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Enantioselective conjugate addition of an α,α-dithioacetonitrile with nitroalkenes using chiral bis(imidazoline)-Pd complexes

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

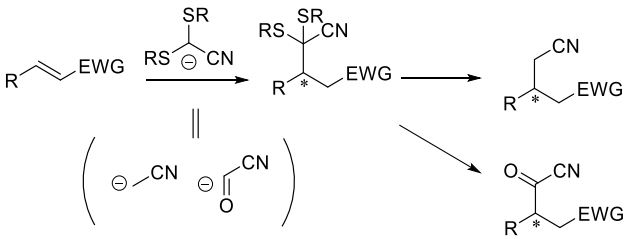
DOI: 10.1039/x0xx00000x

www.rsc.org/

Shuichi Nakamura,*[a,b] Akari Tokunaga,[a] Hikari Saito,[a] Masaru Kondo[a,b]

The enantioselective conjugate addition reaction of an α,α-dithioacetonitrile with nitroalkenes was catalysed by chiral bis(imidazoline)-palladium pincer-type complexes. The reaction was applicable to various nitroalkenes to afford products in good yield with high enantioselectivity. The obtained products can be converted to γ-lactam and biologically active rolipram.

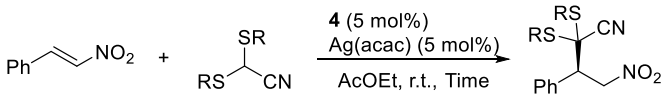
C-C bond formation reaction through the conjugate addition of nucleophiles to electron-deficient alkenes is one of the most important synthetic methods for organic compounds. Furthermore, the enantioselective version of conjugate addition has attracted considerable attention in synthetic chemistry.[1] Therefore, expanding the scope of catalytic stereoselective conjugate addition of α,α-dithioacetals, which are well known as "synthetic chameleon",[2] would be highly desirable.[3] Koga and Tomioka first reported the enantioselective reaction of α-carbanion of α,α-dithioacetals with α,β-unsaturated esters as electron-deficient alkenes using a stoichiometric amount of chiral aminoether ligand to give chiral conjugate addition products.[4] Recently, catalytic enantioselective conjugate addition reactions of 1,3-dithiane-2-thiocarboxylates with nitroalkenes and α,β-unsaturated carbonyl compounds using a cinchona alkaloid-thiourea catalyst was reported by Benaglia and Gaggero's group.[5] Despite the impressive progress achieved in this type of reaction, there is still room for developing the catalytic enantioselective conjugate addition of α,α-dithioacetals to electron-deficient alkenes.[6] On the other hand, α,α-dithioacetonitriles are also an important class of synthetic intermediate, because they can act as cyanomethyl and cyanocarbonyl anion equivalents. Recently, we reported the first highly enantioselective reaction of α,α-dithioacetonitriles with imines using palladium pincer-type complexes with 1,3-bis(imidazolin-2-yl)benzene (Phebim).[7,8] However, to the best of our knowledge, there are no reports for the enantioselective conjugate addition of α,α-dithioacetonitriles to electron-deficient alkenes. Herein our ongoing interest was extended to the catalytic enantioselective reaction of α,α-dithioacetonitriles with nitroalkenes as electron-deficient alkenes using Phebim-Pd complex (Scheme 1).[9]



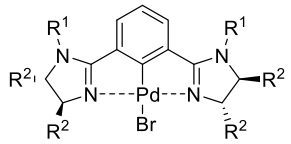
Scheme 1 Enantioselective reaction of α,α-dithioacetonitriles as cyanomethyl and cyanocarbonyl anion equivalents with electron-deficient alkenes

First, we examined the reaction of various α,α-dithioacetonitriles **2** (1.5 equiv.) with nitrostyrene **1a** using 5 mol% of chiral palladium-pincer complexes **4** and Ag(acac) at room temperature in ethyl acetate (Table 1). The reaction of **1a** with 1,3-dithiorane-2-carbonitrile **2a** using Phebim-Pd **4a** gave product **3aa** in good yield with moderate enantioselectivity (entry 1). In order to improve the yield and enantioselectivity, catalytic precursor **4b-g** having various carbonyl and sulfonyl groups on the R^1 group and 2,4,6-trimethylphenyl (mesityl) and 1-naphthyl groups on the R^2 group were examined (entries 2-7). As a result, complex **4f** bearing an acetyl group on the R^1 group and a mesityl group on the R^2 group showed good yield with high enantioselectivity (entry 6). We also examined the reaction of various α,α-dithioacetonitriles **2b-d** with **1a** using **4f**, but the reaction did not give better results than the reaction using **2a** (entries 8-10). When the reaction was carried out at a lower temperature (0 °C), enantioselectivity improved to 98% ee (entry 11).

Table 1 Enantioselective reaction of α,α-dithioacetonitriles **2a-d** with nitrostyrene **1a** using palladium complexes **4a-g**.



1a **2a**: R = -(CH2CH2)- **2b**: R = -(CH2CH2CH2)- **2c**: R = Ph **2d**: R = Et **3aa-ad**



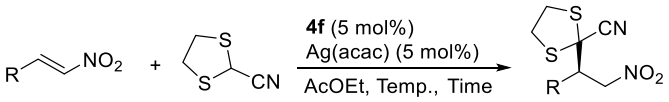
4a: R1 = PhCO, R2 = Ph
4b: R1 = CH3CO, R2 = Ph
4c: R1 = Ms, R2 = Ph
4d: R1 = Ts, R2 = Ph
4e: R1 = Ts, R2 =Mes
4f: R1 = CH3CO, R2 = Mes
4g: R1 = CH3CO, R2 = 1-Naphthyl

Entry	2	4	Time (h)	Yield (%)	Ee (%)
1	**2a**	**4a**	24	80	73
2	**2a**	**4b**	24	93	72
3	**2a**	**4c**	24	26	80
4	**2a**	**4d**	24	95	77
5	**2a**	**4e**	24	72	94
6	**2a**	**4f**	24	92	95
7	**2a**	**4g**	24	89	71
8	**2b**	**4f**	24	85	89
9	**2c**	**4f**	48	-	-
10	**2d**	**4f**	48	-	-
11[a]	**2a**	**4f**	48	99	98

[a] At 0 °C.

With optimized reaction conditions for the reaction of nitrostyrene **1a** with **2a**, we next examined the scope of nitroalkenes for this reaction (Table 2). The reaction of nitroalkenes **1b-g** bearing electron-withdrawing groups such as a fluoro, chloro, bromo, or trifluoromethyl group in the para or meta position by using **4f** gave corresponding products **3ba-ga** in high yield and enantioselectivity (entries 2-7, 77-98% yield, 95-98% ee). Electron-rich nitroalkenes **1h**,**i** having a methyl or methoxy group reacted with **2a** and afforded products **3ha,ia** with excellent enantioselectivity but in moderate yield (entries 8 and 9). Furthermore, nitroalkenes having naphthyl group **1j** or heteroaryl group **1k-m** were tolerable substrates in the reaction giving products **3ka-ma** in moderate to good yield (71-90% yield) with high enantioselectivity (94-98% ee, entries 10-13). In addition, the reaction of nitroalkenes bearing an alkyl group **1n**,**o** also gave products **3na,oa** with high enantioselectivity (entries 14 and 15). To our knowledge, these results are the first examples of the highly enantioselective reaction of α,α-dithioacetonitrile with electron-deficient alkenes.

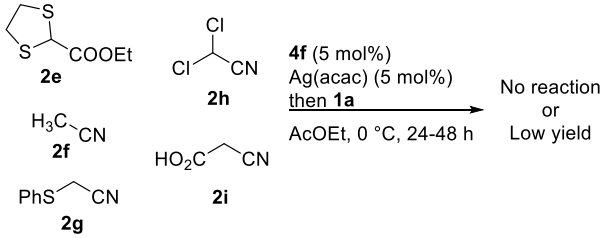
Table 2 Enantioselective reaction of **2a** with various nitroalkenes **1a-o** using **4f**.



1a-o **2a** (1.5 equiv.) **3aa-oa**

Entry	1	R	Product	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	**1a**	Ph	**3aa**	0	48	99	98
2	**1b**	4-FC6H4	**3ba**	rt	9	98	95
3	**1c**	3-FC6H4	**3ca**	rt	48	78	97
4	**1d**	4-ClC6H4	**3da**	rt	24	87	97
5	**1e**	3-ClC6H4	**3ea**	rt	24	77	98
6	**1f**	4-BrC6H4	**3fa**	0	48	80	98
7	**1g**	4-CF3C6H4	**3ga**	rt	24	86	96
8	**1h**	4-CH3C6H4	**3ha**	50	24	47	94
9	**1i**	4-MeOC6H4	**3ia**	0	72	59	98
10	**1j**	2-Naphthyl	**3ja**	rt	48	77	98
11	**1k**	2-Furyl	**3ka**	0	96	71	95
12	**1l**	3-Furyl	**3la**	rt	48	76	94
13	**1m**	2-Thienyl	**3ma**	0	72	91	97
14	**1n**	*n*Pr	**3an**	0	48	72	95
15	**1o**	*i*Bu	**3oa**	rt	24	80	96

On the other hand, the reaction of ethyl 1,3-dithiolane-2-carboxylate **2e** with nitrostyrene **1a** using **4f**-Ag(acac) did not give any product (Scheme 2). In addition, the reaction of various α-acetonitrile carbanion equivalents, such as acetonitrile (**2f**), phenylthioacetonitrile (**2g**), dichloroacetonitrile (**2h**), and cyanoacetic acid (**2i**), did not give products in high yield. These results show that the nitrile and dithiolane group in **2a** were essential in this C-C bond formation reaction.



Scheme 2 Reaction of ethyl 1,3-dithiolane-2-carboxylate **2e** or various acetonitrile carbanion equivalents **2f-i** with nitrostyrene **1a** using the **4f**-Ag system

The proposed reaction mechanism for the reaction of **2a** with nitroalkenes **1** using **4f** is depicted in Figure 1. The palladium acetylacetonate-complex (complex **A**) was formed by the addition of Ag(acac) to **4f** through the exchange reaction of bromide on **4f** to acetylacetonate. The palladium in complex **A** coordinates to the cyano group in **2a** to afford cationic complex **B**, and is deprotonated by acetylacetonate to give the palladium ketenimide complex (complex **C**). Next, the reaction of complex **C** with nitroalkenes proceeds to give complex **D**, which subsequently affords the protonation product and regenerated complex **A**. In order to clarify the proposed reaction cycle, we checked the ESI-Mass spectroscopic analysis for the mixture of **4f**, Ag(acac) and **2a**, in a 1:1:1 ratio. Complex **B** could be observed in this mixture (cation mode, calcd for $C_{56}H_{62}N_5O_2PdS_2$ as complex **B**: 1006.3, found: 1006.3, see supporting information). This result supports the proposed catalytic cycle. We also checked the retro-conjugate addition reaction of product **3aa**, in which the treatment of racemic **3aa** with **4f** and Ag(acac) did not change the enantiopurity.

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Therefore, the stereoselectivity of the reaction would be kinetically controlled.

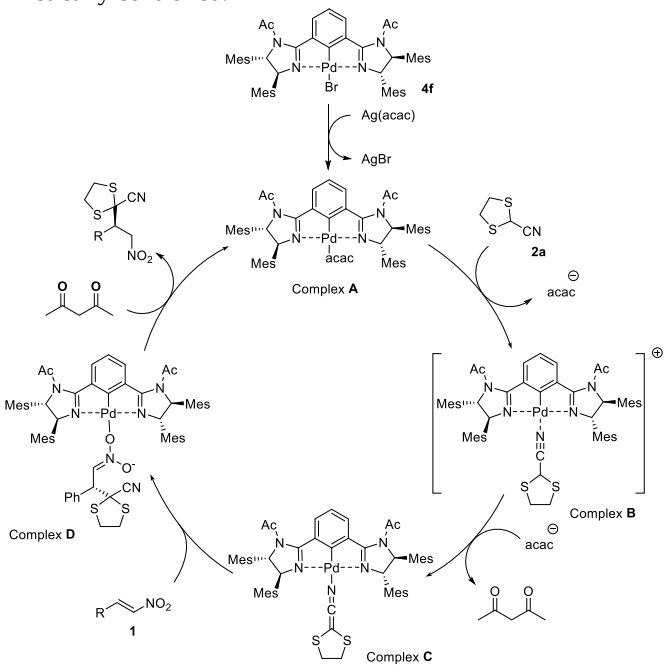


Fig. 1 Assumed reaction mechanism for the reaction of **2a** with nitroalkenes **1** using **4f**

We next examined the DFT calculation of complex **C** between **4f** and the carbanion of **2a** using a Gaussian 16[10] B3LYP/6-31G*, LANL2DZ(Pd) level (Figure 2).[11] Palladium in the complex **C** coordinated to the cyano group in **2a** to form a ketenimide structure. Natural bond orbital (NBO) analysis[12] for complex **C** shows the interaction between the two σ* orbital of the C-S bond and a p orbital of the anionic carbon for **2a**. The stabilization energies for their interaction was estimated to be 9.86 and 9.84 kcal/mol. In the case of the reaction of **2c** and **2d**, the n-σ* stabilization effects are not so large due to the flexibility of substituent on sulfur. Based on the absolute configuration of products, the proposed transition state for the enantioselective reaction of palladium ketenimide with nitroalkenes **1** is shown in Figure 2. Nitroalkenes **1** approach from the *Re*-face of the double bond avoiding steric repulsion between the mesityl group on imidazoline and nitroalkenes to afford the (*R*)-isomer of the product. The fine-tuning of substituent on chiral imidazoline group changes their transition state slightly.

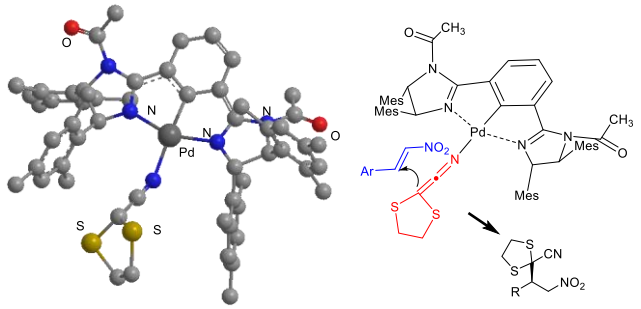
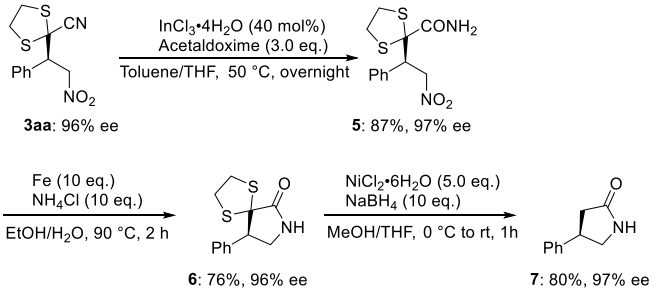


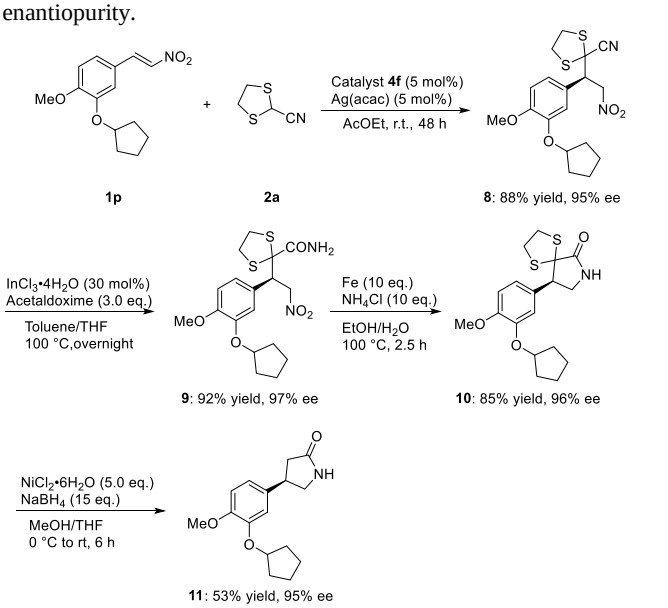
Fig. 2 DFT calculation of the complex between **4f** and **2a** using Gaussian 16 B3LYP/6-31G*, LANL2DZ(Pd) and assumed transition state for the reaction with nitroalkenes **1**. H atoms have been omitted for clarity.

We next examined the transformation of product **3aa** to useful compounds (Scheme 3). The hydrolysis of the cyano group in **3aa** using 40 mol% of $InCl_3{\cdot}4H_2O$ and 3.0 equivalent of acetaldoxime in toluene/THF afforded corresponding amide **5**.[13] Further reduction of the nitro group in **5** using iron and NH_4Cl gave cyclized lactam **6**. Reductive desulfurization of **6** using $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ afforded lactam **7** in good yield without the loss of enantiopurity.[14] The absolute configuration of **21** was assigned to an *R* isomer by comparing with the value of the specific optical rotation from a previous report.[15]



Scheme 3 Transformation of **3aa** to chiral γ-lactam **7**

This procedure can be applied to the synthesis of biologically active rolipram, which is an anti-inflammatory drug and a family member of γ-aminobutyric acid (GABA) derivatives.[16] Furthermore, rolipram is known to be a possible antidepressant and has been reported to have immunosuppressive, and antitumor effects.[17] The reaction of **2a** with **1p** using 5 mol% of **4f** afforded conjugate addition product **8** in high yield with high enantioselectivity (Scheme 4, 88%, 95% ee). Then, the reaction using $InCl_3{\cdot}4H_2O$ and acetaldoxime gave amide **9**, whose nitro group can be reduced to give γ-lactam **10**. The reductive desulfurization of **10** afforded (*R*)-rolipram **11** without the loss of enantiopurity.



Scheme 4 Synthesis of optically active (*R*)-rolipram **11**

Conclusions

The first highly enantioselective reaction of α,α-dithioacetonitriles with nitroalkenes using Phebim-palladium complexes was developed. The reaction is applicable to various nitroalkenes. The obtained product was converted to γ-lactam and (*R*)-rolipram. Further experiments are in progress to study the application of the bis(imidazoline)-palladium pincer complex to other reactions.

This work was partly supported by the Hibi Science Foundation.

Notes and references

[a]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
[b]Frontier Research Institute for Material Science, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

1 For reviews, see: (a) Catalytic Asymmetric Conjugate Reactions, (Ed.: A. Córdova), Wiley-VCH, New York, 2010; (b) A. Alexakis, J.-E. Bäckvall, N. Krause, O. Pmies, M. Diéguez, *Chem. Rev.* 2008, **108**, 2796; (c) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* 2008, **108**, 2824; (d) K. Zheng, X. Liu, X. Feng, *Chem. Rev.* 2018, **118**, 7586.

2 For reviews, see: (a) P. C. B. Page, M. B. van Niel, J. C. Prodger, *Tetrahedron* 1989, **45**, 7643; (b) T.-Y Luh, C.-F. Lee, *Eur. J. Org. Chem.* 2005, 3875. See also: (c) S. Saulnier, M. Ciardi, V. Lopez-Carrillo, A. Gualandi, P. G. Cozzi, *Chem. Eur. J.* 2015, **21**, 13689.

3 For reviews on 1,3-dithianes in natural product synthesis, see: (a) M. Yus, C. Nájera, F. Foubelo, *Tetrahedron* 2003, **59**, 6147; (b) A. B. Smith III, C. M. Adams, *Acc. Chem. Res.* 2004, **37**, 365.

4 K. Tomioka, M. Sudani, Y. Shinmi, K. Koga, *Chem. Lett.* 1985, 329.

5 (a) E. Massolo, M. Benaglia, A. Genoni, R. Annunziata, G. Celentano, N. Gaggero, *Org. Biomol. Chem.* 2015, **13**, 5591; (b) E. Massolo, D. Brenna, F. Cozzi, L. Raimondi, N. Gaggero, M. Benaglia, *Synlett* 2016, **27**, 2716.

6 Terada and co-workers reported the catalytic enantioselective reaction of 2-alkoxycarbonyl-1,3-dithiane with imines using chiral bis(guanidino)iminophosphorane, see: (a) A. Kondoh, M. Oishi, T. Takeda, M. Terada, *Angew. Chem. Int. Ed.* 2015, **54**, 15836. For enantioselective reaction of acyl anion equivalent with some electrophiles, see: (b) S. Nakamura, Y. Ito, L. Wang, T. Toru, *J. Org. Chem.* 2004, **69**, 1581; (c) L. Wang, S. Nakamura, Y. Ito, T. Toru, *Tetrahedron: Asymmetry* 2004, **15**, 3059; (d) L. Wang, S. Nakamura, T. Toru, *Org. Biomol. Chem.* 2004, **2**, 2168. For enantioselective reaction of α-lithiated 1,3-dithiane to aldehydes using stoichiometric amount of (-)-sparteine, see; (e) J. Kang. J. I. Kim, J. H. Lee, *Bull. Korean Chem. Soc.* 1994, **15**, 865. For enantioselective reaction of *N,O*-acetals with aldehydes using (-)-sparteine, see; (f) N. Kise, T. Urai, J. Yoshida, *Tetrahedron: Asymmetry*, 1998, **9**, 3125. For the catalytic enantioselective allylic substitution reaction of 1,3-dithianes, see: (g) K. Yao, D. Liu, Q. Yuan, T. Imamoto, Y. Liu, W. Zhang, *Org. Lett.* 2016, **18**, 6296.

7 (a) M. Kondo, H. Saito, S. Nakamura, *Chem. Commun.* 2017, **53**, 6776. For related recent studies on bis(imidazoline)-palladium pincer-type complexes from our group, see: (b) S. Nakamura, K. Hyodo, Y. Nakamura, N. Shibata, T. Toru, *Adv. Synth. Catal* 2008, **350**, 1443; (c) K. Hyodo, S. Nakamura, K. Tsuji, T. Ogawa, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* 2011, **353**, 3385; (d) K. Hyodo, S. Nakamura, N. Shibata, *Angew. Chem. Int. Ed.* 2012, **51**, 10337; (e) K. Hyodo, M. Kondo, Y. Funahashi, S. Nakamura, *Chem. Eur. J.* 2013, **19**, 4128; (f) M. Kondo, N. Kobayashi, T. Hatanaka, Y. Funahashi, S. Nakamura, *Chem. Eur. J.* 2015, **21**, 9066; (g) M. Kondo, T. Nishi, T. Hatanaka, Y. Funahashi, S. Nakamura, *Angew. Chem. Int. Ed.* 2015, **54**, 8198; (h) S. Nakamura, *J. Synth. Org. Chem. Jpn.* 2015, **73**, 1062; (i) M. Kondo, M. Sugimoto, S. Nakamura, *Chem. Commun.* 2016, ***52***, 13604; (j) M. Kondo, M. Omori, T. Hatanaka, Y. Funahashi, S. Nakamura, *Angew. Chem. Int. Ed.* 2017, **56**, 8677. For related recent studies for imidazoline catalysts from our group, see: (k) S. Nakamura, K. Hyodo, M. Nakamura, D. Nakane, H. Masuda, *Chem. Eur. J.* 2013, **19**, 7304; (l) M. Ohara, Y. Hara, T. Ohnuki, S. Nakamura, *Chem. Eur. J.* 2014, **20**, 8848; (m) S. Nakamura, M. Ohara, M. Koyari, M. Hayashi, K. Hyodo, N. R. Nabisaheb, Y. Funahashi, *Org. Lett.* 2014, **16**, 4452; (n) S. Nakamura, N. Matsuda, M. Ohara, *Chem. Eur. J.* 2016, **22**, 9478; (q) S. Nakamura, D. Hayama, *Angew. Chem. Int. Ed.* 2017, **56**, 8785; (o) S. Nakamura, T. Furukawa, T. Hatanaka, Y. Funahashi, *Chem. Commun.*, 2018, **54**, 3811.

8 Recent reviews for the palladium-catalysed C-C bond formation, see; a) G. Albano, L. A. Aronica, *Eur. J. Org. Chem.* 2017, **2017**, 7204; b) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* 2017, **117**, 8754: c) D. Roy, Y. Uozumi, *Adv. Synth. Catal.* 2018, **360**, 602; d) G. Albano, L. A. Aronica, *Synthesis* 2018, **50**, 1209.

9 For selected examples of asymmetric conjugate addition reaction of α-cyano carbanion with nitroalkenes, see: (a) T. Okino, Y. Hoashi, T. Furukawa, X. N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* 2005 , **127**, 119; (b) H. M. Guo, J. G. Li, G. R. Qu, X. M. Zhang, W. C. Yuan, *Chirality* 2011, **23**, 514; (c) Z. Y. Du, W. Y. Siau, J. Wang, *Tetrahedron Lett.* 2011, **52**,6137; (d) Y. Gao, W. Yang, D. M. Du, *Tetrahedron: Asymmetry* 2012, **23**, 339; (e) T. Arai, I. Oka, T. Morihata, A. Awata, H. Masu, *Chem. Eur. J.* 2013, **19**, 1554; (f) S. Chen, Q. Lou, Y. Ding, S. Zhang, W. Hu, J. Zhao, *Adv. Synth. Catal.* 2015, **357** ,2437; (g) J. Feng, X. Yuan, W. Luo, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* 2016, **22**, 15650; (h) R. S. Tukhvatshin, A. S. Kucherenko, Y. V. Nelyubina, S. G. Zlotin, *ACS Catal.* 2017, **7**, 2981. Selected examples for enantioselective conjugate addition of α-cyano carbanions with other electron-deficient alkenes, see; (i) Y. Kawato, N. Takahashi, N. Kumagai, M. Shibasaki, *Org. Lett.* 2010, **12**, 1484; (j) J. Yao, X. Liu, P. He, Y. Zhu, X. Lian, L. Lin, X. Feng, *Chem. Eur. J.* 2013, **19**, 16424 and references therein. (k) M. B. Cid, S. Duce, S. Morales, E. Rodrigo, J. L. García Ruano, *Org. Lett.* 2010, **12**, 358.

10 E. S. Kim, H. S. Lee, S. H. Kim, J. N. Kim, *Tetrahedron Lett.* 2010, **51**, 1589.

11 J. M. Khurana, D. Magoo, *Synth. Commun.* 2010, **40**, 2908.

12 H. Jin, S. T. Kim, G.-S. Hwang, D. H. Ryu, *J. Org. Chem.* 2016, **81**, 3263.

13 R. L. Macdonald, R. W. Olsen, *Annu. Rev. Neurosci.* 1994. **17**, 569.

14 (a) N. Sommer, P.-A. Löschmann, G.H. Northoff, M. Weller, A. Steinbrecher, J. P. Steinbach, R. Lichtenfels, R. Meyermann, A. Riethmüller, A. Fontana, J. Dichgans, R. Martin, *Nature Med.* 1995, **1**, 24, (b) H. Wachtel, *Neuropharmacology*, 1983, **22**, 267; (c) J. Semmler, H. Wachtel, S. Endres, *Int. J. Immunopharmacology* 1993, **15**, 409.

15 M. J. Frisch and co-workers, Gaussian 16, Revision B.01, Gaussian, Inc., Wallingford CT, 2016.

16 For B3LYP, see: (a) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648. For LANL2DZ, see: (b) T. H. Dunning, P. J. Hay, *Modern Theoretical Chemistry*, Plenum, New York, 1977, vol. 3; (c) P. J. Hay, W. R. Wadt, *J. Chem. Phys.*, 1985, **82**, 270; (d) P. J. Hay, W. R. Wadt, *J. Chem. Phys.*, 1985, **82**, 299.

17 NBO Version 3.1, (a) E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold. See also: (b) A. E. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.* 1985, **83**, 735; (c). A. E. Reed, R. B. Weinstock, Weinhold, *Chem. Rev.* 1988, **88**, 899.