

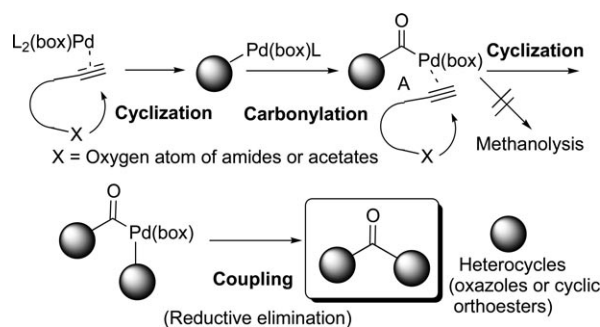
Cyclization–Carbonylation–Cyclization Coupling Reactions of Propargyl Acetates and Amides with Palladium(II)–Bisoxazoline Catalysts

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3(2*H*)-Furanones and oxazoles are common structures in a range of important pharmaceuticals.^[1] Diaryl ketones are also frequently found in natural products and pharmaceuticals,^[2] and they are good precursors for nonsteroidal antiestrogen drugs, such as tamoxifen,^[3] and diarylmethyl compounds, such as histamine H₁ antagonists,^[4a] antitubercular compounds,^[4b] and inhibitors of tubulin polymerization.^[4c] A variety of carbo- and heterocycles can be synthesized by transition-metal-catalyzed reactions of unsaturated systems.^[5] Among the available coupling methods, three-component carbonylation reactions, such as the carbonylative Suzuki reaction, the carbonylative Sonogashira reaction, and the carbonylative Heck reaction, create interesting building blocks.^[6,7] The vinyl and aryl palladium intermediates are formed by the oxidative addition of a carbon–halogen bond to palladium(0). In this context, we propose a CCC coupling reaction: a cyclization–carbonylation–cyclization coupling reaction of propargylic compounds should afford symmetrical ketones with two heterocyclic groups (Scheme 1).^[8]

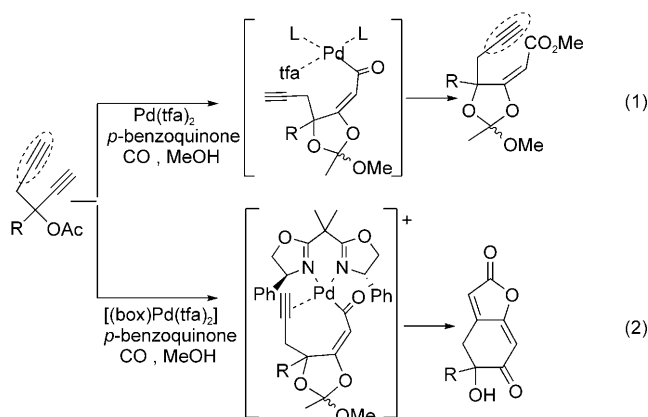
In this transformation, the triple bond of the substrate coordinates to palladium(II) and undergoes nucleophilic attack by the intramolecular nucleophile X followed by CO insertion to produce the acyl palladium intermediate **A**. Coordination of the triple bond of the second molecule induces the second cyclization. Reductive elimination then leads to the formation of a ketone with two heterocyclic groups. We needed to avoid methanolysis of **A** during the second cyclization step and anticipated that the π electrophilicity of the acyl palladium intermediate **A** would play an important role. We believed that the use of bisoxazoline (box) ligands would solve this problem.

Recently, we reported a ligand-controlled tandem carbonylative cyclization of propargyl acetates with 1,4-diyne^[9a] and 1,5-diyne structures (Scheme 2).^[9b] In these systems, if the box



Scheme 1. Our concept of a cyclization–carbonylation–cyclization coupling reaction (CCC coupling reaction) of propargylic compounds.

ligand was absent, the second triple bond did not react. The use of the box ligand caused a significant change in the course of the reaction, and tandem carbonylative cyclization occurred as a result of insertion of the second triple bond. We believe that the box ligand enhances the π electrophilicity of palladium(II)^[9a–d] and thus promotes coordination of the second triple bond in the second part of the tandem reaction. Previously, we also reported that the palladium(II)-mediated cyclization–carbonylation of propargyl acetates affords cyclic orthoesters in the same type of reaction as that shown in Equation (1) of Scheme 2.^[9e,f] We believed the CCC coupling reaction of propargyl acetates **1** (Scheme 3) to be an intermolecular version of the tandem reaction in Equation (2) of Scheme 2. On the basis of our earlier results, we



Scheme 2. Previous studies: ligand-controlled tandem carbonylative cyclization of propargyl acetates. tfa = trifluoroacetate.

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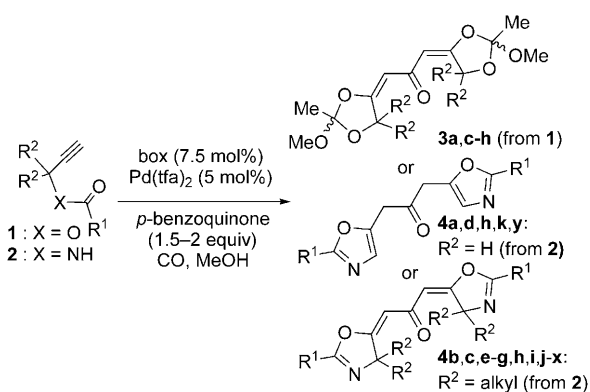
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Scheme 3. [(box)Pd(tfa)₂]-catalyzed CCC coupling reaction of propargyl acetates **1** and amides **2**.

hypothesized that the [(box)Pd^{II}] complexes should strongly activate the triple bond of the second molecule and thus enable the CCC coupling reaction of **1**. Consequently, we report herein the [(box)Pd(tfa)₂]-catalyzed CCC coupling reaction of propargyl acetates **1** and amides **2** (Scheme 3).

We previously reported the [(CH₃CN)PdCl₂]-catalyzed cyclization–carbonylation of propargyl acetates **1** to form monomeric esters **5** in 61–99% yield.^[9c,f] In the present study,

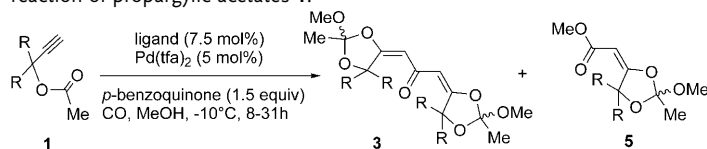
we initially screened some box ligands (Scheme 4) for the CCC coupling reaction of **1a** according to our hypothesis. As expected, the CCC coupling reaction occurred smoothly in the presence of the box ligands to afford **3a** in 52–63% yield together with trace amounts of **5a** (Table 1, entries 1–4). In our previous studies,^[9a–d,g] substituents at the C4 position of the box ligands played an important role in promoting the attempted reactions. In this case, however, all box ligands exhibited similar activity. Among them, the simple box ligand L4 gave the best result (Table 1, entry 4). Pure **3a** was readily obtained by recrystallization from methanol, and the structure of **3a** was determined by X-ray crystallographic analysis.^[10] In the absence of a box ligand, the monomeric ester **5a** was obtained as the major product (Table 1, entry 5), in agreement with our previous results with the catalyst [(CH₃CN)₂PdCl₂].^[9c,f] The use of [(–)-sparteine]Pd(tfa)₂ and [(2,2′-bipyridine)PdCl₂] led to no reaction. Internal acetylenes also gave no reaction. Furthermore, CH₂Cl₂ and *N,N*-dimethylformamide were not suitable as solvents.

Scheme 4. Box ligands.

Having optimized the reaction conditions, we examined the reaction of different substrates with the simple box ligand L4. The cyclic substrates **1a–d** and acyclic substrates **1e–g** were transformed in moderate to good yields (Table 1, entries 4 and 6–11). The *gem*-dialkyl effect^[11] plays a fundamental role in the success of the reaction: the CCC coupling of simple propargyl acetate (**1h**) did not proceed (Table 1, entry 12). Instead, the reaction afforded methyl (*E*)-4-acetoxy-3-methoxy-2-butenate^[12] in 4% yield through intermolecular methoxycarbonylation.^[9c]

Previously, Bacchi et al. reported that the palladium(II)-catalyzed cyclization–carbonylation of propargyl amide **2c** afforded a mixture of the *E* and *Z* isomers of the 5-((methoxycarbonyl)methylene)oxazoline **7c** in 90% yield (*E/Z* 83:7) together with the dimeric ketone **4c** in 8% yield.^[13,14] Although the yield of **4c** could be

Table 1: CCC coupling (cyclization–carbonylation–cyclization coupling) reaction of propargyl acetates **1**.

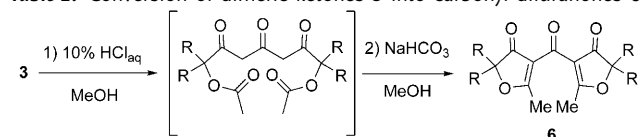


Entry	R	Ligand	Yield of 3 [%]	Yield of 5 [%]
1 ^[a]	–(CH ₂) ₅ –	(<i>S</i>)-Phbox (L1)	3a : 56	5a : 2
2 ^[a]	–(CH ₂) ₅ –	(<i>S</i>)-iPrbox (L2)	3a : 52	5a : 2
3 ^[a]	–(CH ₂) ₅ –	(<i>R</i>)-Bnbox (L3)	3a : 55	trace
4	–(CH ₂) ₅ –	box (L4) ^[b]	3a : 63	5a : 3
5 ^[a]	–(CH ₂) ₅ –	none	3a : 11	5a : 37
6	–(CH ₂) ₄ –	box (L4) ^[b]	3b : 62	trace
7	–(CH ₂) ₆ –	box (L4) ^[b]	3c : 59	trace
8	–(CH ₂) ₂ -NBoc- (CH ₂) ₂ –	box (L4) ^[b]	3d : 85	–
9	Bn	box (L4) ^[b]	3e : 85	–
10	Et	box (L4) ^[b]	3f : 65	trace
11	Me	box (L4) ^[b]	3g : 76	–
12 ^[a]	H	box (L4) ^[b]	–	–

[a] The reaction was carried out at 0°C for 24 h. [b] The isolated complex [(L4)Pd(tfa)₂] (5 mol%) was employed as the catalyst. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

To demonstrate the value of compounds **3**, we converted the dimeric ketones into carbonyl difuranones **6** by a two-step procedure (Table 2). Acid hydrolysis of **3** gave the corresponding triketones, which were treated with a base to afford **6** in moderate to good yields through a Knoevenagel–Claisen-type double condensation.

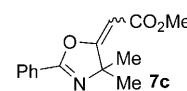
Table 2: Conversion of dimeric ketones **3** into carbonyl difuranones **6**.



Entry	R	<i>t</i> (step 1) [h]	<i>t</i> (step 2) [days]	Yield of 6 [%]
1	–(CH ₂) ₅ –	0.5	3	6a : 83
2	–(CH ₂) ₄ –	0.5	5	6b : 60
3	–(CH ₂) ₆ –	0.5	3.5	6c : 81
4	Bn	72	1.5 ^[a]	6e : 61
5	Et	0.5	4	6f : 69
6	Me	0.5	5	6g : 62

[a] K₂CO₃ was used instead of NaHCO₃.

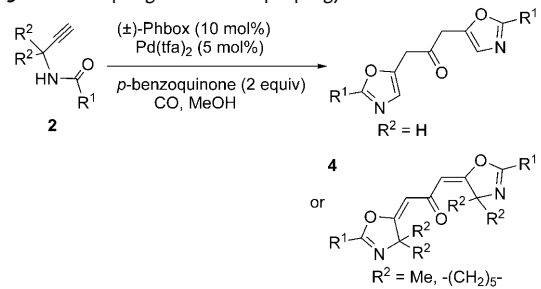
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increased by carrying out the reaction at higher concentrations ((*E*)-**7c**: 30%, (*Z*)-**7c**: 7%, **4c**: 43%), only this one example of a CCC coupling product was presented.

To investigate the generality of the CCC coupling reaction, we attempted the [(box)Pd^{II}]-catalyzed carbonylation of propargyl amides. As expected, the reaction proceeded smoothly in the presence of the (±)-Phbox ligand **L1** to afford the dimeric ketones **4** in good to excellent yields (Table 3).^[15,16] For benzamides **2a–c** and 4-substituted benza-

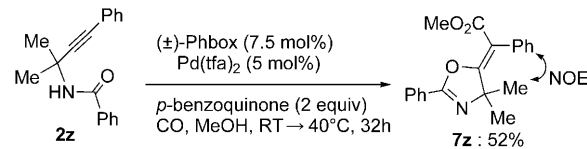
Table 3: CCC coupling reaction of propargylic amides **2**.



Entry	R ¹	R ²	T [°C]	t [h]	Yield of 4 [%]
1	Ph	H	0	12	4a : 90
2	Ph	-(CH ₂) ₅ -	0	3	4b : 97
3	Ph	Me	0	2	4c : 99
4	4-MeOC ₆ H ₄	H	0	6	4d : 90
5	4-MeOC ₆ H ₄	-(CH ₂) ₅ -	-10	11	4e : 92
6	4-MeOC ₆ H ₄	Me	-10	5	4f : 99
7	4-MeC ₆ H ₄	Me	-10	6	4g : 99
8	4-ClC ₆ H ₄	H	0	5	4h : 92
9	4-ClC ₆ H ₄	-(CH ₂) ₅ -	0	5	4i : 89
10	4-ClC ₆ H ₄	Me	0	5	4j : 95
11	4-BrC ₆ H ₄	H	0	5	4k : 90
12	4-BrC ₆ H ₄	-(CH ₂) ₅ -	0	5	4l : 95
13	4-BrC ₆ H ₄	Me	0	3	4m : 96
14	3-furyl	-(CH ₂) ₅ -	-30→-20	24	4n : 89
15	3-furyl	Me	-20	24	4o : 93
16	2-furyl	Me	0	3	4p : 84
17	2-indolyl	Me	-30→-20	24	4q : 95
18	3-indolyl	-(CH ₂) ₅ -	-30→-20	24	4r : 92
19	CH ₂ =CH	-(CH ₂) ₅ -	0	3	4s : 93
20	CH ₂ =CH	Me	0	3	4t : 85
21	cinnamoyl	Me	0	3	4u : 99
22	Me	Me	-30→-10	70	4v : 87
23	Et	Me	-30→-10	70	4w : 79
24	cyclohexyl	-(CH ₂) ₅ -	-20	12	4x : 82
25	Me	H	RT	24	–

mides **2d–g**, the reaction proceeded well (Table 3, entries 1–7). Br and Cl substituents were tolerated on the benzoic acid moiety under the reaction conditions, and products **4h–m** were obtained in good to excellent yields (Table 3, entries 8–13). Furan and indole derivatives **2n–r** also underwent conversion in good yields (Table 3, entries 14–18). Substrates **2s–u** containing alkenyl groups as the R¹ substituent were also found to be suitable (Table 3, entries 19–21), as were the alkyl amides **2v–x** (Table 3, entries 22–24). The substituent at the propargylic position was found to be important for this type of reaction: the reaction of α-unsubstituted alkyl amide **2y** gave a complex mixture (Table 3, entry 25).

Steric hindrance in the acyl palladium intermediate also seems to play an important role in the dimerization. The reaction of internal acetylene **2z** afforded the (*Z*)-5-((methoxycarbonyl)methylene)oxazoline **7z** in 52% yield together with recovered starting material (39%; Scheme 5). The configuration of (*Z*)-**7z** was confirmed by NOE experiments to be that shown in Scheme 5.



Scheme 5. Reaction of the internal acetylene **2z**.

In conclusion, we have presented a cyclization–carbonylation–cyclization coupling reaction (CCC coupling reaction) of propargylic acetates and amides catalyzed by [(box)Pd^{II}] complexes. Symmetrical ketones containing two heterocyclic groups were obtained in moderate to excellent yields. We believe that the box ligand enhances the π electrophilicity of palladium(II)^[9a–d] and thus promotes coordination of the triple bond of a second molecule to the acyl palladium intermediate **A** to enable the dimerization reaction to take place. We are currently investigating other new tandem reactions based on the cyclization–carbonylation–cyclization strategy presented herein for the synthesis of other types of ketones containing two heterocyclic groups.

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- [1] a) D. K. Dalvie, A. S. Kalgutkar, S. C. Khojasteh-Bakht, R. S. Obach, J. P. O'Donnell, *Chem. Res. Toxicol.* **2002**, *15*, 269; b) S. L. McGovern, E. Caselli, N. Grigorieff, B. K. Shoichet, *J. Med. Chem.* **2002**, *45*, 1712; c) M. Murcia-Soler, F. Pérez-Giménez, F. J. García-March, M. T. Salabert-Salvador, W. Díaz-Villanueva, M. J. Castro-Bleda, A. Villanueva-Pareja, *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1031; d) S. S. Shin, Y. Byun, K. M. Lim, J. K. Choi, K.-W. Lee, J. H. Moh, J. K. Kim, Y. S. Jeong, J. Y. Kim, Y. H. Choi, H.-J. Koh, Y.-H. Park, Y. I. Oh, M.-S. Noh, S. Chung, *J. Med. Chem.* **2004**, *47*, 792; e) A. Carotti, A. Carrieri, S. Chimichi, M. Boccalini, B. Cosimelli, C. Gnerre, A. Carotti, P.-A. Carrupt, B. Testa, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3551; f) S. Chimichi, M. Boccalini, B. Cosimelli, F. Dall'Acqua, G. Viola, *Tetrahedron* **2003**, *59*, 5215; g) T. Sasaki, J. Yamakoshi, M. Saito, K. Kasai, T. Matsudo, M. Kikuchi, T. Koga, K. Mori, *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2145; h) R. A. Mack, W. I. Zazulak, L. A. Radov, J. E. Baer, J. D. Stewart, P. H. Elzer, C. R. Kinsolving, V. S. Georgiev, *J. Med. Chem.* **1988**, *31*, 1910.
- [2] H. Neumann, A. Brennfürer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645, and references therein.
- [3] a) A. Nguyen, S. Top, P. Pigeon, A. Vessières, E. A. Hillard, M.-A. Plamont, M. Huché, C. Rigamonti, G. Jaouen, *Chem. Eur. J.* **2009**, *15*, 684; b) E. Y. H. Chao, J. L. Collins, S. Gaillard, A. B.

- Miller, L. Wang, L. A. Orband-Miller, R. T. Nolte, D. P. McDonnell, T. M. Willson, W. J. Zuercher, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 821; c) R. K. Pandey, R. D. Wakharkar, P. Kumar, *Synth. Commun.* **2005**, *35*, 2795; d) C. Olier-Reuchet, D. J. Aitken, R. Bucourt, H.-P. Husson, *Tetrahedron Lett.* **1995**, *36*, 8221; e) P. L. Coe, C. E. Scriven, *J. Chem. Soc. Perkin Trans. 1* **1986**, 475.
- [4] a) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454; b) S. K. Das, G. Panda, V. Chaturvedi, Y. S. Manju, A. K. Gaikwad, S. Sinha, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5586; c) C. Álvarez, R. Álvarez, P. Corchete, J. L. López, C. Pérez-Melero, R. Peláez, M. Medarde, *Bioorg. Med. Chem.* **2008**, *16*, 5952.
- [5] a) *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. II (Ed.: E. Negishi), Wiley, New York, **2002**, p. 2309; for reviews, see: b) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515; c) K. C. Majumdar, B. Chattopadhyay, P. K. Maji, S. K. Chattopadhyay, S. Samanta, *Heterocycles* **2010**, *81*, 795; d) K. C. Majumdar, P. Debnath, B. Roy, *Heterocycles* **2009**, *78*, 2661; e) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; f) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285; g) B. C. G. Soderberg, *Coord. Chem. Rev.* **2004**, *248*, 1085; h) S. A. Vizer, K. B. Yerzhanov, A. A. A. Al Quntar, V. M. Dembitsky, *Tetrahedron* **2004**, *60*, 5499; i) J. Muzart, *Tetrahedron* **2005**, *61*, 5955; j) N. Asao, *Synlett* **2006**, 1645; k) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; for the tandem dimerization and cyclization of acetylenic compounds, see: l) A. Jeevanandam, K. Narkunan, Y.-C. Ling, *J. Org. Chem.* **2001**, *66*, 6014; m) H. A. Wegner, S. Ahles, M. Neuburger, *Chem. Eur. J.* **2008**, *14*, 11310; n) M. G. Auzias, M. Neuburger, H. A. Wegner, *Synlett* **2010**, 2443.
- [6] For reviews on palladium-catalyzed carbonylation, see: a) A. Brennfürer, H. Neumann, M. Beller, *ChemCatChem* **2009**, *1*, 28; b) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027; c) C. F. J. Barnard, *Organometallics* **2008**, *27*, 5402.
- [7] A. Brennfürer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114, and references therein.
- [8] Recently, we reported a CCC coupling reaction of allenyl ketones without a bisoxazoline ligand. The reactivity of allenyl compounds is high enough to induce dimer formation: a) K. Kato, T. Mochida, H. Takayama, M. Kimura, H. Moriyama, A. Takeshita, Y. Kanno, Y. Inoue, H. Akita, *Tetrahedron Lett.* **2009**, *50*, 4744; for selected examples of dimerization or coupling reactions of allenyl compounds, see: b) J. A. Marshall, E. D. Robinson, *J. Org. Chem.* **1990**, *55*, 3450; c) J. A. Marshall, C. A. Sehon, *J. Org. Chem.* **1995**, *60*, 5966; d) A. S. K. Hashmi, *Angew. Chem.* **1995**, *107*, 1749; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581; e) A. S. K. Hashmi, T. L. Ruppert, T. Knöfel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295; f) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; g) S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941; h) S. Ma, J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447; i) S. Ma, Z. Yu, *Chem. Eur. J.* **2004**, *10*, 2078; j) S. Ma, Z. Yu, Z. Gu, *Chem. Eur. J.* **2005**, *11*, 2351; k) Y. Deng, J. Li, S. Ma, *Chem. Eur. J.* **2008**, *14*, 4263; l) B. Alcaide, P. Almendros, T. Martínez del Campo, *Eur. J. Org. Chem.* **2007**, 2844; m) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Eur. J.* **2009**, *15*, 9987.
- [9] a) K. Kato, R. Teraguchi, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin, O. V. Gusev, *Synlett* **2007**, 638; b) K. Kato, R. Teraguchi, S. Motodate, A. Uchida, T. Mochida, T. A. Peganova, N. V. Vologdin, H. Akita, *Chem. Commun.* **2008**, 3687; c) K. Kato, S. Motodate, T. Mochida, T. Kobayashi, H. Akita, *Angew. Chem.* **2009**, *121*, 3376; *Angew. Chem. Int. Ed.* **2009**, *48*, 3326; d) S. Motodate, T. Kobayashi, M. Fujii, T. Mochida, T. Kusakabe, S. Katoh, H. Akita, K. Kato, *Chem. Asian J.* **2010**, *5*, 2221; e) K. Kato, Y. Yamamoto, H. Akita, *Tetrahedron Lett.* **2002**, *43*, 6587; f) K. Kato, H. Nouchi, K. Ishikura, S. Takaishi, S. Motodate, H. Tanaka, K. Okudaira, T. Mochida, R. Nishigaki, K. Shigenobu, H. Akita, *Tetrahedron* **2006**, *62*, 2545; g) T. Kusakabe, K. Kato, S. Takaishi, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin, O. V. Gusev, *Tetrahedron* **2008**, *64*, 319.
- [10] CCDC 799108 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. See the Supporting Information.
- [11] P. G. Sammes, D. J. Weller, *Synthesis* **1995**, 1205.
- [12] L. Duc, J. F. McGarrrity, T. Meul, A. Warm, *Synthesis* **1992**, 391.
- [13] For selected examples of palladium-catalyzed reactions of propargyl amides, see: a) A. Bacchi, M. Costa, N. Della Cà, B. Gabriele, G. Salerno, S. Cassoni, *J. Org. Chem.* **2005**, *70*, 4971; b) M. Costa, N. Della Cà, B. Gabriele, C. Massera, G. Salerno, M. Soliani, *J. Org. Chem.* **2004**, *69*, 2469; c) A. Arcadi, S. Cacchi, V. Carnicelli, F. Marinelli, *Tetrahedron* **1994**, *50*, 437; d) A. Lei, X. Lu, *Org. Lett.* **2000**, *2*, 2699; e) A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli, *Org. Lett.* **2001**, *3*, 2501; f) E. M. Beccalli, E. Borsini, G. Broggini, G. Palmisano, S. Sottocornola, *J. Org. Chem.* **2008**, *73*, 4746; g) E. Merkul, T. J. J. Müller, *Chem. Commun.* **2006**, 4817; h) A. Saito, A. Matsumoto, Y. Hanzawa, *Tetrahedron Lett.* **2010**, *51*, 2247.
- [14] A. Bacchi, M. Costa, B. Gabriele, G. Pelizzi, G. Salerno, *J. Org. Chem.* **2002**, *67*, 4450. In this case, the carbonylation of **2a** afforded maleic diester derivatives (derived from oxidative bisalkoxycarbonylation of the triple bond) in 69 % yield together with oxazole **7a** (14 %).
- [15] For preliminary experiments, see the Supporting Information.
- [16] The CCC cross-coupling reaction of amide **2v** (1 equiv) with acetate **1g** (1 equiv) catalyzed by [(L4)Pd(tfa)₂] (5 mol %) under our reaction conditions (−10 °C, 24 h) afforded an unsymmetrical ketone in 18 % yield together with dimeric ketones **4v** (37 %) and **3g** (7 %).