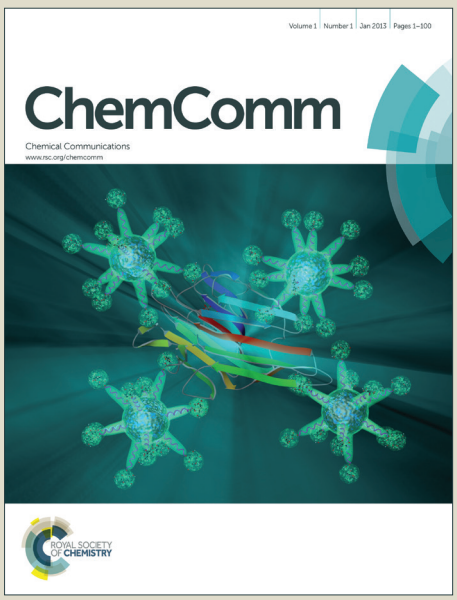
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

A new protocol for nickel-catalysed regio- and stereoselective hydrocyanation of allenes

Cite this: DOI: 10.1039/x0xx00000x

Shigeru Arai,* Hiroto Hori, Yuka Amako and Atsushi Nishida

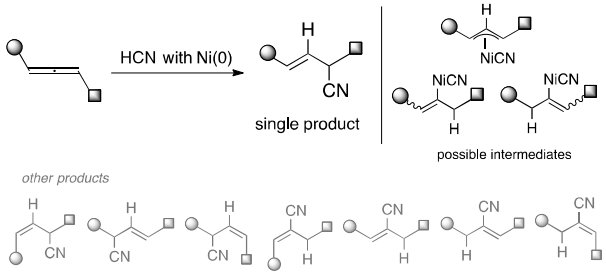
Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

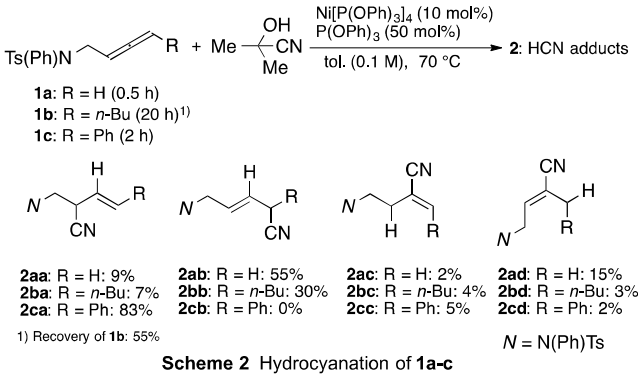
Regio- and stereoselective hydrocyanation under nickel catalysis is described. This report shows that allenyl C—C double bonds are discriminated and converted to the corresponding carbonitriles as a single product. The key functionalities for achieving high regio- and stereocontrol are aryl and cyclopropyl groups in the substrates.

Since a cyano group has a potential utility in pharmaceuticals and biologically important compounds[1] and equivalent to a carbonyl group and related functionalities, its introduction has been a useful synthetic tool in synthetic chemistry. Particularly, metal-catalysed hydrocyanation with the use of non-activated C—C multiple bonds has been one of the most powerful cyanation protocols. Since the pioneering work on nickel-catalysed hydrocyanation using simple and non-activated olefins reported in the 1970s,[2] facile access to various carbonitriles through the use of this transformation has been very advantageous,[3-5] however higher regioselectivity has been observed only with vinylarenes.[2]



Scheme 1 Nickel-catalyzed hydrocyanation of allenes

On the other hand, we previously reported that the allene functionality plays a key role in cyanative cyclisation[6a,c] and 3-component coupling reaction[6a,d] however simple allenes are unsuitable substrates because the two C—C double bonds are not effectively discriminated during hydrocyanation. Only one example for this chemistry reported in 1985 shows both the chemical reactivity and selectivity are significantly improved.[5a] This need for improvement is based on the unique reactivity of allenes to give a total 5 possible organonickel intermediates and a maximum of 8 HCN adducts that could be obtained from the starting allenes with Ni(0) and HCN (Scheme 1). In this communication, we set a challenging goal of highly regio- and stereocontrolled hydrocyanation using allenes to establish an unprecedented synthetic method for various carbonitriles.[7-9]

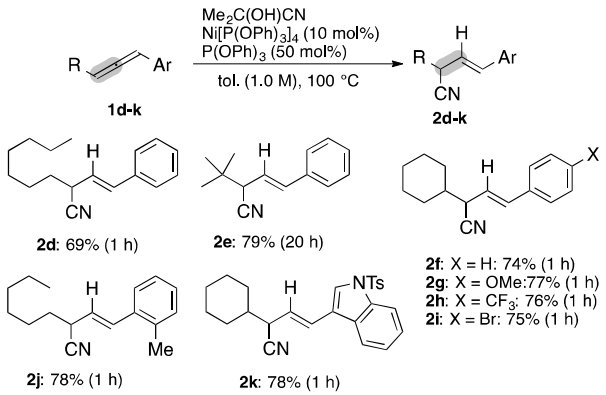


Scheme 2 Hydrocyanation of **1a-c**

Initially, we investigated the substituent effect in the nickel-catalysed hydrocyanation of allenes **1a-c** using acetonecyanohydrin (AC) (Scheme 2). The results indicate that the substituents on allenes greatly influenced the regioselectivity and reaction efficiency. For example, mono-substituted allene (**1a**) gave **2ab** in 55% yield as a major adduct within 30 min, however the product selectivity among **2aa-ad** was not satisfactory. The yields are determined by 1H NMR. In the case of **1b**, which contains an alkyl chain on R, reduced reactivity was observed, and this resulted in lower conversion of **2bb** of only 30% even after 20 h, with the recovery of **1b** in 55% yield. These observations are quite similar to those reported by Sakakibara and co-workers.[5a] On the other hand, we were pleased to find that aryl-substituted allene (**1c**) had much higher reactivity and was almost exclusively converted to **2ca** in 83% yield. The structures of all the major adducts from **1a-c** include newly formed C—H bonds on allenyl *sp* carbons, which explains why π-allyl but not alkenyl

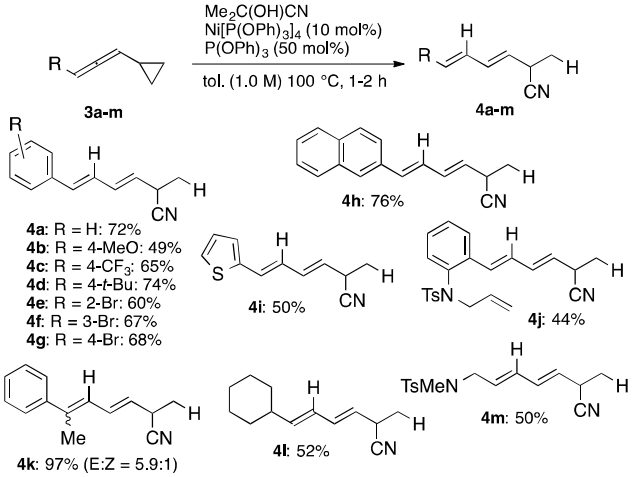
nickel intermediates could be generated predominantly and a phenyl group strongly determined the regiochemistry in the reductive elimination step (C—CN bond formation), because a *trans*-styryl moiety in **2ca** would be thermodynamically favoured. In this reaction, various ligands such as PAr_3 (Ar = Ph, 4-CF_3Ph, 2-MePh), $P(OMe)_3$, dppb and xantphos instead of triphenylphosphite gave no significant difference however dppe dramatically decreased the reaction rate (20 h) and electron donating phosphines such as PCy_3 and P(4-MeOPh)$_3$ completely prevented the reaction.

This protocol could be applied to various 1,3-disubstituted allenes that have aryl functionalities. Regio- and stereochemistry in products are predictable to be achieved in good to excellent yields (Scheme 3). For example, primary, secondary and tertiary alkyl groups in **2d-f** were all suitable, and the aromatic ring including indole (**2g-k**) could contain a wide variety of functional groups to be transformed to the corresponding adducts in 74-78% yield.



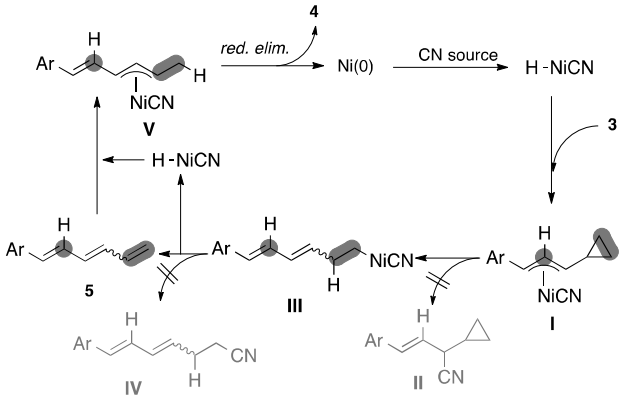
Scheme 3 Substrate scope of hydrocyanation using **1d-k**

If the π -allyl nickel species have a sufficient life-time and reactivity, an alternative transformation could be developed, since the regiochemistry of the C—Ni bonds in the reaction intermediates are predictable. Thus, we next examined remote cyanation *via* sequential C—C bond cleavage of cyclopropanes[10] through the use of **3** (Scheme 4). When **3a** was used under optimum conditions, *trans*,*trans*-**4a** was exclusively obtained in 72% yield as a sole HCN adduct together with *trans*-*trans*-**5a** in 10% yield. The condition survey using **3a** under lower temperature (70 °C) or with the reduced amount of AC gave lower conversion to **4a**. Using arylphosphines, alkylphosphites and bidendentate phosphines instead were all ineffective to increase the yield of **3a** and resulted in the formation of triene as a major product. As described in the reaction of **1**, ligand screening gave no any positive effect. The substrate scope shows that various functionalities such as methoxy, trifluoromethyl, *tert*-butyl and bromo groups on the benzene ring (**3b-g**), 2-naphthyl (**3h**), thiophene (**3i**), aniline moieties (**3j**) as well as trisubstituted allene (**3k**) could all be applicable in this transformation to give **4** in moderate to good yields. Furthermore, cyclohexyl and aminoalkyl groups instead of an aryl moiety in **3** could both be used in this cyanation to give **4l** and **4m** *via* cyclopropane cleavage, respectively.



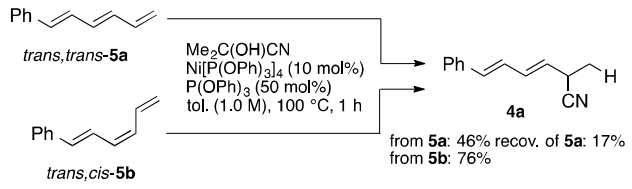
Scheme 4 Cyanative cyclopropane cleavage using **3**

A plausible reaction pathway is outlined in Scheme 5. The initial step would be the regioselective hydronickelation of **3** to form π-allyl nickel species **I**. Sequential C—C bond breaking *via* cyclopropane cleavage gives **III** that would be quickly converted to triene **5** *via* β-H elimination rather than reductive elimination to give the primary carbonitrile **IV**. A second hydronickelation would selectively proceed at the terminal C—C double bond of **5** to give π -allyl nickel species **V** again, and the reaction could be terminated by formation of **4** together with Ni(0) *via* regioselective reductive elimination. Both a sequential formation of a C—Ni bond and **V** determines the regiochemistry of the C—CN bond in the products. Since **β**-C and **β**-H elimination from **I** to **5** should be quite rapid, side products such as **II** and **IV** were not observed at all through this reaction.

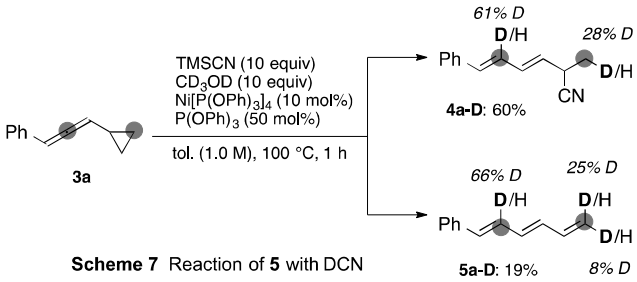


Scheme 5 A plausible reaction pathway

Trans,trans-**5a** could be isolated from the reaction mixture and we performed further investigations to confirm the above reaction mechanism. When *trans*,*trans*- and *trans*,*cis*-trienes were independently used under nickel catalysis, **4a** was exclusively obtained from both substrates as a single product in respective yields of 46% and 76% (Scheme 6). These results indicate that similar π -allyl nickel species such as **V** would be generated during these reactions and a trans dienyl moiety in **4a** is more favoured, as observed in hydrocyanation starting from arylallenes.

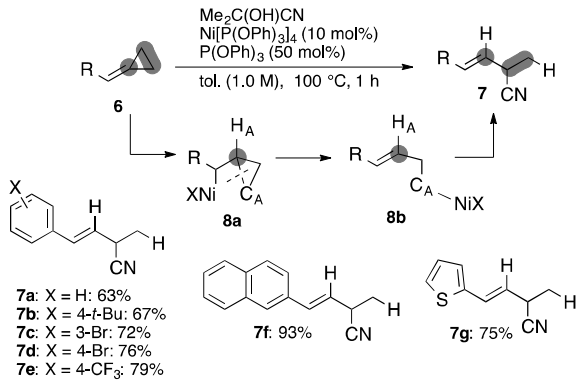


Scheme 6 Hydrocyanation of triene **5**



Scheme 7 Reaction of **5** with DCN

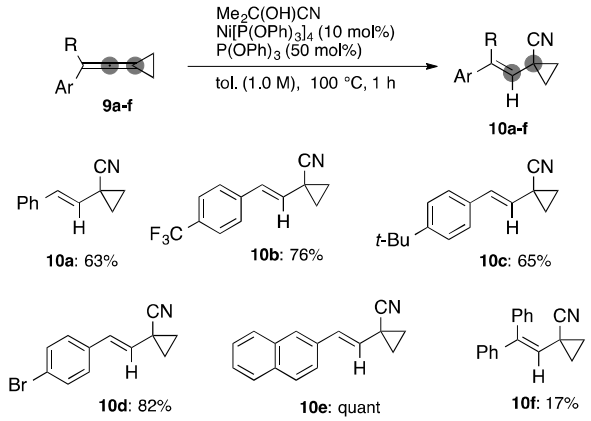
In the reaction of **3a** using DCN (prepared *in-situ* from CD_3OD with TMSCN)[11], D was effectively incorporated at both the allenyl *sp* carbon and cyclopropyl methylene to give **4a-D** in 60% yield. D was also incorporated at the two sp^2 carbons of the recovered triene of **5a-D**, which was isolated in 19% yield (Scheme 7). The deuteration ratio in these products is similar, which strongly suggests that the reaction pathway includes the formation of two C—H bonds. Due to the *in-situ* generation of HCN through **β**-H elimination (**III** to **5**), the 100% incorporation of D in both products would be prevented even if an excess amount of D source was used. Based on the above results, the reaction pathway includes C—H bond formation (hydronickelation) on specific carbons and triene formation as a precursor of the HCN adducts. Furthermore, the reaction using **3a** with Ni(0) in the absence of cyanohydrin was examined, and was found to result in the recovery of **3a** without the observation of any trienes **5**.[12] This result suggests that a hydride source is essential for starting the reaction and a nickelacyclobutane intermediate would be unsuitable. These results reasonably explain the above reaction pathway *via* a hydronickelation—**β**-C elimination—**β**-H elimination—hydronickelation—reductive elimination sequence without the observation of any side products such as **II** or **IV**.



Scheme 8 Hydrocyanation of **6**

For further application, we next chose alkylydenecyclopropanes[13,14] as allene analogues and used them under nickel catalysis (Scheme 8). As expected, the regio- and stereoselective cyanation of **6** proceeded smoothly to give **7** as a sole product. Its structure suggests that the initial C—H bond exclusively formed at a more substituted sp^2 carbon. Subsequent cleavage of a C—C_A bond, but not C—H_A bond, in the plausible intermediate **8a** should occur to **8b** selectively and a similar sequence as in the formation of **4**, i.e., β-H elimination, regioselective hydronickelation and reductive elimination, would achieve regioselective cyanation to form **7**. The substrate scope indicates that various aryl functionalities (**6a-g**) including bromophenyl and thiophene groups could be used to give the corresponding stereo-defined adducts of **7a-g** in 63-93% yield.

To confirm the most favoured functionality to determine the reaction pathway and regio- and stereochemistry through this cyanation, we next turned to use vinilydenecyclopropane **9** that contains both allenyl and alkylidenecyclopropyl double bonds (Scheme 9). When **9a** was employed under nickel catalysis, the corresponding single product **10a** was exclusively obtained in regio- and stereoselective fashion. Its structure suggests that the hydrocyanation would be triggered by C_{sp}-H bond formation selectively, and a cyano group was regioselectively installed without any cleavage of cyclopropane rings at all. Various functionalities in substrates (**9b-e**) were applicable for this transformation and the corresponding products **10** were obtained in 63% to quantitative yield, exclusively, however **10f** was obtained in 17% yield due to the lower reactivity of tetrasubstituted allene **9f**.



Scheme 9 Hydrocyanation of **9**

Conclusions

In conclusion, we have demonstrated a new protocol for nickel-catalysed hydrocyanation of allenes to give a single product and achieved the sequential transformation *via* regio- and stereoselective cyclopropane cleavage. This method could be also applicable for alkylidene- and vinylidenecyclopropanes to be converted to the corresponding cyanoadducts in regioselective manner. We believe that these cyanations offer a new and important synthetic tool for Ni-catalysed transformation, and further studies are currently underway.

This research was supported by a JSPS KAKEHNHI Grant (21590003), The Uehara Memorial Foundation (to S.A.) and NANOHANA Competition 2014 in Chiba University (to Y.A.).

Notes and references

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, Japan. E-mail: araisgr@chiba-u.jp

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 (a) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem*. **2010**, *53*, 7902-7917; (b) R. L. Eoff, Monica, L. Guzman and P. A. Crooks, *E. J. Med. Chem*. **2015**, *92*, 212-220.

2 (a) B. W. Taylor and H.-E. Swift, *J. Catal*. **1972**, *26*, 254-260; (b) T. Funabiki and Y. Yamazaki, *J. Chem. Soc. Chem. Commun*. **1979**, 1110-1111; (c) W. R. Jackson and C. G. Lovel, *J. Chem. Soc. Chem. Commun*. **1982**, 1231-1232; (d) N. J. Fitzmaurice, W. R. Jackson and P. Perlmutter, *J. Organomet. Chem*. **1985**, *285*, 375-381. (d) T. V. Rajanbabu, *Organic Reactions*, **2011**, *vol. 75*, 1-73.

3 (a) A. Falk, A.-L. Goderz and H.-G. Schmalz, *Angew. Chem. Int. Ed*. **2012**, *51*, 1617-1621; (b) W. Goertz, P. C. J. Kamer, P. W. N. M. van Leeuwen and D. Vogt, *Chem. Eur. J*. **2001**, *7*, 1614-1618; (c) T. V. Rajanbabu and A. L. Casalnuovo, *J. Am. Chem. Soc*. **1992**, *114*, 6265-6266; For reviews, see: (d) L. Bini, C. Muller and D. Vogt, *ChemCatChem* **2010**, *2*, 590-608; (e) L. Bini, C. Muller and D. Vogt, *Chem. Commun*. **2010**, *46*, 8325-8334; For 1,3-diene, (f) B. Saha and T. V. Rajanbabu, *Org. Lett*. **2006**, *8*, 4657-4659; (g) J. Wilting, M. Janssen, C. Muller and D. Vogt, *J. Am. Chem. Soc*. **2006**, *128*, 11374-11375; For cobalt catalysis, (h) B. Gasper and E. M. Carreira, *Angew. Chem. Int. Ed*. **2007**, *46*, 4519-4522.

4 For alkynes, W. R. Jackson and C. G. Lovel, *J. Chem. Soc. Chem. Commun*. **1982**, 1231-1232.

5 For allene, (a) Y. Sakakibara, S. Matsuzaka, S. Nagamine, M. Sakai and N. Uchino, *Nippon Kagaku Kaishi*, **1985**, 409-415; For alternative cyanations, see (b) A. Yamamoto, Y. Ikeda and M. Suginome, *Tetrahedron Lett*. **2009**, *50*, 3168-3170; (c) Y. Hirata, T. Inui, Y. Nakao and T. Hiyama, *J. Am. Chem. Soc*. **2009**, *131*, 6624-6631; (d) N. Chatani, T, Takeyasu and T. Hanafusa, *Tetrahedron Lett*. **1986**, *27*, 1841-1844.

6 (a) S. Arai, Y. Amako, X. Yang and A. Nishida, *Angew. Chem. Int. Ed.* **2013**, *52*, 8147-8150; (b) T. Igarashi, S. Arai and A. Nishida, *J. Org. Chem*. **2013**, *78*, 4366-4372; (c) Y. Amako, H. Hori, S. Arai and A. Nishida, *J. Org. Chem*. **2013**, *78*, 10763-10775; (d) X. Yang, S. Arai and A. Nishida, *Adv. Synth. Catal*. **2013**, *355*, 2974-2981; Alternative cyanation under palladium catalysis: (e) S. Arai, T. Sato, Y. Koike, M. Hayashi and A. Nishida, *Angew. Chem. Int. Ed*. **2009**, *48*, 4528-4531; (f) S. Arai, Y. Koike, H. Hada and A. Nishida, *J. Am. Chem. Soc*. **2010**, *132*, 4522-4523; (g) S. Arai and A. Nishida, *Synlett* **2012**, 23, 2880-2893.

7 Selected examples for carbocyanation, see (a) Y. Nakao, *Bull. Chem. Soc*. **2012**, *85*, 731-745; (b) Y. Cheng, Z. Duan, Y. Zhongxian, Y. Zhu and Y. Wu, *Org. Lett*. **2008**, *10*, 901-904; (c) M. P. Watson, and E. N. Jacobsen, *J. Am. Chem. Soc*. **2008**, *130*, 12594-12595; (d) C.-Y. Ho, *Chem. Commun*. **2010**, *46*, 466-468; (e) Y. Minami, H. Yoshiyasu, Y. Nakao and T. Hiyama, *Angew. Chem. Int. Ed*. **2013**, *52*, 883-887.

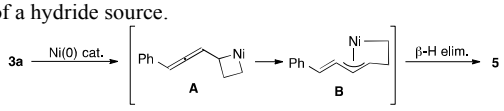
8 For aminocyanation, (a) Y. Miyazaki, N. Ohta, K. Semba and Y. Nakao, *J. Am. Chem. Soc*. **2014**, *136*, 3732-3735; (b) B. Rao and X. Zeng. *Org. Lett*. **2014**, *16*, 314-317; (c) Z. Pan, S. M. Pound, N. R. Rondla and C. J. Douglas, *Angew. Chem. Int. Ed*. **2014**, *53*, 5170-5174; (d) L. Xu, X.-Q. Mou, Z.-M. Chen and S.-H. Wang, *Chem. Commun*. **2014**, *50*, 10676-10679; (e) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu and Q. Zhang, *Angew. Chem. Int. Ed*. **2013**, *52*, 2529-2533; (f) G. Qiu, X. Qiu and J. Wu, *Adv. Synth. Catal*. **2013**, *355*, 3205-3209.

9 For oxycyanation, D. C. Koester, M. Kobayashi, D. B. Werz and Y. Nakao, *J. Am. Chem. Soc*. **2012**, *134*, 6544-6547.

10 (a) G. Zuo and J. Louie, *Angew. Chem. Int. Ed*. **2004**, *43*, 2277-2279; (b) L. Liu, and J. Montgomery, *J. Am. Chem. Soc*. **2006**, *128*, 5348-5349; (c) S. Ogoshi, M. Nagata, and H. Kurosawa, *J. Am. Chem. Soc*. **2006**, *128*, 5350-5351.

11 J. M. Keith and E. N. Jacobsen, *Org. Lett*. **2004**, *6*, 153-155.

12 This result indicates that the generation of **A** and/or **B** is unlikely and **3a** is an unsuitable precursor for transformation to **5** in the absence of a hydride source.



13 For methylenecyclopropane, (a) H. Taniguchi, T. Ohmura and M. Suginome, *J. Am. Chem. Soc*. **2009**, *131*, 11298-11299; (b) K. Ogata, D, Shimada, S. Shouchi, S, Fukuzawa, *Org. Lett*. **2013**, *15*, 1182-1185; For review, see (c) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev*. **2014**, *114*, 7317-7420.

14 For alkylidenecyclopropane, see (a) S. Saito, K. Maeda, R. Yamasaki, T. Kitamura, M. Nakagawa, K. Kato, I. Azumaya and H. Masu, *Angew. Chem. Int. Ed*. **2010**, *49*, 1830-1833; (b) M. Ohashi, T. Taniguchi and S. Ogoshi, *Organometallics*. **2010**, *29*, 2386-2389; For mechanistic insight, see (c) S. Komagawa, C. Wang, K. Morokuma, S. Saito and M. Uchiyama, *J. Am. Chem. Soc*. **2013**, *135*, 14508-14510.