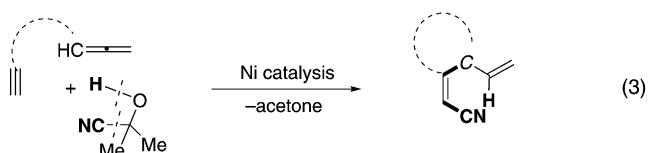
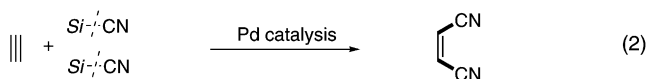
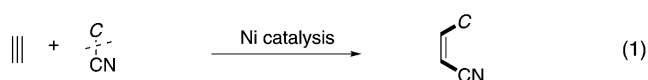


Hydrocyanative Cyclization and Three-Component Cross-Coupling Reaction between Allenes and Alkynes under Nickel Catalysis**

Shigeru Arai,* Yuka Amako, Xiaofei Yang, and Atsushi Nishida

Since a cyano group is equivalent to a carbonyl group and related functionalities, its introduction into organic molecules, particularly by a catalytic protocol, is an important topic in synthetic chemistry. Recent research in this area has focused on the carbocyanation of simple, non-activated C–C multiple bonds under nickel catalysis (Scheme 1),^[1] including direct C–



Scheme 1. Nickel- and palladium-catalyzed carbocyanation.

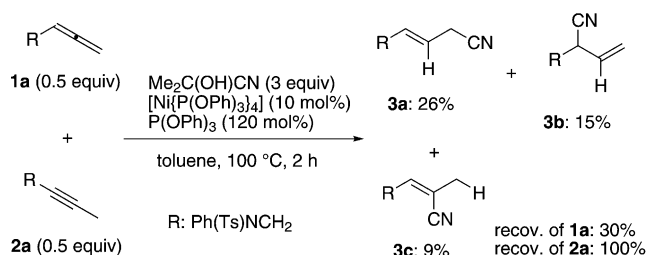
CN bond cleavage and transfer of the resulting two moieties to each alkynyl carbon atom by cooperative catalysis with Ni⁰ and Lewis acid catalysis [Eq. (1)]. We also succeeded in an alternative cyanation reaction that does not involve C–CN bond cleavage [Eq. (2)]. This method involves nucleophilic cyanation (cyanopalladation)^[2] and enables the connection of three components by the action of a single catalyst. These transformations have been applied to novel cyclization^[2a,c] and cycloaddition^[2d,e] reactions.

To establish a more general and facile protocol for carbocyanation and carbocyanative cyclization through the addition of a cyano group to C–C multiple bonds, we focused on the reactivity of allenes, which readily generate a carbanion equivalent under transition-metal catalysis. Herein, we report an alternative carbocyanation strategy that involves the

hydrometalation of allenes followed by the carbocyanation of alkynes in a regio- and stereoselective manner [Eq. (3)].

The nickel-catalyzed hydrocyanation of various C–C multiple bonds, both alkenes^[3] and alkynes,^[4] is one of the most fundamental cyanation procedures. However, further synthetic applications, such as ring formation and/or multi-component coupling reactions, have not been well investigated. To the best of our knowledge, only one example of the nickel-catalyzed hydrocyanation of allenes has been reported.^[5] Therefore, we initially evaluated the reactivities of allenes and alkynes.

When both **1a** and **2a** were treated with acetone cyanohydrin^[6] (AC) under nickel catalysis,^[4] three products **3a–c** were obtained, all of which were derived from **1a**, and **2a** was recovered quantitatively (Scheme 2). This result



Scheme 2. Competitive study with **1a** and **2a**. Ts = *p*-toluenesulfonyl.

suggests that the allene functionality is easily discriminated from an alkyne under hydronicellation conditions. Therefore, we next investigated sequential C–C bond-forming reactions of allenynes substrates (Scheme 3).

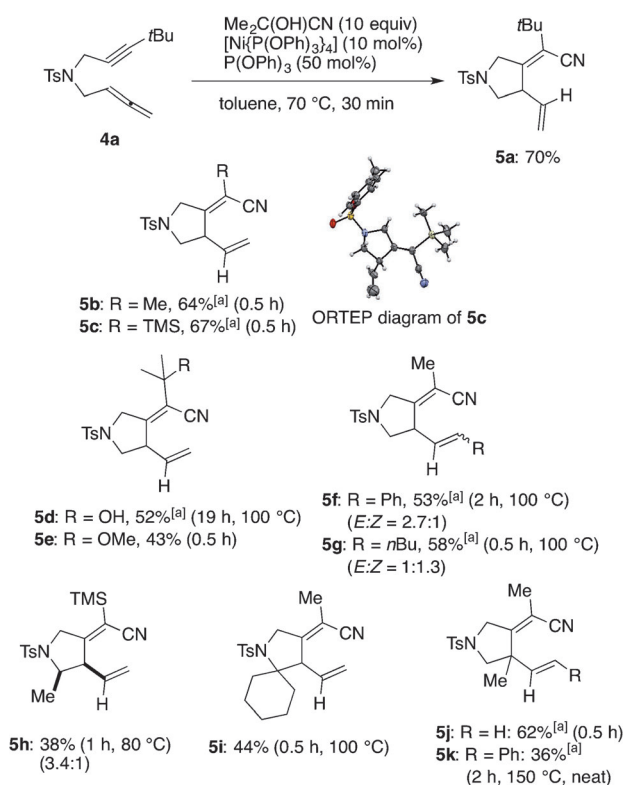
When **4a** was treated with AC under nickel catalysis, the reaction proceeded smoothly at 70 °C to give **5a** in 70 % yield, with complete stereoselectivity in the formation of the tetrasubstituted olefin. The structural assignment of the product was confirmed by X-ray crystallography of **5c**,^[7] which was obtained when **4c** was used as the substrate. We found that various functionalities on the alkyne, di- and trisubstituted allenes, free OH and ether groups, and substituents on the pyrrolidine ring were compatible with this cyclization reaction. A quaternary carbon center was also constructed at the allylic position of **5j** and **5k** in the cyclization.

The reaction starts with a regioselective hydronicellation of the allene. Once a Ni–H species is generated, hydride attack at the central carbon atom of the allene would give a π -allylnickel intermediate **7a**. A subsequent 5-*exo* cyclization to give **7c**, followed by elimination, would give the tetrasubstituted alkene **5** stereoselectively together with Ni⁰. When

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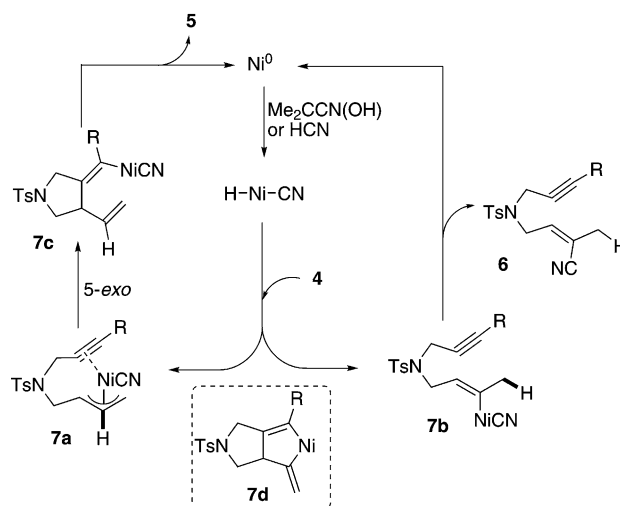
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201303883>.



Scheme 3. Nickel-catalyzed hydrocyanative allenyne cyclization. [a] The reaction was carried out with AC (20 equiv).

the initial C–H bond formation occurs at the terminal allenyl carbon atom, the resulting organonickel species **7b** is not suitable for cyclization and gives **6** through reductive elimination. In fact, **6a** (R = *t*Bu) was obtained in 20% yield as the sole side product. The stereoisomers observed in **5f** and **5g** suggest the possibility of a π -allylnickel intermediate in this catalytic transformation. Since a cyano functionality is added exclusively to a C–C triple bond in a regio- and stereoselective fashion, it is unlikely that the two vinyl–nickel bonds in **7d**, which could be generated by the oxidative cyclization of **4**, react specifically with AC through protonation to give **7c** (Scheme 4).^[8]

Having developed a new hydrocyanative cyclization of **4**, we next turned our attention to a three-component coupling reaction^[9,10] between allenes and alkynes. After careful investigation, the reaction of **1a**, alkynoate **8a**, and AC gave a sole three-component-coupling product **9aa**. The nickel-catalyzed reaction required a higher temperature (100 °C), and its rate depended strongly on the presence of an external phosphite. For example, P(OPh)₃ (20 mol%) promoted the reaction to give **9aa** as the sole coupling product in 52% yield within 20 min, and the reaction rate decreased dramatically in its absence (Table 1, entries 1 and 2). In the presence of trimethylphosphite, the best ligand tested, the reaction was complete within 15 min (Table 1, entry 3). The bulkier ligand P(OEt)₃ was inert: **9aa** was obtained in only 7% yield even after 24 h, and **1a** was recovered in 70% yield (Table 1, entry 4). This result suggests that a deactivated nickel species is probably formed, such as Ni(CN)₂, which is known to be



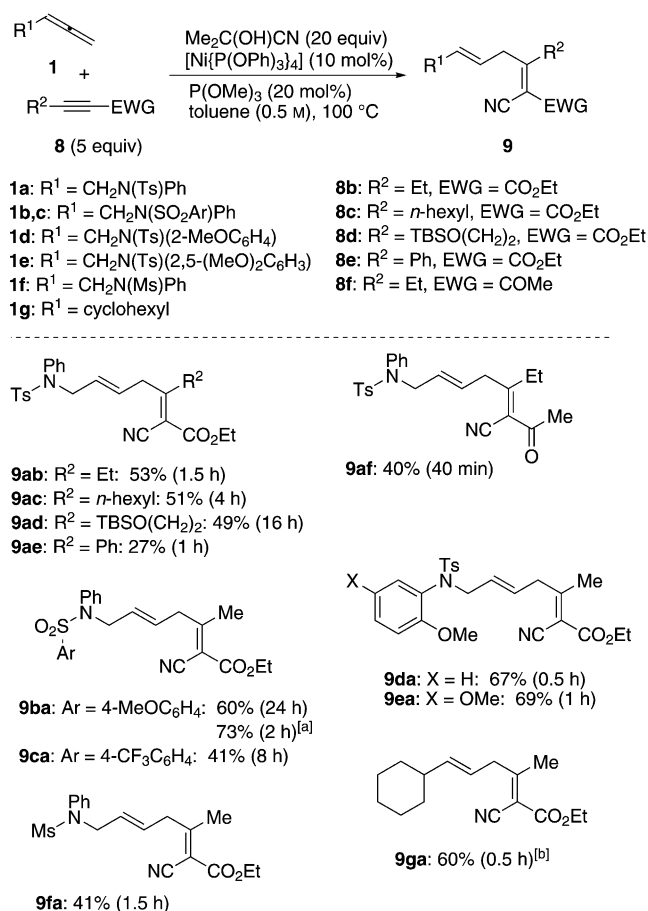
Scheme 4. Plausible catalytic pathway.

Table 1: Three-component coupling reaction of **1a**, **8a**, and AC.

R: Ph(Ts)NCH₂				
Entry	L	t	9aa [%]	Other compounds [%]
1	none	22 h	25	1a : 43
2	P(OPh) ₃	20 min	52	3a : 6
3	P(OMe) ₃	15 min	61	3a : 30
4	P(OEt) ₃	24 h	7	1a : 70

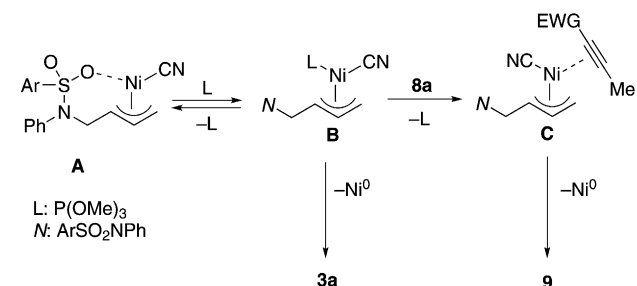
a poisoned catalyst in hydrocyanation reactions.^[3] The side product **3a** was produced by the simple hydrocyanation of the allene.

Under the optimized conditions, various combinations of **1** and **8** were investigated (Scheme 5). The reactions of **8b–d** with **1a** gave **9ab**, **9ac**, and **9ad** in 53, 51, and 49% yield, respectively, whereas a lower yield was observed with **8e** (27%). In the case of ketone **8f**, the desired coupling product **9af** was obtained exclusively in 40% yield in a stereoselective manner. Interestingly, we found that the reaction was quite sensitive to the effect of the arylsulfonyl group in **1**. For example, the 4-methoxy group in **1b** hindered the reaction (**9ba**: 60% yield, 24 h), but this effect depended on the amount of P(OMe)₃ in the reaction mixture. The presence of 50 mol% of P(OMe)₃ accelerated the cross-coupling reaction to give **9ba** in 73% yield within only 2 h. In the case of **1c**, there was no critical substituent effect on the reaction rate, and **9ca** was obtained in 41% yield within 8 h. The substituents on the aniline moiety had no effect, and the reaction gave **9da** and **9ea** in 67 and 69%, respectively, within 1 h. A mesyl group was also compatible with the reaction (**9fa** was formed in 41% yield), and the allene **1g**, which does not possess a sulfonamide functionality, did not require the use of P(OMe)₃ at all for a smooth reaction.



Scheme 5. Scope of the three-component coupling reaction. [a] The reaction was carried out with $\text{P}(\text{OMe})_3$ (50 mol %). [b] The reaction was carried out in the absence of $\text{P}(\text{OMe})_3$. EWG = electron-withdrawing group, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

On the basis of the above observations, plausible intermediates for a sequential cross-coupling reaction to give **9** are shown in Scheme 6. Initial hydrometalation of the allene gives the π -allyl Ni^{II} species **A**, which could be stabilized by the Lewis basicity of a neighboring SO_2 functionality. The 4-methoxy group increases the electron density of the SO_2 functionality and thus contributes to the stabilization of **A** to prevent the subsequent insertion of **8**. When a methoxy group is installed on the other aromatic ring in **1** (see **1d,e**),



Scheme 6. Plausible key intermediates in the three-component coupling reaction.

this effect is not significant, and the subsequent insertion into the C–C triple bond proceeds smoothly.

Although the role of trimethylphosphite is still unclear, this ligand has the following key features: 1) its suitable Lewis basicity^[11] promotes the replacement of the sulfone to give **B**, and 2) its ready dissociation from Ni^{II} promotes the coordination of the alkyne (**B** $\rightarrow$ **C**). In the absence of $\text{P}(\text{OMe})_3$, the reaction was quite slow, and the presence of a stoichiometric amount (100 mol %) mainly led to **3a**, which indicates that excess phosphite prevents the coordination of the alkyne to the Ni^{II} center and its insertion via **C**. The presence of a 4-methoxy group on ArSO_2 led to a decrease in the reaction rate, but when the amount of $\text{P}(\text{OMe})_3$ used was increased to 50 mol %, the yield of the coupling product improved. This result suggests that an appropriate amount of $\text{P}(\text{OMe})_3$ is effective in cleaving the $\text{SO}_2\text{--Ni}$ bond to promote the formation of **B** from **A**. $\text{P}(\text{OMe})_3$ was not essential in the reaction of **1g** because there were no Lewis basic functionalities to prevent the insertion of **8** to give **9**.

In summary, we have developed a new hydrocyanative cyclization and three-component cross-coupling reaction under nickel catalysis. These protocols offer 1) a new method for the addition of a CN functionality to C–C triple bonds, 2) a highly regio- and stereoselective synthesis of tetrasubstituted alkenes with a single catalyst, and 3) a metal-waste-free three-component cross-coupling process. These transformations may provide a new perspective for the synthesis of highly functionalized organic molecules through cyanation, and further studies are currently under way.

Experimental Section

Synthesis of 5a: A mixture of **4a** (48.2 mg, 0.15 mmol), $\text{P}(\text{OPh})_3$ (20 mL, 0.096 mmol), $[\text{Ni}(\text{P}(\text{OPh})_3)_4]$ (19.7 mg, 0.035 mmol, 10 mol %), and acetone cyanohydrin (139 μL , 1.5 mmol) in toluene (1.5 mL) was heated for 30 min at 70 °C under an argon atmosphere and then poured onto silica gel. Purified by column chromatography (hexane/AcOEt 5:1) provided **5a** (36.4 mg, 0.11 mmol, 70%; m.p.: 90–91 °C) as a colorless solid and **6a** (10.2 mg, 0.03 mmol, 20%) as a colorless oil.

Synthesis of 9aa: A mixture of **1a** (91.2 mg, 0.3 mmol), **8a** (166.0 mg, 1.5 mmol), $\text{P}(\text{OMe})_3$ (7.1 μL , 0.06 mmol), $[\text{Ni}(\text{P}(\text{OPh})_3)_4]$ (39.0 mg, 0.03 mmol, 10 mol %), and acetone cyanohydrin (507 μL , 6.0 mmol) in toluene (0.6 mL) was heated for 15 min at 100 °C under an argon atmosphere and then poured onto silica gel. Purification by column chromatography (hexane/AcOEt 10:1) gave **9aa** (95.1 mg, 61%) as a colorless oil and **3a** (28.9 mg, 30%) as a colorless oil.

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- [1] For recent developments in nickel-catalyzed carbocyanation, see: a) Y. Hirata, T. Yukawa, N. Kashiwara, Y. Nakao, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 10964–10973; b) Y. Hirata, T. Inui, Y. Nakao, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 6624–6631; c) A. Yada, T. Yukawa, H. Idei, Y. Nakao, T. Hiyama, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 619–634; d) A. Yada, S. Ebata, H. Idei, D. Zhang, Y. Nakao, T. Hiyama, *Bull. Chem. Soc.*

- Jpn. Chem. Soc.* **2010**, *83*, 1170–1184; e) Y. Nakao, A. Yada, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 10024–10027; f) C.-Y. Ho, *Chem. Commun.* **2010**, *46*, 466–468; g) Y. Minami, H. Yoshiyasu, Y. Nakao, T. Hiyama, *Angew. Chem.* **2013**, *125*, 917–921; *Angew. Chem. Int. Ed.* **2013**, *52*, 883–887; h) T. Igarashi, S. Arai, A. Nishida, *J. Org. Chem.* **2013**, *78*, 4366.
- [2] a) S. Arai, T. Sato, Y. Koike, M. Hayashi, A. Nishida, *Angew. Chem.* **2009**, *121*, 4598–4601; *Angew. Chem. Int. Ed.* **2009**, *48*, 4528–4531; b) S. Arai, T. Sato, A. Nishida, *Adv. Synth. Catal.* **2009**, *351*, 1897–1904; c) S. Arai, Y. Koike, A. Nishida, *Adv. Synth. Catal.* **2010**, *352*, 893–900; d) S. Arai, Y. Koike, H. Hada, A. Nishida, *J. Am. Chem. Soc.* **2010**, *132*, 4522–4523; e) S. Arai, Y. Koike, H. Hada, A. Nishida, *J. Org. Chem.* **2010**, *75*, 7573–7579; f) S. Arai, A. Nishida, *Synlett* **2012**, 2880.
- [3] a) A. Falk, A.-L. Goderz, H.-G. Schmalz, *Angew. Chem.* **2013**, *125*, 1617–1621; *Angew. Chem. Int. Ed.* **2013**, *52*, 1576–1580; b) W. Goertz, P. C. J. Kamer, P. W. N. M. van Leeuwen, D. Vogt, *Chem. Eur. J.* **2001**, *7*, 1614–1618; c) T. V. Rajanbabu, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1992**, *114*, 6265–6266; for recent reviews, see: d) L. Bini, C. Müller, D. Vogt, *ChemCatChem* **2010**, *2*, 590–608; e) L. Bini, C. Müller, D. Vogt, *Chem. Commun.* **2010**, *46*, 8325–8334; for 1,3-dienes, see f) B. Saha, T. V. Rajanbabu, *Org. Lett.* **2006**, *8*, 4657–4659; g) J. Wilting, M. Janssen, C. Müller, D. Vogt, *J. Am. Chem. Soc.* **2006**, *128*, 11374–11375; for a review of nickel-catalyzed multicomponent coupling reactions, see: h) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980–3998; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908.
- [4] For C–C triple bonds, see: W. R. Jackson, C. G. Lovel, *J. Chem. Soc. Chem. Commun.* **1982**, 1231–1232.
- [5] Y. Sakakibara, S. Matsuzaka, S. Nagamine, M. Sakai, N. Uchino, *Nippon Kagaku Kaishi* **1985**, 409–415.
- [6] M. Sundermeier, A. Zapf, M. Beller, *Angew. Chem.* **2003**, *115*, 1700; *Angew. Chem. Int. Ed.* **2003**, *42*, 1661.
- [7] CCDC 860058 (**5c**) 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.
- [8] The ligands on Ni⁰ strongly affect the reaction pathway, whether hydrometalation or oxidative cyclization, in the presence of a hydride source; see: a) Y. Sato, M. Takimoto, M. Mori, *J. Am. Chem. Soc.* **2000**, *122*, 1624–1634; b) A. Malik, M. R. Chaulagain, J. Montgomery, *Org. Lett.* **2009**, *11*, 5734–5737.
- [9] For previous studies on nickel-catalyzed three-component coupling reactions with allenes, see: a) M.-S. Wu, D. K. Rayabarapu, C.-H. Cheng, *J. Am. Chem. Soc.* **2003**, *125*, 12426–12427; b) E. Shirakawa, Y. Yamamoto, Y. Nakao, S. Oda, T. Tsuchimoto, T. Hiyama, *Angew. Chem.* **2004**, *116*, 3530–3533; *Angew. Chem. Int. Ed.* **2004**, *43*, 3448–3451; c) S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 7320–7321; for palladium catalysis, see: d) Y. Fujii, J. Terao, H. Kuniyasu, N. Kambe, *J. Organomet. Chem.* **2007**, *692*, 375–381; for other examples of stepwise coupling reactions, see: e) I. R. Cooper, R. Grigg, W. S. MacLachlan, M. Thornton-Pett, V. Sridharan, *Chem. Commun.* **2002**, 1372–1373; f) M. Takimoto, M. Kawamura, M. Mori, *Org. Lett.* **2003**, *5*, 2599–2601; g) H. E. Burks, S. Liu, J. P. Morken, *J. Am. Chem. Soc.* **2007**, *129*, 8766–8773; h) Y. Yoshida, K. Murakami, H. Yorimitsu, K. Ohshima, *J. Am. Chem. Soc.* **2010**, *132*, 8878–8879.
- [10] For recent examples of nickel-catalyzed multicomponent coupling reactions, see: a) J. Terao, F. Bando, N. Kambe, *Chem. Commun.* **2009**, 7336–7338; b) K. Ogata, J. Sunagawa, S. Fukuzawa, *Angew. Chem.* **2009**, *121*, 6194–6196; *Angew. Chem. Int. Ed.* **2009**, *48*, 6078–6080; c) K. Ogata, Y. Atsumi, S. Fukuzawa, *Org. Lett.* **2010**, *12*, 4536–4539; d) T. Mori, T. Nakamura, M. Kimura, *Org. Lett.* **2011**, *13*, 2266–2269; e) K. Ogata, Y. Atsumi, D. Shimada, S. Fukuzawa, *Angew. Chem.* **2011**, *123*, 6018–6021; *Angew. Chem. Int. Ed.* **2011**, *50*, 5896–5899.
- [11] For coordination by a heteroatom to a nickel(II) center in reaction intermediates, see: a) M. Ohashi, I. Takeda, M. Ikawa, S. Ogoshi, *J. Am. Chem. Soc.* **2011**, *133*, 18018–18021; b) M. Ohashi, O. Kishizaki, H. Ikeda, S. Ogoshi, *J. Am. Chem. Soc.* **2009**, *131*, 9160–9161; c) S. Ogoshi, T. Haba, M. Ohashi, *J. Am. Chem. Soc.* **2009**, *131*, 10351–10352; d) S. Ogoshi, H. Ikeda, H. Kurosawa, *Angew. Chem.* **2007**, *119*, 5018–5020; *Angew. Chem. Int. Ed.* **2007**, *46*, 4930–4932.