Dipolar Cycloadditions

International Edition: DOI: 10.1002/anie.201600257
German Edition: DOI: 10.1002/ange.201600257

Cross-Cycloaddition of Two Different Isocyanides: Chemoselective Heterodimerization and [3+2]-Cyclization of 1,4-Diazabutatriene

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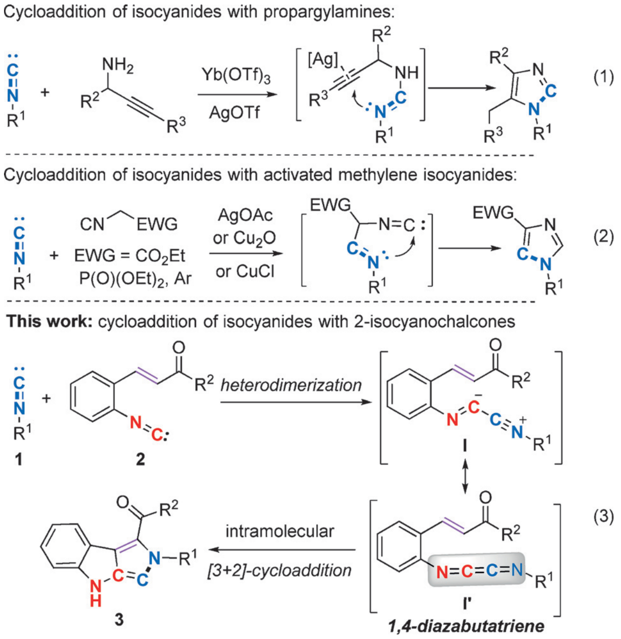
Abstract: *A new cross-cycloaddition reaction between a wide range of isocyanides and 2-isocyanochalcones (or analogues) was developed for the expeditious synthesis of pyrrolo[3,4-b]indoles under thermal conditions. On the basis of the experimental results and DFT calculations, a mechanism for this domino reaction is proposed involving chemoselective heterodimerization of two different isocyanides to form 1,4-diazabutatriene intermediates, followed by an intramolecular [3+2]-cycloaddition and 1,3-proton shift.*

Isocyanides are versatile building blocks in organic synthesis because of their unique modes of reaction.[1] Accordingly, ioscyanides are widely employed in valuable reactions that require α-addition, α-acidity, and a readiness to react with radicals. These include, Passerini[2] and Ugi reactions,[3] transition-metal catalyzed isocyanide insertion,[4] [3+2]-cycloaddition of activated methylene isocyanides with polar multiple bonds,[5] and radical insertions.[6] Recently, a new isocyano group reactivity profile was realized by Zhu and co-workers where the isocyano functional group formally acts as a polarized triple bond, allowing synthesis of imidazoles (Scheme 1, Eq. (1)).[7] This type of polarized reactivity is also exhibited in the cross-cycloaddition of isocyanides with activated methylene isocyanides (Scheme 1, Eq. (2)).[8] In spite of these intensive research efforts, exploiting the new reactivity profile of the isocyano functional group remains highly desirable.

In 1977, Lange and Höfle proposed a transient 1,4-diazabutatriene intermediate after C–C homodimerization of two imidoyl isocyanides and formation of 4,4′-bis-(quinazolines).[9] Subsequently, only a few examples have dealt with this highly unstable intermediate. In 1999, Beckert provided evidence for the existence of 1,4-diazabutatriene by reduction of bis-imidoyl chlorides of oxalic acid.[10] Subsequently, Cheng and co-workers reported the homodimerization of 2-pyridylisonitriles.[11] To date, the reactivity mode of dimerization has been restricted to the homodimerization of isocyanides.[9,11] Heterodimerization of two different isocyanide moieties to generate a nonsymmetrical 1,4-diazabutatriene has not yet been established.[12] As a continuation of our studies on isocyanide chemistry,[13] herein, we report a new and general cross-cycloaddition based on the heterodimerization between isocyanides **1** and 2-isocyanochalcones (and analogues thereof) **2** (Scheme 1, Eq. (3)). In this reaction, the highly reactive 1,4-diazabutatriene tautomers **I** and **I′** are 1,3-dipole equivalents, which allow the intramolecular [3+2]-cycloaddition to furnish pyrrolo[3,4-b]indoles[11] under relatively mild thermal conditions.



Scheme 1. New reactivity profile of the isocyano functional group.

Pyrrolo[3,4-*b*]indoles are valuable fused heterocycles with broad synthetic applications.[14] Additionally, they are stable analogues of indole-2,3-quinodimethanes used for preparation of carbazoles, carbolines, and related heterocyclic systems, through cycloaddition reactions.[15,16] Moreover, the pyrrolo[3,4-*b*]indole derivatives show a broad spectrum of pharmacological activity.[13] Although many methods for the construction of pyrrolo[3,4-*b*]indoles have been developed, a preformed indole precursor is generally required.[14,17] Our method provides an alternative approach, involving formation of two pyrrole rings from chalcone derivatives in a tandem process (Scheme 1, Eq. (3)).

Herein, the reaction of ethyl 4-isocyanobenzoate **1a** with 2-isocyanochalcone **2a** was employed as a model to optimize the reaction conditions (Table 1). When a mixture of **1a**

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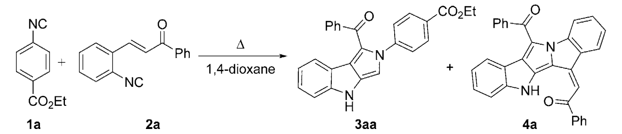
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201600257.

Table 1: Optimization of reaction conditions.[a]



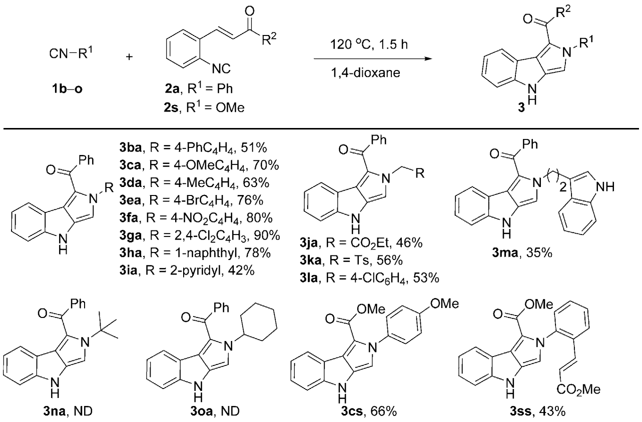
Entry	*T* [°C]	Conc. [M]	Yield [%][b] of **3aa**	Yield [%][b] of **4a**
1	120	0.1	76	20
2	120	0.2	81	14
3	120	0.05	61	28
4	100	0.2	74	17
5	140	0.2	80	16
6[c]	120	0.2	83	13
7[d]	120	0.2	64	22

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), air atmosphere, 120 °C, in a sealed tube for 1.5 h. [b] Yield of isolated products. [c] **1a** (3.0 equiv) was used. [d] **1a** (1.0 equiv) was used.

(0.4 mmol) and **2a** (0.2 mmol) was heated at 120 °C in 1,4-dioxane (2 mL, $c = 0.1$ M) for 1.5 h, the tricyclic product pyrrolo[3,4-*b*]indole **3aa** was obtained in 76 % yield, along with pyrrolo[1,2-*a*:3,4-*b*′]diindole **4a** in 20 % yield (Table 1, entry 1). Selected solvents, such as ethanol, acetonitrile, *N*,*N*-dimethylformamide (DMF), 1,2-dichloroethane, and *tert*-butanol, were also examined but gave **3aa** in lower yields (Supporting Information, Table S1). When the reaction was conducted at a higher concentration (0.2 M), the yield of **3aa** increased up to 81 % (Table 1, entry 2 and entry 6 (with 3.0 equiv of **1a**)). In comparison, lower concentration led to a decreased yield of **3aa** (61 %; Table 1, entry 3 and entry 7 (with 1.0 equiv of **1a**)). When the reaction was performed at 100 °C, **3aa** was produced in 74 % yield (Table 1, entry 4).

With the optimal conditions in hand (Table 1, entry 2), the scope of viable isocyanide substrates **1** was examined; the results are summarized in Table 2. In general, the reaction tolerated a wide range of substrates **1**, producing a series of polysubstituted pyrrolo[3,4-*b*]indoles (**3ba–ma**, **3cs**, **3ss**) in good to high yields within 1.5 h by reactions of isocyanides **1** with 2-isocynochalcone **2a** and its analogue **2s**. Aryl isocyanides **1** with *p*-phenyl (**1b**), electron-donating (**1c** and **1d**) or withdrawing groups (**1e–g**), α-naphthyl isocyanide (**1h**), 2-pyridyl isocyanide (**1i**), isocyanoacetate (**1j**), TosMIC (**1k**), 4-chlorobenzyl isocyanide (**1l**), and 3-(2-isocyanoethyl)-1*H*-indole (**1m**) were effective isocyanide components. In cases involving reaction of *tert*-butyl isocyanide **1n** and cyclohexyl isocyanide **1o** with 2-isocyanochalcone **2a**, the corresponding products **3na** and **3oa** could not be detected, possibly because of the steric disruption imposed by *tert*-butyl and cyclohexyl groups during reactivity. Additionally, when 2-isocyanocinnamate **2s** was treated with 4-methoxyphenyl isocyanide **1c**, the desired pyrrolo[3,4-*b*]indole **3cs** was obtained in 66 % yield (Table 2). In contrast, in the absence of **1c**, pyrrolo[3,4-*b*]indole **3ss**[18] was produced in 43 % yield after homodimerization of **2s** (Table 2).

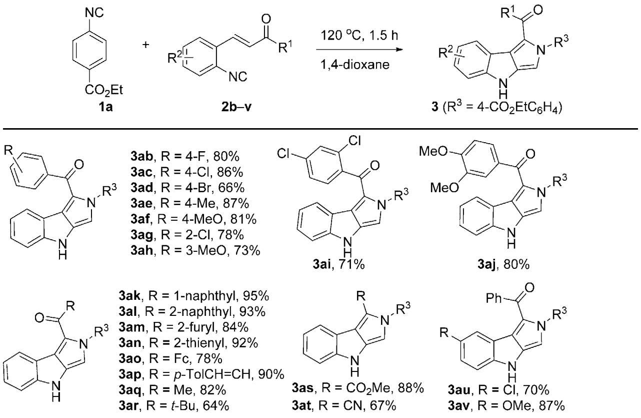
Table 2: Scope of isocyanides **1**.[a,b]



[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), in dry 1,4-dioxane (1 mL), air atmosphere, at 120 °C, in a sealed tube. [b] Yield of isolated products.

Subsequently, the scope of the reaction was evaluated with respect to 2-isocyanochalcones and analogues **2**; results are summarized in Table 3. The reaction tolerates a wide range of isocyanides **2** bearing various R^1 groups, such as *para*- (**3ab–af**), *ortho*- (**3ag**), or *meta*-substituted aryl (**3ah**), disubstituted aryl (**3ai** and **3aj**), α- or β-naphthyl (**3ak** and **3al**), hetereoaryl (**3am** and **3an**), ferrocenyl (Fc, **3ao**), *p*-tolyl vinyl (**3ap**), alkyl (**3aq** and **3ar**), and alkyloxy groups (**3as**).

Table 3: Scope of isocyanides **2**.[a,b]



[a] Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), in dry 1,4-dioxane (1 mL), air atmosphere, at 120 °C, in a sealed tube. [b] Yield of isolated products.

Besides the carbonyl- and alkoxycarbonyl-substituted substrates **2**, cyano-substituted isocyanide **2t** was also well-tolerated and 1-cyanopyrrolo[3,4-*b*]indole **3at** was obtained in high yield. Additionally, the trisubstituted pyrrolo[3,4-*b*]indoles **3au** and **3av** were produced in high yields from the corresponding substrates **2**, bearing either electron-donating or electron-withdrawing R^2 groups.

Control experiments were performed so as to shed light on the reaction mechanism taking place. When a reaction mixture containing isocyanide **1a** with 2-isocyanochalcone **2a** was subjected to Fukuyama's conditions (nBu$_3$SnH/AIBN),[19] a complex mixture was obtained containing trace amounts of the desired product **3aa** (Supporting Information, Scheme S2, Eq. (1)). Additionally, the desired pyrrolo[3,4-*b*]indole **3aw** was not observed upon reaction of **1a** with isocyanide **2w**

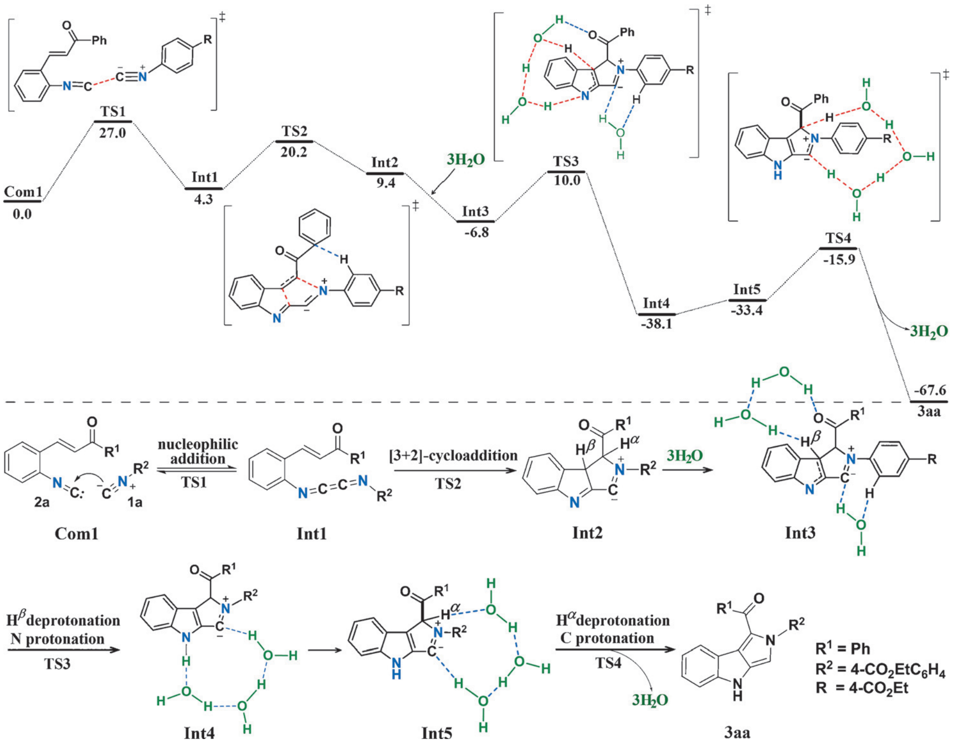


Figure 1. DFT computed energy surface for the cross-cycloaddition of isocyanides **1a** and **2a**. Relative free energies are given in kcal mol^{-1}.

under our standard conditions (Supporting Information, Scheme S2, Eq. (2)); in Fukuyama's indole synthesis, the corresponding product was produced in 83% yield upon reaction of **2w** via a radical pathway.[19b] These results demonstrate that the mechanism of cross-cycloaddition of two isocyanides proceeds by a non-radical pathway (Table 2 and Table 3).

To gain further insight into the mechanism involved, density functional theory calculations were conducted at a B3LYP-D2/6-31+G** level and interrogated computationally. A heterodimerization and [3+2]-cycloaddition cascade was proposed in which 1,4-diazabutatriene serves as a reactive intermediate, in close comparison with the homodimerization of isocyanides.[9,11] As shown in Figure 1, the free-energy profile indicates that the reaction initiating from complex **Com1** (**1a** and **2a**), proceeds through nucleophilic attack of the isocyanide carbon of **1a** on the isocyanide carbon of **2a**, to form 1,4-diazabutatriene **Int1** via **TS1** (TS = transition state) with an activation barrier of 27.0 kcal mol^{-1}. Subsequent intramolecular [3+2]-cyclization takes place from **Int1** by way of **TS2** to form adduct **Int2** with an activation barrier of 15.9 kcal mol^{-1}. Subsequently, three-water molecules[20,21] associate with **Int2** to form **Int3**, which undergoes successive 1,3-proton shifts via transition states **TS3** and **TS4**, with activation barriers of 16.8 and 17.5 kcal mol^{-1}, respectively. Finally, the water-cluster is released from **Int5** to afford product **3aa**. Although **Int4** coverts to **Int5** endergonically with a relative free energy of 4.7 kcal mol^{-1} during the conversion of **Int3** into product **3aa**, **Int5** is favored for the subsequent H$^{\alpha}$ deprotonation and imidoyl anion protonation process. Thus, hydrogen bonding interactions are likely to be the intrinsic driving force that promotes H-shifts via **Int3**, **Int4**, and **Int5**, even in the presence of trace amounts of water.[20,21]

In summary, we have developed a new and practical tandem cross-cycloaddition between two isocyanides under thermal conditions. In this reaction, both the heterodimerization of two different isocyanides and the [3+2]-cycloaddition of the highly reactive 1,4-diazabutatriene intermediate with polarized C=C double bonds, are unprecedented. The new domino reaction was used to efficiently construct highly functionalized pyrrolo[3,4-*b*]indoles from a series of isocyanides and isocyanochalcones (and analogues) by formation of three new bonds and two pyrrole rings. Further studies on this new reactivity mode are in progress.

Acknowledgements

Financial support provided by the NNSFC (21172030 and 21572031) is gratefully acknowledged.

Keywords: 1,4-diazabutatriene · cross-cycloaddition · heterodimerization · isocyanides · pyrrolo[3,4-*b*]indoles

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 7077–7080
Angew. Chem. **2016**, *128*, 7193–7196

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[1] For recent reviews, see: a) *Isocyanide Chemistry Applications in Synthesis and Materials Science* (Ed.: V. Nenajdenko), Wiley-VCH, Weinheim, **2012**; b) A. V. Lygin, A. D. Meijere, *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124; *Angew. Chem.* **2010**, *122*, 9280–9311.

[2] L. Banfi, R. Riva in *Organic Reactions, Vol. 65* (Ed.: A. B. Charette), Wiley, New York, **2005**, pp. 1–140.

[3] A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.

[4] For reviews on transition metal-catalyzed processes, see: a) V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin, V. Y. Kukushkin, *Chem. Rev.* **2015**, *115*, 2698–2779; b) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2013**, *52*, 7084–7097; *Angew. Chem.* **2013**, *125*, 7222–7236; c) G. Y. P. Qiu, Q. P. Ding, J. Wu, *Chem. Soc. Rev.* **2013**, *42*, 5257–5269.

[5] a) D. V. Leusen, A. M. V. Leusen, *Org. React.* **2001**, *57*, 417–666; b) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331.

[6] For a review, see: B. Zhang, S. Armido, *Chem. Soc. Rev.* **2015**, *44*, 3505–3521.

[7] S. Tong, Q. Wang, M. X. Wang, J. P. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 1293–1297; *Angew. Chem.* **2015**, *127*, 1309–1313.

[8] a) C. Kanazawa, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 10662 – 10663; b) B. Pooi, J. Lee, K. Choi, H. Hirao, S. H. Hong, *J. Org. Chem.* **2014**, *79*, 9231 – 9245.

[9] G. Höfle, B. Lange, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 727 – 728; *Angew. Chem.* **1977**, *89*, 742 – 743.

[10] M. Wenzel, F. Lehmann, R. Beckert, W. Günther, H. Görls, *Monatsh. Chem.* **1999**, *130*, 1373 – 1382.

[11] N. Shao, G.-X. Pang, X.-R. Wang, R.-J. Wu, Y. Cheng, *Tetrahedron* **2010**, *66*, 7302 – 7308.

[12] a) For a review on heavy allenes and cumulenes, see: J. Escudié, H. Ranaivonjatovo, L. Rigon, *Chem. Rev.* **2000**, *100*, 3639 – 3696; b) E. Iravani, B. Neumüller, *Organometallics* **2005**, *24*, 842 – 847.

[13] a) Y. F. Li, X. X. Xu, J. Tan, C. Y. Xia, D. Zhang, Q. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1775 – 1777; b) X. X. Xu, L. J. Zhang, X. Q. Liu, L. Pan, Q. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 9271 – 9274; *Angew. Chem.* **2013**, *125*, 9441 – 9444; c) J. Tan, X. X. Xu, L. J. Zhang, Y. F. Li, Q. Liu, *Angew. Chem. Int. Ed.* **2009**, *48*, 2868 – 2872; *Angew. Chem.* **2009**, *121*, 2912 – 2916; d) J. Du, X. X. Xu, Y. F. Li, L. Pan, Q. Liu, *Org. Lett.* **2014**, *16*, 4004 – 4007.

[14] For a review of pyrrolo[3,4-*b*]indoles, see: C.-K. Sha, *Adv. Nitrogen Heterocycl.* **1996**, *2*, 147 – 178.

[15] U. Pindur, H. Erfanian-Abdoust, *Chem. Rev.* **1989**, *89*, 1681 – 1689.

[16] A. V. Ivachtchenko, E. B. Frolov, O. D. Mitkin, S. E. Tkachenko, A. V. Khvat, *Chem. Heterocycl. Compd.* **2010**, *46*, 170 – 178.

[17] a) For a review, see: G. W. Gribble, *Pure. Appl. Chem.* **2003**, *75*, 1417 – 1432; b) E. T. Pelkey, J. Jiang, G. W. Gribble, *J. Indian Chem. Soc.* **2013**, *90*, 1525 – 1536; c) D. Solé, M.-L. Bennasar, I. Jiménez, *Org. Biomol. Chem.* **2011**, *9*, 4535 – 4544; d) S. Roy, T. L. S. Kishbaugh, J. P. Jasinski, G. W. Gribble, *Tetrahedron Lett.* **2007**, *48*, 1313 – 1316; e) G. W. Gribble, E. T. Pelkey, W. M. Simon, H. A. Trujillo, *Tetrahedron* **2000**, *56*, 10133 – 10140.

[18] CCDC 1406596(**3ss**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19] For a review, see: a) H. Tokuyama, T. Fukuyama, *Chem. Rec.* **2002**, *2*, 37 – 45; b) T. Fukuyama, X. Chen, G. Peng, *J. Am. Chem. Soc.* **1994**, *116*, 3127 – 3128; c) Y. Kobayashi, T. Fukuyama, *J. Heterocycl. Chem.* **1998**, *35*, 1043 – 1055; d) H. Tokuyama, Y. Kaburagi, X. Chen, T. Fukuyama, *Synthesis* **2000**, 429 – 434.

[20] For promotion of H-shift by trace amounts of water, see: a) Y. Z. Xia, Y. Liang, Y. Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y. H. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3470 – 3471; b) F. Q. Shi, X. Li, Y. Z. Xia, L. M. Zhang, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 15503 – 15512; c) H. Y. Yuan, Y. Zheng, Z. X. Fang, X. H. Bi, J. P. Zhang, *Green Chem.* **2014**, *16*, 2653 – 2663.

[21] a) G. Kovács, G. Schubert, F. Joó, I. Pápai, *Organometallics* **2005**, *24*, 3059 – 3065; b) H. S. Chu, Z. Xu, S. M. Ng, C. P. Lau, Z. Lin, *Eur. J. Inorg. Chem.* **2000**, 993 – 1000.

Received: January 9, 2016
Revised: March 3, 2016