Asymmetric Synthesis

International Edition: DOI: 10.1002/anie.201702429
German Edition: DOI: 10.1002/ange.201702429

Catalytic Enantioselective Reaction of Allenylnitriles with Imines Using Chiral Bis(imidazoline)s Palladium(II) Pincer Complexes

*Masaru Kondo, Masashi Omori, Tsubasa Hatanaka, Yasuhiro Funahashi, and Shuichi Nakamura**

Abstract: *The first highly enantioselective reaction of allenylnitriles with imines has been developed. Excellent yields and enantioselectivities were observed for the reaction with various imines using chiral Phebim-Pd^{II} complexes. This process offers a simple and efficient synthetic route for various functionalized α-vinylidene-β-aminonitriles and their derivatives.*

Allene compounds and their derivatives have been proven to be useful building blocks for the preparation of pharmaceutical targets,[1] and their unique reactivity renders them versatile intermediates in organic syntheses.[2] Therefore, their synthetic importance has prompted large interest to develop the asymmetric synthesis of chiral compounds having an allenyl group.[3] One of the most efficient methods for the preparation of chiral compounds having an allenyl group is the stereoselective addition of allenyl compounds carrying electron-withdrawing groups with electrophiles. There are several reports for the enantioselective addition reaction of allenylesters with imines,[4,5] carbonyl compounds,[6] and activated olefins,[7] however, to the best of our knowledge, there are no reports on the catalytic enantioselective reaction of allenylnitriles with imines (Figure 1).[8] On the other hand, we recently developed the activation of nitrile compounds using chiral bis(imidazoline) palladium(II) pincer complexes.[9,10] In these catalyst systems, palladium catalysts enhanced the acidity of the α-proton in alkylnitriles to give palladium ketenimides, which react with imines to give products. We expected that the bis(imidazoline) palladium system could be applied to the reaction of allenylnitriles with imines, because allenylnitriles have reasonable acidity (pK_a = 21.0 in DMSO), similar to allylnitrile (pK_a = 20.7 in DMSO).[11] Therefore, chiral palladium catalysts activate the acidity of allenylnitriles, then the carbanion of allenylnitriles attacks imines to give chiral α-vinylidene-β-aminonitriles. Herein, we report the first highly enantioselective reaction of allenylnitriles with imines using palladium(II) pincer complexes with chiral bis(imidazoline)s as a chiral Lewis acid catalyst.

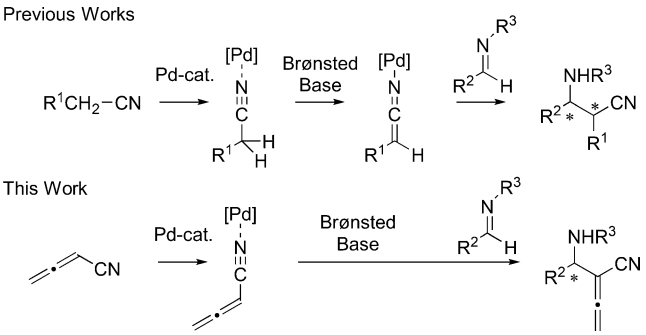


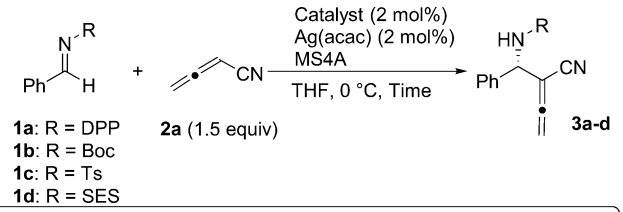
Figure 1. Palladium pincer complexes activate nitrile compounds.

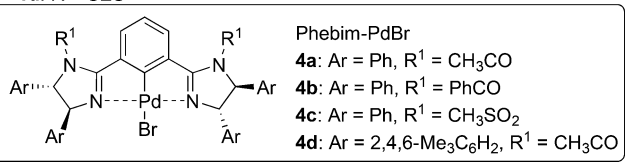
The enantioselective reaction of allenylnitrile **2a** (1.5 equiv) with various imines **1** (1.0 equiv) was carried out by using palladium catalysts **4a–d** (2 mol%) and silver acetylacetonate (2 mol%) in THF (Table 1). Although the reaction of *N*-diphenylphosphinoyl imine **1a** (R = DPP) and *N*-Boc imine **1b** with allenylnitrile **2a** using catalyst **4a** and Ag(acac) did not afford any products (entries 1 and 2), the reaction of *N*-tosyl imine gave product **3c** in 73% yield with 54% *ee* (entry 3). Furthermore, the reaction with *N*-trimethylsilylethanesulfonyl imine **1d** (R = SES) gave product **3d** in moderate yield with 71% *ee* (entry 4). In order to improve enantioselectivity, we optimized the structure of bis(imidazoline) catalysts **4b–d** (entries 5–7). As a result, the reaction using catalyst **4d** having an acetyl group (R^1) and 2,4,6-trimethylphenyl group (Ar) emerged as the most suitable catalyst for this reaction giving product **3d** with high enantioselectivity but low yield due to the generation of a by-product by the over-reaction of product with imines (entry 7). To our delight, the reaction at a lower temperature suppressed the generation of by-product to give product **3d** in good yield with high enantioselectivity (entry 8). Finally, the addition of 20 mol% of trimethylsilylalcohol (TMSOH) improved the reactivity and yield of the product (entry 9).

Next, we examined the reaction of **2a** with various imines **1d–p** using **4d**, Ag(acac), and TMSOH (Table 2). The reaction of various imines **1e–j** having an electron-withdrawing group, such as a fluoro, chloro, bromo, and trifluoromethyl group, in the *meta* or *para* position gave products **3e–j** in high yield with high enantioselectivity (63–88%, 99% *ee*, entries 1–7). The reaction with imines **1k** bearing an elec-

[*] M. Kondo, M. Omori, Prof. S. Nakamura
Department of Life Science and Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
E-mail: snakamur@nitech.ac.jp
M. Kondo, Prof. S. Nakamura
Frontier Research Institute for Material Science
Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Prof. T. Hatanaka, Prof. Y. Funahashi
Department of Chemistry, Graduate School of Science
Osaka University
1-1 Machikaneyama, Toyonaka, Osaka 560-0043 (Japan)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201702429.

Table 1: Optimization of the reaction of allenylnitrile **2a** with various imines **1a–d** using **4**–Ag(acac).

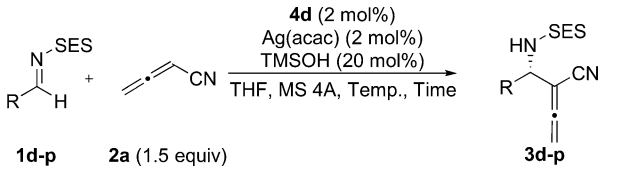




Entry	**1**	Catalyst	*t* [h]	Yield [%]	*ee* [%]
1	**1a**	**4a**	72	–	–
2	**1b**	**4a**	72	–	–
3	**1c**	**4a**	48	73	54
4	**1d**	**4a**	72	49	71
5	**1d**	**4b**	72	14	65
6	**1d**	**4c**	72	trace	–
7	**1d**	**4d**	72	47	91
8[a]	**1d**	**4d**	72	82	99
9[a,b]	**1d**	**4d**	24	88	99

[a] The reaction was carried out at −60 °C. [b] TMSOH (20 mol %) was added.

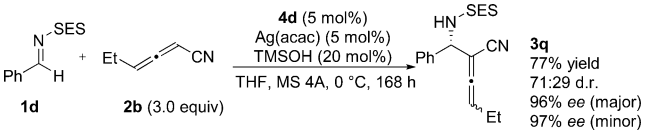
Table 2: The reaction of allenylnitrile **2a** with various imines **1d–p** using **4d**–Ag(acac).



Entry	**1**	R	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	**1d**	Ph	−60	24	88	99
2	**1e**	3-FC_6H_4	−60	24	88	99
3	**1f**	4-FC_6H_4	−60	24	88	99
4	**1g**	3-ClC_6H_4	−60	96	74	99
5	**1h**	4-ClC_6H_4	−60	48	63	99
6	**1i**	3-BrC_6H_4	−60	24	84	99
7	**1j**	3-$CF_3C_6H_4$	−60	24	80	99
8[a]	**1k**	3-$MeOC_6H_4$	−30	168	62	98
9[a]	**1l**	3-PhC_6H_4	−60	72	85	99
10	**1m**	1-Naphthyl	−60	144	71	91
11	**1n**	2-Naphthyl	−60	168	63	96
12	**1o**	2-Furyl	−60	168	70	99
13[a]	**1p**	4-$ClC_6H_4CH{=}CH$	10	168	64	86
14[b]	**1d**	Ph	−60	24	89	99

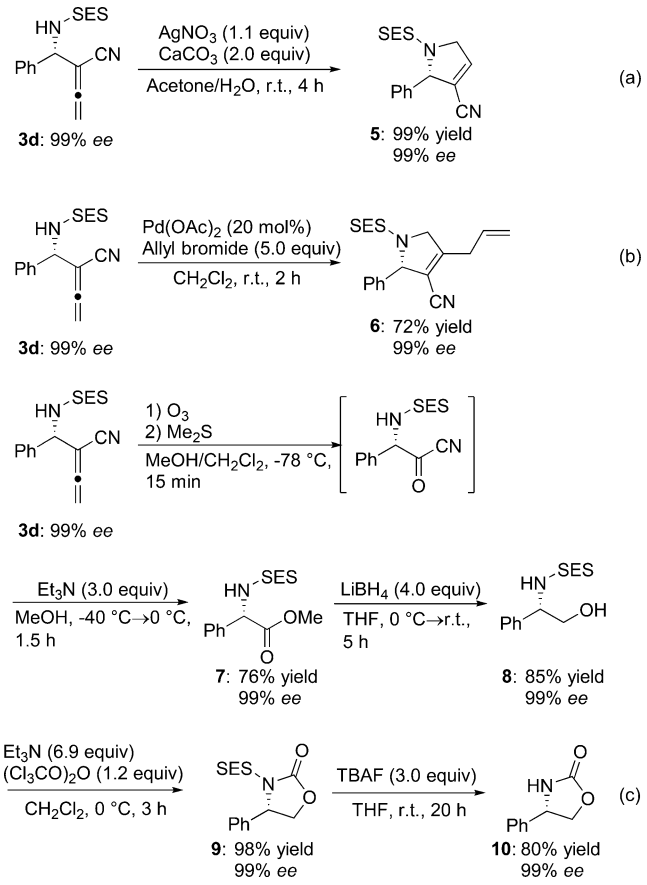
[a] The reaction was carried out using 5 mol % of **4d** and Ag (acac). [b] 1.0 g of **1d** was used.

tron-donating methoxy group showed high enantioselectivity but moderate yield (entry 8). The reaction with biphenyl imine **1l** also gave product **3l** in 85 % yield with 99 % *ee* (entry 9). Naphthyl and a heteroatom containing imines **1m–o** also gave products **3m–o** with high enantioselectivity (entries 10–12). The reaction of conjugated imine **1p** was tolerated in this reaction condition and gave product **3p** with good stereoselectivity (entry 13). To test the scalability, a gram-scale reaction was performed using 2 mol % of the catalyst **4d** (entry 14). The reaction of **1d** (1.0 g) with **2a** proceeded to give the product **3d** in 89 % yield with 99 % *ee*. Furthermore, the reaction of 3.0 equiv of racemic terminal ethyl-substituted allenylnitrile **2b** with imine **1d** gave a diastereomer mixture of product **3q** in good yield with high enantioselectivity (Scheme 1).[12] To the best of our knowledge, these results are first examples of the enantioselective reaction of allenylnitriles with imines.



Scheme 1. Reaction of racemic terminal ethyl-substituted allenylnitrile **2b** with imine **1d** using **4d**–Ag(acac) catalyst.

We next examined the transformation of α-vinylidene-β-aminonitrile **3d**. The reaction of **3d** using silver(I) nitrate and calcium carbonate in acetone/water gave the intramolecular cyclization product **5** in high yield without the loss of enantiopurity (Scheme 2a).[13] Palladium acetate catalyzed



Scheme 2. Transformation of α-vinylidene-β-aminonitriles to chiral 2,5-dihydro-1*H*-pyrroles **5**, **6** and oxazolidinone **10**.

the coupling-cyclization of **3d** with allyl bromide, and afforded product **6** in moderate yield without racemization (Scheme 2b).[14] Ozonolysis of **3d** gave acyl cyanide,[15] which was directly converted into amino acid methyl ester **7** using MeOH and Et_3N.[16] The reduction of **7** with $LiBH_4$ afforded amino alcohol **8**,[17] which was cyclized to oxazolidinone **9**.[18] Cleavage of the SES group from **9** using TBAF gave **10** without any loss of enantiopurity (Scheme 2c). The absolute configuration of **10** was determined as (*S*), based on the value of the specific rotation from a previous paper.[19]

The assumed catalytic cycle for the reaction of allenylnitrile with imines is shown in Figure 2. The addition of Ag(acac) to palladium complex **4** evokes the exchange reaction of bromide in **4** to acetylacetonate (complex **A**). Coordination of the palladium in complex **A** to the cyano

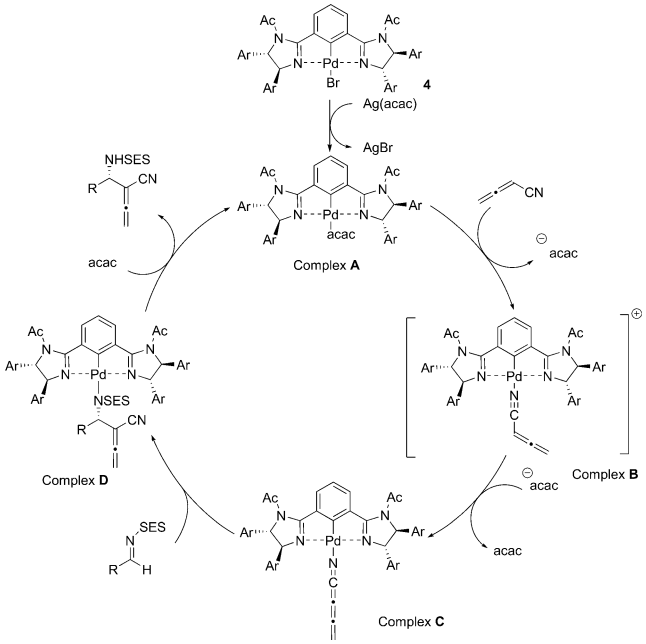
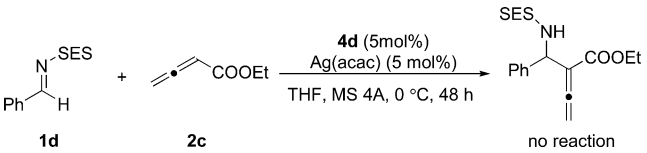


Figure 2. Proposed reaction cycle of the reaction of allenylnitrile with imines using **4**–Ag^{I}.

group in allenylnitrile affords cationic complex **B**, which was observed by ESI-Mass analysis of the mixture of **4d**, Ag(acac) and allenylnitrile in a 1:1:1 ratio (cation mode, calcd for $C_{56}H_{60}N_5O_2Pd$: 940.4, found: 940.3, see the Supporting Information). Complex **C** then reacts with *N*-SES imines to give complex **D**, which subsequently undergoes protonation and decomplexation, resulting in products **3** and regenerated complex **A**.[20]

In order to clarify the activation of allenylnitrile by palladium catalyst, the reaction of allenylester **2c** with **1d** using the **4d** was examined (Scheme 3). However, the reaction of allenylester **2c** with **1d** using **4d**–Ag(acac) catalyst did not give any products. This reactivity is in sharp contrast to the reaction of **2a** with **1d** using **4d**–Ag(acac). This result implied that the palladium pincer complex selectively coordinates and activates the cyano group in **2a**.



Scheme 3. Reaction of allenylester **2c** with imine **1d** using **4d**–Ag.

We examined the optimization of the structure of complex **4d** and allenylnitrile **2a** using the Gaussian09[21] B3LYP/LANL2DZ method (Figure 3). The optimization results

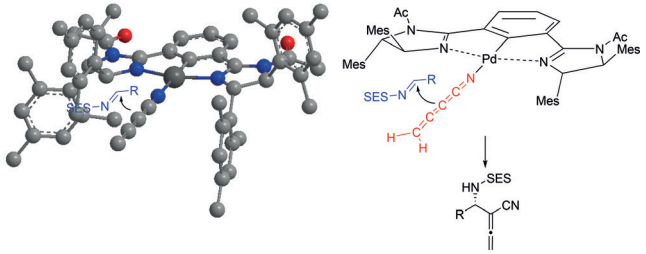


Figure 3. The optimized structure of the complex and the proposed transition state for the reaction of allenylnitrile with an imine using **4d**.

showed that the cumulene-type intermediate and nitrogen in allenylnitrile coordinate the palladium cation. Based on the calculation result and the absolute configuration of products, the assumed transition state for the reaction of palladium cumulene-type intermediate with imines using **4d** is depicted in Figure 3.

Avoiding steric repulsion between the substituent on imine and the mesityl group in **4d**, the imine approaches the cumulene-type intermediate of allenylnitrile to give the (*S*)-isomer.

In conclusion, we developed the first highly enantioselective reaction of allenylnitrile with imines using chiral phebim-Pd^{II} catalyst. Various imines can be applicable in the process. This process offers a simple and efficient synthetic route for α-vinylidene-β-aminonitriles and their derivatives. Further studies are in progress to determine the potential of these catalytic systems to other processes.

Acknowledgements

This work was partly supported by a Grant-in-Aid for Scientific Research from the MEXT (Japan) and Tokyo Ohka Foundation.

Conflict of interest

The authors declare no conflict of interest.

Keywords: allenyl compounds · asymmetric synthesis · Lewis acids · pincer complex

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 8677–8680
Angew. Chem. **2017**, *129*, 8803–8806

[1] a) A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; *Angew. Chem.* **2004**, *116*, 1216; b) N. Krause, A. Hoffmann-Röder in *Modern Allene Chemistry* (Eds.: N. Krause, A. Hoffmann-Röder), Wiley-VCH, Weinheim, **2004**, p. 997.

[2] For reviews, see: a) D. R. Taylor, *Chem. Rev.* **1967**, *67*, 317; b) D. J. Pasto, *Tetrahedron* **1984**, *40*, 2805; c) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102; d) P. Rivera-Fuentes, F. Diederich, *Angew. Chem. Int. Ed.* **2012**, *51*, 2818; *Angew. Chem.* **2012**, *124*, 2872; e) S. Yu, S. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 3074; *Angew. Chem.* **2012**, *124*, 3128; f) R. K. Neff, D. E. Frantz, *Tetrahedron* **2015**, *71*, 7. Selected examples, see: g) X. Pu, X. Qi, J. M. Ready, *J. Am. Chem. Soc.* **2009**, *131*, 10364; h) J. R. Zbieg, E. L. McInturff, J. C. Leung, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 1141; i) C. S. Adams, L. A. Boralsky, I. A. Guzei, J. M. Schomaker, *J. Am. Chem. Soc.* **2012**, *134*, 10807; j) F. Grillet, K. M. Brummond, *J. Org. Chem.* **2013**, *78*, 3737; k) T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2013**, *113*, 4862.

[3] For reviews, see: a) H. Ohno, Y. Nagaoka, K. Tomioka in *Modern Allene Chemistry* (Eds.: N. Krause, A. Hoffmann-Röder), Wiley-VCH, Weinheim, **2004**, p. 141; b) M. Ogasawara, *Tetrahedron: Asymmetry* **2009**, *20*, 259; c) D. Tejedor, G. Méndez-Abt, L. Cotos, F. García-Tellado, *Chem. Soc. Rev.* **2013**, *42*, 458; d) R. K. Neff, D. E. Frantz, *ACS Catal.* **2014**, *4*, 519; e) S. Shirakawa, S. Liu, S. Kaneko, *Chem. Asian J.* **2016**, *11*, 330.

[4] a) B. J. Cowen, L. B. Saunders, S. J. Miller, *J. Am. Chem. Soc.* **2009**, *131*, 6105; b) T. Hashimoto, K. Sakata, F. Tamakuni, M. J. Dutton, K. Maruoka, *Nat. Chem.* **2013**, *5*, 240; c) C. T. Mbofana, S. J. Miller, *J. Am. Chem. Soc.* **2014**, *136*, 3285; d) Enantioselective intermolecular cycloaddition reaction of allenoates with imines: L. Jean, A. Marinetti, *Tetrahedron Lett.* **2006**, *47*, 2141; e) A. Scherer, J. A. Gladysz, *Tetrahedron Lett.* **2006**, *47*, 6335; f) N. Fleury-Brégeot, L. Jean, P. Retailleau, A. Marinetti, *Tetrahedron* **2007**, *63*, 11920; g) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660; h) I. P. Andrews, O. Kwon, *Chem. Sci.* **2012**, *3*, 2510; i) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2012**, *51*, 767; *Angew. Chem.* **2012**, *124*, 791; j) C. E. Henry, Q. Xu, Y. C. Fan, T. J. Martin, L. Belding, T. Dudding, O. Kwon, *J. Am. Chem. Soc.* **2014**, *136*, 11890; k) Enantioselective intermolecular cycloaddition reaction of allenoates with imines: J.-B. Denis, G. Masson, P. Retailleau, J. Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5356; *Angew. Chem.* **2011**, *123*, 5468; l) X. Han, W.-L. Chan, W. Yao, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2016**, *55*, 6492; *Angew. Chem.* **2016**, *128*, 6602; m) M. G. Sankar, M. Garcia-Castro, C. Golz, C. Strohmann, K. Kumar, *RSC Adv.* **2016**, *6*, 56537.

[5] For enantioselective allenylation of imines using chiral catalysts, see: a) H. Kagoshima, T. Uzawa, T. Akiyama, *Chem. Lett.* **2002**, 298; b) Y.-Y. Huang, A. Chakrabarti, N. Morita, U. Schneider, S. Kobayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 11121; *Angew. Chem.* **2011**, *123*, 11317; c) N. W. Mszar, F. Haeffner, A. H. Hoveyda, *J. Am. Chem. Soc.* **2014**, *136*, 3362; d) H. Wu, F. Haeffner, A. H. Hoveyda, *J. Am. Chem. Soc.* **2014**, *136*, 3780; e) J. D. Sieber, V. V. Angeles-Dunham, D. Chennamadhavuni, D. R. Fandrick, N. Haddad, N. Grinberg, D. Kurouski, H. Lee, J. J. Song, N. K. Yee, A. E. Mattson, C. H. Senanayake, *Adv. Synth. Catal.* **2016**, *358*, 3062.

[6] a) J. Bang, H. Kim, J. Kim, C.-M. Yu, *Org. Lett.* **2015**, *17*, 1573; b) G. Wang, X. Liu, Y. Chen, J. Yang, J. Li, L. Lin, X. Feng, *ACS Catal.* **2016**, *6*, 2482.

[7] Enantioselective reaction of allenoates with α,β-unsaturated carbonyl compounds, see: a) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988; b) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726; c) D. Wang, G.-P. Wang, Y.-L. Sun, S.-F. Zhu, Q.-L. Zhou, M. Shi, *Chem. Sci.* **2015**, *6*, 7319; d) Enantioselective reaction of allenoates with α,β-unsaturated nitriles, see: H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang, G. Zhao, *Angew. Chem. Int. Ed.* **2010**, *49*, 4467; *Angew. Chem.* **2010**, *122*, 4569; e) M. Schuler, A. Voituriez, A. Marinetti, *Tetrahedron: Asymmetry* **2010**, *21*, 1569; f) M. Gicquel, Y. Zhang, P. Aillard, P. Retailleau, A. Voituriez, A. Marinetti, *Angew. Chem. Int. Ed.* **2015**, *54*, 5470; *Angew. Chem.* **2015**, *127*, 5560.

[8] There is only one report for the enantioselective reaction of allenylnitrile with benzylidenemalononitrile, see: Ref. [7f].

[9] a) K. Hyodo, M. Kondo, Y. Funahashi, S. Nakamura, *Chem. Eur. J.* **2013**, *19*, 4128, and references therein; b) M. Kondo, N. Kobayashi, T. Hatanaka, Y. Funahashi, S. Nakamura, *Chem. Eur. J.* **2015**, *21*, 9066; c) M. Kondo, T. Nishi, T. Hatanaka, Y. Funahashi, S. Nakamura, *Angew. Chem. Int. Ed.* **2015**, *54*, 8198; *Angew. Chem.* **2015**, *127*, 8316; d) S. Nakamura, *J. Synth. Org. Chem. Jpn.* **2015**, *73*, 1062; e) M. Kondo, M. Sugimoto, S. Nakamura, *Chem. Commun.* **2016**, *52*, 13604; f) For selected examples on related recent studies for imidazoline catalysts from our group, see: S. Nakamura, M. Ohara, Y. Nakamura, N. Shibata, T. Toru, *Chem. Eur. J.* **2010**, *16*, 2360; g) M. Ohara, S. Nakamura, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 3285; h) S. Nakamura, M. Ohara, M. Koyari, M. Hayashi, K. Hyodo, N. R. Nabisaheb, Y. Funahashi, *Org. Lett.* **2014**, *16*, 4452; i) S. Nakamura, N. Matsuda, M. Ohara, *Chem. Eur. J.* **2016**, *22*, 9478.

[10] For palladium pincer complexes with bis(imidazoline)s, see: a) X.-Q. Hao, J.-F. Gong, C.-X. Du, L.-Y. Wu, Y.-J. Wu, M.-P. Song, *Tetrahedron Lett.* **2006**, *47*, 5033; b) C. Li, Q.-L. Bian, S. Xu, W.-L. Duan, *Org. Chem. Front.* **2014**, *1*, 541, and references therein.

[11] Calculated by the Gaussian 09 B3LYP/6-31G + (d,p) level.

[12] We also examined the reaction of aliphatic imines, however the reaction did not afford any products.

[13] a) D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy, T. Gallagher, *J. Chem. Soc. Chem. Commun.* **1989**, 1073; b) H. Ohno, A. Toda, Y. Miwa, T. Taga, E. Osawa, Y. Yamaoka, N. Fujii, T. Ibuka, *J. Org. Chem.* **1999**, *64*, 2992; c) Y.-Y. Huang, A. Chakrabarti, N. Morita, U. Schneider, S. Kobayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 11121; *Angew. Chem.* **2011**, *123*, 11317.

[14] a) M. O. Amombo, A. Hausherr, H.-U. Reissig, *Synlett* **1999**, 1871; b) S. Ma, F. Yu, W. Gao, *J. Org. Chem.* **2003**, *68*, 5943; c) L. Su, T.-S. Zhu, M.-H. Xu, *Org. Lett.* **2014**, *16*, 4118; See also Ref. [4a].

[15] Review for ozonolysis of allene compounds, see: R. F. Langler, R. K. Raheja, K. Schank, H. Beck, *Helv. Chim. Acta* **2001**, *84*, 1943.

[16] K. S. Yang, A. E. Nibbs, Y. E. Türkmen, V. H. Rawal, *J. Am. Chem. Soc.* **2013**, *135*, 16050; See also Ref. [4a].

[17] S. Norsikian, M. Beretta, A. Cannillo, A. Martin, P. Retailleau, J.-M. Beau, *Chem. Commun.* **2015**, *51*, 9991.

[18] D. L. Boger, G. Schüle, *J. Org. Chem.* **1998**, *63*, 6421.

[19] C. J. MacNevin, R. L. Moore, D. C. Liotta, *J. Org. Chem.* **2008**, *73*, 1264.

[20] The role of TMSOH probably assists the protonation of complex **D**. We cannot rule out the possibility of Lewis acid activation of nitrile compounds or imines by silver cation.

[21] M. J. Frisch, et al., Gaussian 09, Revision C.02, Gaussian, Inc., Wallingford, CT, **2010**.

Manuscript received: March 7, 2017
Version of record online: June 19, 2017

