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Asymmetric Cyclizative Dimerization of (*ortho*-Alkynyl Phenyl) (Methoxymethyl) Sulfides with Palladium(II) Bisoxazoline Catalyst

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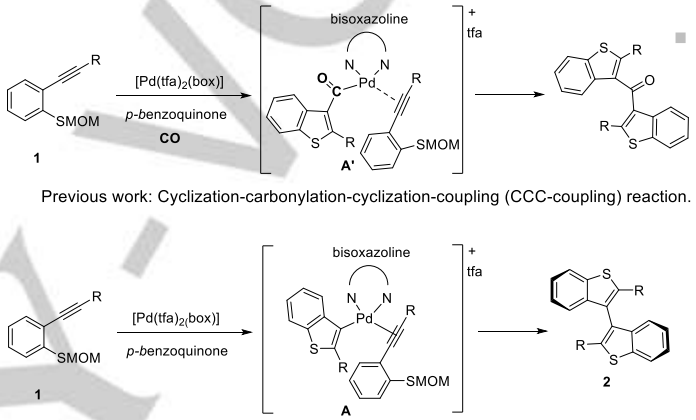
Dedicated to Professor Dr. Kiyoshi Sakai on the occasion of his 88th birthday

Abstract: The first example of an asymmetric cyclizative dimerization of (*ortho*-alkynylphenyl) (methoxymethyl) sulfides with a palladium(II) bisoxazoline (box) catalyst has been developed. The box ligand enhances the alkynophilicity of benzothienyl palladium(II) intermediate **A** and thus promotes coordination of the second alkyne substrate, leading to the dimerization. The characteristic properties of the box ligand were supported by density functional theory (DFT) calculations of the intermediate. Axially chiral bibenzothiophenes were obtained in good yields with good enantioselectivities.

Axially chiral biaryl scaffolds are important structural motifs in natural products, pharmaceuticals, functional materials, and chiral ligands.[1] Although a number of synthetic strategies have been developed, the catalytic asymmetric synthesis of axially chiral C-C bonded bi-heteroaryls is still challenging.[2] Benzothiophenes are present in several drug candidates,[3] and are widespread in materials chemistry.[4] Among them, bibenzothiophenes are also an important class of compounds in functional materials[5a,b,g,j-n] and ligands.[5h,i] However, conventional methods for the synthesis of axially chiral bibenzothiophenes have been restricted to the optical resolution of racemates and diastereselective Stille coupling reactions using chiral auxiliaries.[5g-n] Cyclizative dimerization of nucleophile-bearing alkynes is a synthetically efficient transformation for the synthesis of bi-heteroaryls, because the construction of two heteroaryls and the coupling reaction occur in a one-step procedure.[6,7] A few examples of cyclizative dimerization of alkynyl ketones,[6a] *o*-alkynylanilines,[6i,l,m,o] *o*-alkynylphenols[6e] and homopropargylic amines[6p] have been reported, affording bifurans, bisindoles, bibenzofurans and bipyrroles in good to low yields in racemic form. If the cyclizative dimerization could be expanded to the synthesis of axially chiral biaryls, the process would be more valuable.

Previously, we reported the cyclization-carbonylation-cyclization-coupling reaction (CCC-coupling reaction) of (*o*-alkynylphenyl) (methoxymethyl) sulfides **1** catalyzed by palladium(II) bisoxazoline (box) complexes (Scheme 1, previous work).[8b] Symmetrical ketones bearing two benzothiophenes were obtained in a one-step procedure. We believe that the box ligand enhances the alkynophilicity of the acyl palladium intermediate **A'**,[8] and thus promotes coordination of the second



Scheme 1. Previous work and this work.

triple bond, leading to the dimerization. If this characteristic property of the box ligand could be applied to the benzothienyl palladium intermediate **A**, enantioselective cyclizative dimerization of **1** can be realized (Scheme 1, this work). Consequently, we report herein the first example of the palladium(II) box complex catalyzed asymmetric cyclizative dimerization of (*ortho*-alkynylphenyl) (methoxymethyl) sulfides **1**.

Initially, we screened several kinds of bidentate ligands such as diamine **L1**, phosphine **L2**, sulfoxide **L3**, phox **L4**, bipyridine **L5** and box **L6** for the cyclizative dimerization of **1a**[9] (Table 1, entries 1-6). Interestingly, *N*-coordinate ligands bearing C=N **L5** and **L6** were effective for this reaction, affording dimer **2a** (41-54%) along with **3a** (26-32%) (entries 5 and 6). Next, optically active box analogues **L7**-**L12** were tested in the reaction (entries 7-13). Higher reaction temperature caused an increased yield of the monomer **3a** (entries 7 and 8). Among them, **L11** and **L12** gave good enantioselectivities, but not satisfactory yields. Although we investigated the protecting groups and counter ions of palladium, better results could not be obtained.[10] The use of increased amounts of catalyst (10-14 mol%) gave good yields and enantioselectivities (entries 14 and 15). Recently, we reported the CCC-coupling reaction of **1** using molecular oxygen as the terminal oxidant.[8e] Thus, we investigated the reaction of **1a** using the [Pd(**L11**)(tfa)$_2$] (14 mol%) / *p*-benzoquinone (10 mol%) / $CuCl_2$ (10 mol%) catalytic system under an oxygen atmosphere (balloon) (Table 1, entry 16). Although **2a** was obtained in 74% yield (84% ee), the reaction time was quite long.

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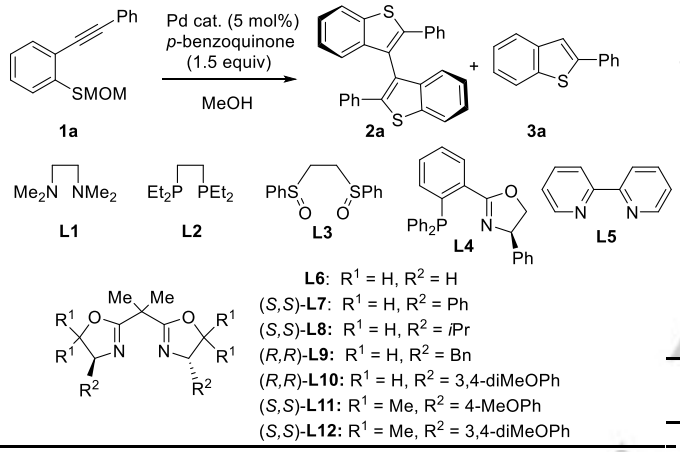
With the optimal conditions in hand, we investigated the substrate scope (Table 2). Both aryl-substituted alkynes **1a**-**1c** and alkyl-substituted alkynes **1d**, **1e** gave good yields and high enantioselectivities (entries 1-5). A thienyl group was well tolerated (entry 6). The reaction of **1g**-**1n** bearing additional substituents (R^2 and R^3) provided the desired products in good yields and enantioselectivities (entries 7-14). Introduction of a Me group as a substituent in the R^2 position shortened the reaction time (entries 7-11). On the other hand, halogen substituents slowed down the reaction (entries 15-17). The products **2o**-**2q** were obtained in low yields but good enantioselectivities, along with benzothiophenes **3o**-**3q** (5-18%) and recovery of starting materials (15-65%). Interestingly, introduction of a methyl group (R^2) into the substrates **1r** and **1s** improved the reaction, producing **2r** and **2s** in good yields and enantioselectivities (entries 18 and 19). The absolute configurations of **2a** and **2q** were determined by X-ray crystallographic analysis.[10]

Table 1. Optimization of the reaction conditions.

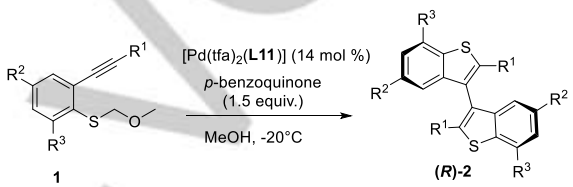


L6: R^1 = H, R^2 = H
(*S*,*S*)-**L7**: R^1 = H, R^2 = Ph
(*S*,*S*)-**L8**: R^1 = H, R^2 = *i*Pr
(*R*,*R*)-**L9**: R^1 = H, R^2 = Bn
(*R*,*R*)-**L10**: R^1 = H, R^2 = 3,4-diMeOPh
(*S*,*S*)-**L11**: R^1 = Me, R^2 = 4-MeOPh
(*S*,*S*)-**L12**: R^1 = Me, R^2 = 3,4-diMeOPh

Entry	Catalyst	Conditions	Yield % of **2a** (ee %)	Yield % of **3a**
1[a]	$Pd(tfa)_2$ / **L1**	0ºC, 3days	-	7
2	$Pd(tfa)_2$ / **L2**	0ºC, 3days	-	82
3	$Pd(tfa)_2$ / **L3**	0ºC, 3days	-	87
4	$Pd(tfa)_2$ / **L4**	0ºC, 3days	trace	74
5	$PdCl_2$ / **L5**[b]	0ºC, 3days	41	32
6	$Pd(tfa)_2$ / **L6**	0ºC, 4days	54	26
7	$Pd(tfa)_2$ / **L7**	5ºC, 3days	64 (46)	22
8	$Pd(tfa)_2$ / **L7**	-20ºC ~ -10ºC, 5days	85 (56)	6
9	$Pd(tfa)_2$ / **L8**	5ºC, 4days	24 (48)	66
10	$Pd(tfa)_2$ / **L9**	5ºC, 2days	40 (-43)	45
11	$Pd(tfa)_2$ / **L10**	-20ºC, 5days	73 (-63)	5
12	$Pd(tfa)_2$ / **L11**	-20ºC, 4days	61 (87)	7
13	$Pd(tfa)_2$ / **L12**	-20ºC ~ -10ºC, 4days	68 (91)	6
14[c]	$Pd(tfa)_2$ / **L11**	-20ºC, 4days	78 (90)	5
15[d]	$Pd(tfa)_2$ / **L11**	-20ºC , 3days	81 (90)	5
16[d,e]	$Pd(tfa)_2$ / **L11**	-5ºC ~ -0ºC, 7days	74 (84)	16

[a] Recovery 75%. [b] Commercially available complex was employed. [c] [Pd $(tfa)_2$(**L11**)] (10 mol%). [d] [Pd$(tfa)_2$(**L11**)] (14 mol%), [e] *p*-benzoquinone (10 mol%), $CuCl_2$ (10 mol%), O_2 balloon.

Table 2. Substrate scope.



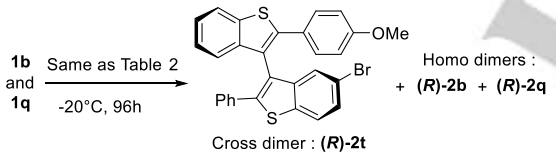
Entry	SM	R^1	R^2	R^3	Time (h)	Yield % (ee %)
1	**1a**	Ph	H	H	72	81 (90)
2	**1b**	4-MeOPh	H	H	96	86 (84)
3	**1c**	4-MePh	H	H	96	90 (85)
4	**1d**	Phenethyl	H	H	96	79 (98)
5	**1e**	Cyclopropyl	H	H	72	83 (90)
6	**1f**	3-Thienyl	H	H	96	90 (85)
7	**1g**	Ph	Me	H	24	90 (93)
8	**1h**	4-MeOPh	Me	H	16	91 (88)
9	**1i**	3-Thienyl	Me	H	48	92 (85)
10	**1j**	4-*t*BuPh	Me	H	17	92 (86)
11	**1k**	Cyclopropyl	Me	H	16	90 (87)
12	**1l**	Phenethyl	Me	H	72	83 (98)
13	**1m**	Ph	Me	Me	42	95 (82)
14	**1n**	Ph	H	Me	96	88 (86)
15[a]	**1o**	4-BrPh	H	H	96	47 (91)
16[b]	**1p**	4-ClPh	H	H	96	47 (92)
17[c]	**1q**	Ph	Br	H	96	25 (82)
18	**1r**	4-BrPh	Me	H	96	95 (93)
19	**1s**	4-ClPh	Me	H	96	92 (95)

[a] **3o** (9%), recovery (24%). [b] **3p** (18%), recovery (15%). [c] **3q** (5%), recovery (60%).

To gain mechanistic insights into this transformation, we conducted control experiments. When the reaction was performed under an argon atmosphere, it gave similar results to those above. When the benzothiophene **3a** was subjected to the

reaction conditions, no reaction occurred, and **3a** was recovered quantitatively, indicating that oxidative coupling of the benzothiophene **3** does not occur. In our previous work, the CCC-coupling reaction of **1o** and **1p** proceeded well, affording the corresponding ketones bearing two benzothiophene rings in good yields (Scheme 1). [8b,10] We wondered why the present reactions of **1o**-**1q** were slow (Table 2, entries 15-17) given that the reaction conditions of the CCC-coupling reaction were almost the same as that of the present reaction with the exception of the CO atmosphere. Thus, a crossover experiment was performed using **1b** and **1q** as substrates (Table 3). The reaction of a 1 : 1 mixture of **1b** and **1q** afforded three kinds of dimers: **2t** (cross: 37% yield), **2b** (homo: 42% yield) and **2q** (homo: 27% yield). Compared with the results of entry 17 (Table 2), the conversion of **1q** was slightly increased (Table 3, entry 1). Moreover, the use of a 2 : 1 (**1b** : **1q**) mixture of substrates gave the cross coupling product **2t** in 75% yield with 88% ee. Eventually, 80% of **1q** was converted to the dimers (Table 3, entry 2). In these reactions, two kinds of benzothienyl palladium complexes **Bb** and **Bq** should be produced (Figure 1). In the case of the complex **Bb**, coordination of the triple bond of the second substrate induces the second cyclization leading to the dimers **2t** and **2b**. On the other hand, coordination of a second substrate **1q** to the complex **Bq** may be unfavorable. These results suggest that electronic effects of the initially constructed benzothiophene moiety in the intermediates **Bb** and **Bq** play an important role in the coordination of the second substrate (and second cyclization).

Table 3. Crossover experiment.



Entry	Ratio of **1b** : **1q**	Yield % of **2t** (ee %)	Yield % of **2b** (ee %)	Yield % of **2q** (ee %)
1	1 : 1	37 (91)	42 (77)	27 (94)
2	2 : 1	75[a] (88)	48 (85)	5 (94)

[a] Calculated based on **1q**.

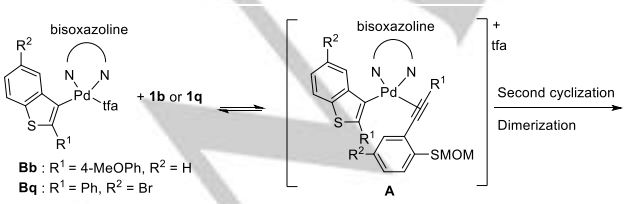
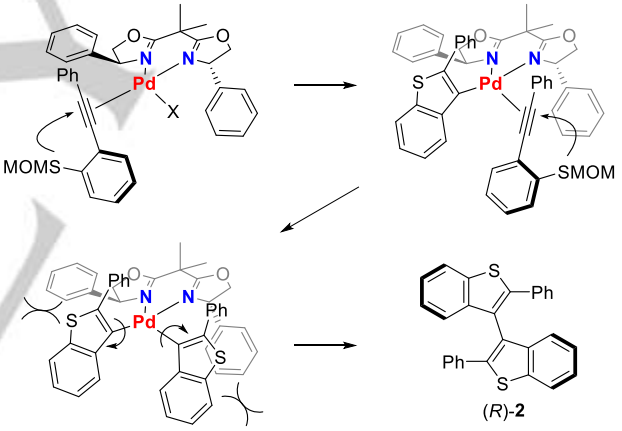


Figure 1. Coordination of the triple bond of a second substrate to the palladium intermediate **Bb** or **Bq**..

To understand the role of the box ligand, DFT calculations were performed on complexes with box and other ligands (**L1**, **L2**, **L3**, **L5** and **L6**). The calculations revealed that the affinity for the second substrate was significantly higher for the complexes with **L5** and **L6** that stabilized intermediate **A**. These results account for the formation of dimers when using **L5** and **L6**. The stabilization of intermediate **A** is ascribed to the π-conjugation of these ligands, which accept the electron density from the heteroaryl ring formed by the first substrate, which is a strong sigma donor ligand. [10]

As a working hypothesis, a tentative model for the observed stereochemical outcome of the cyclizative dimerization is proposed as shown in Scheme 2. It is assumed that: (1) the sulfur atom attacks from underneath the palladium complex to avoid the phenyl group of the box ligand, leading to intermediate **A**; (2) the phenyl group of the benzothiophene moiety is situated over the palladium, such that the second cyclization should occur from the underside of intermediate **A** to avoid steric hindrance on the upper side; and (3) the product (*R*)-**2** is formed by reductive elimination and clockwise rotations of the Pd-C (aryl) bonds, which is favored over counterclockwise rotations due to steric reasons. DFT calculations supported our working model. [10]



Scheme 2. Working model of the cyclizative dimerization.

In conclusion, we have developed an asymmetric cyclizative dimerization of (*ortho*-alkynylphenyl) (methoxymethyl) sulfides with a palladium(II) bisoxazoline (box) catalyst. The construction of two benzothiophenes and the coupling reaction occurred in a one-step procedure with control of axial chirality. The products were obtained in good yields and optical purities. DFT calculations indicated that the box ligand enhances the alkynophilicity of benzothienyl palladium(II) intermediate **A** and thus promotes coordination of the second alkyne substrate, leading to the dimerization. Detailed investigations of the reaction and the extension of this process are currently underway in our laboratories.

Experimental Section

Typical experimental procedure: A solution of **1a** (76.3 mg, 0.30 mmol) and *p*-benzoquinone (48.6 mg, 0.45 mmol) in MeOH (3 mL) was cooled to -20 ºC. A MeOH solution (1 mL) of [Pd(tfa)$_2$(**L11**)] (32.7 mg, 0.042 mmol) was added to the stirred solution. The remaining complex was washed in MeOH (1 mL) twice. After stirring for 72h at -20ºC, the mixture was diluted with CH_2Cl_2 (40 mL) and washed with 3% NaOH (40 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) twice, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane / ethyl acetate (100/1) afforded dimer **2a** as colorless needles.

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Keywords: bisoxazoline • palladium •bibenzothiophene • cyclization • dimerization

[1] For reviews see: a) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J.Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384-5427; *Angew. Chem.* **2005**, *117*, 5518-5563; b) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563-639; c) D. Zhao, J. You, C. Hu, *Chem. Eur. J.* **2011**, *17*, 5466-5492; d) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009; *Angew. Chem.* **2012**, *124*, 9092-9142; e) Y. Yang, J. Lan, J. You, *Chem. Rev*. **2017**, *117*, 8787–8863.

[2] For reviews see: a) D. Zhang, Q. Wang, *Coord. Chem. Rev.* **2015**, *286*, 1-16; b) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418-3430; c) P. Loxq, E. Manoury, R. Poli, E. Deydier, A. Labande, *Coord. Chem. Rev*. **2016**, *308*, 131-190; d) K. Tanaka, *Chem. Asian J.* **2009**, *4*, 508-518; e) D. Bonne, J. Podriguez, *Chem. Commun.* **2017**, *53*, 12385-12393; For recent examples see: f) J. Zhang, A.-J. Cui, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2016**, *138,* 5242-5245; g) O. Quinonero, M. Jean, N. Vanthuyne, C. Roussel, D. Bonne,T. Constantieux, C. Bressy, X. Bugaut, J. Rodriguez, *Angew. Chem. Int. Ed*. **2016**, *55*, 1401-1405; *Angew. Chem.* **2016**, *128*, 1423-1427; h) H.-H. Zhang, C.-S. Wang, C. Li, G.-J. Mei, Y. Li, F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 116-121; *Angew. Chem.* **2017**, *129*, 122-127; i) V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne, J. Rodriguez, *J. Am. Chem. Soc.* **2017**, *139,* 2140-2143. j) Q.-J. Yao, S. Zhang, B.-B. Zhan, B.-F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 6617-6621; *Angew. Chem.* **2017**, *129*, 6717-6712; k) Y.-H. Chen, L.-W. Qi, F. Fang, B. Tan, *Angew. Chem. Int. Ed.* **2017**, *56*, 16308–16312; *Angew. Chem.* **2017**, *129*, 16526–16530; l) V. Hornillos, J. A. Carmona, A. Ros, J. Iglesias-Siggenza, J. Llpez-Serrano, R. Fernández, J. M. Lassaletta, *Angew. Chem. Int. Ed.* **2018**, *57*, 3777–3781; *Angew. Chem*. **2018**, *130*, 3839–3843; m) A. Link. C. Sparr, *Angew. Chem. Int. Ed*. **2018**, *57*, 7136–7139; *Angew. Chem*. **2018**, *130*, 7254–7257; n) Y. Liu, X. Wu, S. Li, L. Xue, C. Shan, Z. Zhao, H. Yan, *Angew. Chem. Int. Ed.* **2018**, *57*, 6491–6495; *Angew. Chem*. **2018**, *130*, 6601–6605; o) T.-R. Li, M.-M. Zhang, B.-C. Wang, L.-Q. Lu, W.-J. Xiao, *Org. Lett.* **2018**, *20*, 3237–3240; p) H. Forkosh, V. Vershinin, H. Reiss, D. Pappo, *Org. Lett.* **2018**, *20*, 2459–2463; q) S. Jia, Z. Chen, N. Zhang, Y. Tan, Y. Liu, J. Deng, H. Yan, *J. Am. Chem. Soc.* **2018**, *140,*7056-7060; r) L.-W. Oi, J.-H. Mao, J. Zhang, *Nat. Chem.* **2018**, *10*, 58-64

[3] a) K. G. Pinney, A. D. Bounds, K. M. Dingeman, V. P. Mocharla, G. R. Pettit, R. Bai, E. Hamel, *Bioorg. Med. Chem. Lett.* **1999**, *9*,1081-1086; b) C.-H. Cho, B. Neuenswander, G. H. Lushington, R. C. Larock, *J. Comb. Chem.* **2009**, *11*, 900-906; c) C.-H. Cho, B. Neuenswander, R. C. Larock, *J. Comb. Chem.* **2010**,*12*, 278-285; d) S. A. Scott, C. T. Spencer, M. C. O'Reilly, K. A. Brown, Robert R. Lavieri, C.l-H. Cho, D.-I. Jung, R. C. Larock, H. A. Brown, C. W. Lindsley, *ACS Chem. Biol.* **2015**, *10,* 421-432.

[4] a) H. Ebata, T. Izawa, E. Miyazaki, K. Takimiya, M. Ikeda, H. Kuwabara, T. Yui, *J. Am. Chem. Soc.* **2007**, *129,* 15732-15733; b) S. Zhang, X. Quao, Y. Chen, Y. Wang, R. M. Edkins, Z. Liu, H. Li, Q. Fang, *Org. Lett.* **2014**, *16*, 342–345; c) X. Liu, Y. Wang, J. Gao, L. Jiang, X. Qi, W. Hao, S. Zou, H. Zhang, H. Li, W. Hu, *Chem. Commun.* **2014**, *50*, 442-444; d) G. Schweicher, V. Lemaur, C. Niebel, C. Ruzié, Y. Diao, O. Goto, W.-Y. Lee, Y. Kim, J.-B. Arlin, J. Karpinska, A. R. Kennedy, S. R. Parkin, Y. Olivier, S. C. B. Mannsfeld, J. Cornil, Y. H. Geerts, Z. Bao, *Adv. Mater*. **2015**, *27*, 3066–3072; e) M. Matsumura, A. Muranaka, R. Kurihara, M. Kanai, K. Yoshida, N. Kakusawa, D. Hashizum, M. Uchiyama, S. Yasuike, *Tetrahedron* **2016**, *72*, 8085-8090; f) F. Chen, T. Tanaka, Y. S. Hong, T. Mori, D. Kim, A. Osuka, *Angew. Chem. Int. Ed.* **2017**, *56*, 14688–14693; *Angew. Chem.* **2017**, *129*, 14880–14885.

[5] For synthesis of racemic bibenzothiophenes, see: a) F. Sannicolò, S. Rizzo, T. Benincori, W. Kutner, K. Nowryta, J. W. Sobczak, V. Bonometti, L. Falciola, P. R. Mussini, M. Pierini, *Electrochem. Chem. Acta* **2010**, *55*, 8352–8364; b) T. Shoji, E. Shimomura, Y. Inoue, M. Maruyama, A. Yamamoto, K. Fujimori, S. Ito, M. Yasunami, N. Morita, *Heterocycles* **2013**, *87*, 303-306; c) K. Liu, F. Jia, H. Xi, Y. Li, X. Zheng, Q. Guo, B. Shen, Z. Li, *Org. Lett.* **2013**, *15*, 2026–2029; d) T. Wirtanen, M. K. Mäkelä, J. Sarfraz, P. Ihalainen, S. Hietala, M. Melchionna, J. Helaja, *Adv. Synth. Catal.* **2015**, *357*, 37183‑3726; e) A. Guta, B. L. Flynn, *Org. Lett.* **2017**, *19*, 1939–1941; f) L. Bering, F. M. Paulussen, A. P. Antonchick, *Org. Lett.* **2018**, *20*, 1978–1981; For optical resolution of racemic bibenzothiophenes, see: g) T. Benincori, E. Brenna, F. Sannicolò, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, T. Pilati, *J. Org. Chem.* **1996**, *61,* 6244–6251; h) L. F. Tietze, K. Thede, *Synlett* **2000**, 1470–1472; i) M. Mézlová, H. Petříčková, P. Maloň, V. Kozmík, J. Svoboda, *Collect. Czech. Chem. Commun.* **2003**, *68*, 1020–1038; j) F. Sannicolò, S. Arnaboldi, T. Benincori, V. Bonometti, R. Cirilli, L. Dunsch, W. Kutner, G. Longhi, P. R. Mussini, M. Panigati, M. Pierini, S. Rizzo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2623‑26275; *Angew. Chem*. **2014**, *126*, 2661‑266; k) F. Sannicolò, P. R. Mussini, T. Benincori, R. Cirilli, S. Abbate, S. Arnaboldi, S. Casolo, E. Castiglioni, G. Longhi, R.Martinazzo, M. Panigati,M. Pappini, E. Quartapelle Procopio and S. Rizzo, *Chem. Eur. J.* **2014**, *20*, 15298–15302; l) E. Q. Procopio, T. Benincori, G. Appoloni, P. R. Mussini, S. Arnaboldi, C. Carbonera, R. Cirilli, A. Cominetti, L. Longo, R. Martinazzo, M. Panigati, R. Pò, *New J. Chem.* **2017**, *41*, 10009-10019; m) K. Uematsu, K. Noguchi, K. Nakano, *Phys. Chem. Chem. Phys.* **2018**, *20*, 3286-3295; Using chiral auxiliaries, see: n) K. Tanaka, H. Suzuki, H. Osuga, *J. Org. Chem.* **1997**, *62,* 4465–4470.

[6] Cyclizative dimerization of alkynes, see: a) A. Jeevanandam, K. Narkunan, T.-C.Ling, *J. Org. Chem.* **2001***, 66*, 6014-6020; b) R. Cao, H. Sun, X. Li, *Organometallics*, **2008**, *27*, 1944-1947; c) H. A. Hegner, S. Ahles, M. Neuburger, *Cem. Eur. J.* **2008**, *14*, 11310-11313; d) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Eur. J.* **2009**, *15*, 9987-9989; e) M. G. Auzis, M. Neuburger, H. Wegner, *Synlett* **2010**, 2443-2448; f) B. S. Young, F.Köhler, R. Herges, M. Haley, *J. Org. Chem.* **2011***, 76*, 8483-8487; g) B. Yao, C. Jaccoud, Q. Wang, J. Zhu, *Cem. Eur. J.* **2012**, *18*, 5864-5868; h) X. Wang, S. Dong, Z. Yao, H. Wang, Z. Xu, *Org. Lett.* **2013**, *16*, 22–25; i) J. E. Perea-Buceta, T. Wirtanen, O.-V. Laukkanen, M. K. Mäkelä, M. Nieger, M. Melchionna, N. Huittinen, J. A. Lopez-Sanchez, J. Helaja, *Angew. Chem. Int. Ed.* **2013**, *52*, 11835–11839; *Angew. Chem*. **2013**, *125*, 12051-12055; j) Y.-F. Yu,, C. Shu, C.-H. Shen, T.-Y. Li, L.-W. Ye, *Chem. Asian J.* **2013**, *8*, 2920-2924; k) B. Yao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12992-12996; *Angew. Chem.* **2013**, *125*, 12051-12055; l) M. Yamashita, T. Noro, A. Iida, *Tetrahedron Lett.* **2013**, *54*, 6848–6851; m) E. Kumaran, W. Y. Fan, W. K. Leong, *Org. Lett.* **2014**, *16*, 1342–1345; n) J. Sheng, C. Fan, Y. Ding, X. Fan, J. Wu, *Chem. Commun.* **2014**, *50*, 4188-4191; o) B. Yao, Q. Wang, J. Zhu, *Chem. Eur. J.* **2015**, *21*, 7413-7416; p) Z. Qi, Y. Jiang, B. Yuan, Y. Niu, R. Yan, , *Org. Lett.* **2018**, *20*, 5048–5052.

[7] Cyclizative dimerization of allenes, see: a) S. Ma, Z. Yu, *Angew. Chem. Int. Ed*. **2002**, *41*, 1775–1778; *Angew. Chem.* **2002**, *114*, 1853–1856; b) S. Ma, Z. Yu, Z. Gu, *Chem. Eur. J.* **2005**, *11*, 2351–2356; c) S. Ma, Z. Gu, Z. Yu, *J. Org. Chem.* **2005**, *70*, 6291–6294; d) A. S. K. Hashmi, M. C. Blanco, D. Fischer, J.W. Bats, *Eur. J. Org. Chem.* **2006**, 1387–1389.

[8] [(Box)Pd^{II}] catalyzed carbonylative reactions based on our hypothesis; a) S. Yasuhara, M. Sasa, T. Kusakabe, H. Takayama, M. Kimura, T. Mochida, K. Kato, *Angew. Chem. Int. Ed.* **2011**, *50,* 3912-3915; *Angew. Chem.* **2011**, *123,* 3998-4001; b) Y. Jiang, T. Kusakabe, K. Takahashi, K. Kato, K. *Org. Biomol. Chem.* **2014**, *12,* 3380-3385; c) K. Kato, S. Motodate, T. Mochida, T. Kobayashi and H. Akita, *Angew. Chem. Int. Ed.*, **2009**, *48*, 3326-3328; *Angew. Chem.* **2009**, *121*, 3376-3378; d) T. Kusakabe, T. Takahashi, R. Shen, A. Ikeda, Y. Kanno, Y. Inouye, H. Sasai, T.Mochida, K. Kato, *Angew. Chem. Int. Ed.* **2013**, *52,* 7845-7849; *Angew. Chem.* **2013**, *125,* 7999-8003; e) R. Shen, T. Kusakabe, T. Yatsu, Y. Kanno, K. Takahashi, K. Nemoto, K. Kato, *Molecules* **2016**, *21,* 1177.

[9] (α-alkoxy alkyl) (*ortho*-alkynyl phenyl) sulfides **1** are good precursors for the synthesis of benzo[*b*]thiophenes; a) I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem.* **2006**, *118,* 4585; *Angew. Chem. Int. Ed.* **2006**, *45,* 4473.

[10] See the Supporting Information.

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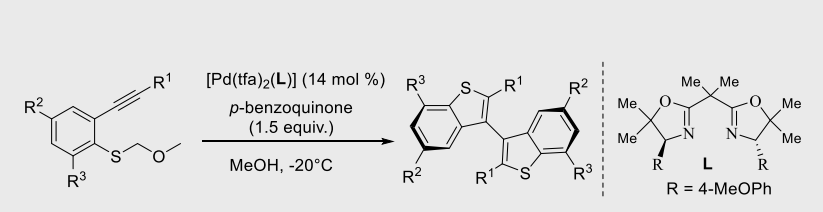

The first example of an asymmetric cyclizative dimerization of (*ortho*-alkynylphenyl) (methoxymethyl) sulfides with a palladium(II) bisoxazoline (box) catalyst has been developed. Axially chiral bibenzothiophenes were obtained in good yields and enantioselectivities. (20 examples, 25-95% yield (84-98% ee))

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Asymmetric Cyclizative Dimerization of (*ortho*-Alkynylphenyl) (Methoxymethyl) Sulfides with Palladium(II) Bisoxazoline Catalyst