqueron, J.-P. Vors, M. A. Ciufolini, *Org. Lett.* **2010**, *12*, 3942 – 3945; c) J. Wu, W. Chen, M. Hu, H. Zou, Y. Yu, *Org. Lett.* **2010**, *12*, 616 – 619; d) R. Mossetti, T. Pirali, G. C. Tron, J. Zhu, *Org. Lett.* **2010**, *12*, 820 – 823; e) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956 – 963; f) I. Cano, E. Alvarez, M. C. Nicasio, P. J. Pérez, *J. Am. Chem. Soc.* **2011**, *133*, 191 – 193; g) P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem.* **2011**, *123*, 9093 – 9097; *Angew. Chem. Int. Ed.* **2011**, *50*, 8931 – 8935; h) Y. Li, X. Xu, J. Tan, C. Xia, D. Zhang, Q. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1775 – 1777; i) C. Lalli, M. J. Bouma, D. Bonne, G. Masson, J. Zhu, *Chem. Eur. J.* **2011**, *17*, 880 – 889; j) T. Lechel, M. Gerhard, D. Trawny, B. Brusilowskij, L. Schefzig, R. Zimmer, D. Lentz, C. A. Schalley, H.-U. Reissig, *Chem. Eur. J.* **2011**, *17*, 7480 – 7491; k) S. V. Kumar, B. Saraiah, N. C. Misra, H. Ila, *J. Org. Chem.* **2012**, *77*, 10752 – 10763; l) C. L. Zhong, B. Y. Tang, P. Yin, Y. Chen, L. He, *J. Org. Chem.* **2012**, *77*, 4271 – 4277; m) L. El Kaim, L. Grimaud, P. Patil, *Synlett* **2012**, *23*, 1361 – 1363; n) Y. Luo, K. Ji, Y. Li, L. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 17412 – 17415; o) X. Xu, P. Y. Zavalij, W. Hu, M. P. Doyle, *Chem. Commun.* **2012**, *48*, 11522 – 11524; p) A. Y. Shaw, Z. Xu, C. Hulme, *Tetrahedron Lett.* **2012**, *53*, 1998 – 2000; q) Z. Xu, C. Zhang, N. Jiao, *Angew. Chem.* **2012**, *124*, 11529 – 11532; *Angew. Chem. Int. Ed.* **2012**, *51*, 11367 – 11370; r) X. Li, L. Huang, H. Chen, W. Wu, H. Huang, H. Jiang, *Chem. Sci.* **2012**, *3*, 3463 – 3467; s) H. V. Wachenfeldt, P. Röse, F. Paulsen, N. Loganathan, D. Strand, *Chem. Eur. J.* **2013**, *19*, 7982 – 7988.

