

HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 919 - 927. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 19th June, 2014, Accepted, 10th September, 2014, Published online, 19th September, 2014
DOI: 10.3987/COM-14-S(K)39

**AN EFFICIENT DOMINO SONOGASHIRA/DOUBLE
CARBOPALLADATION/C–H-ACTIVATION REACTION LEADING TO
FLUORESCENT POLYCYCLIC AROMATIC HYDROCARBONS**

Lutz F. Tietze* and Christoph Eichhorst

Institute of Organic and Biomolecular Chemistry, Georg-August University,
Tammannstraße 2, 37077, Göttingen, Germany. E-mail: ltietze@gwdg.de

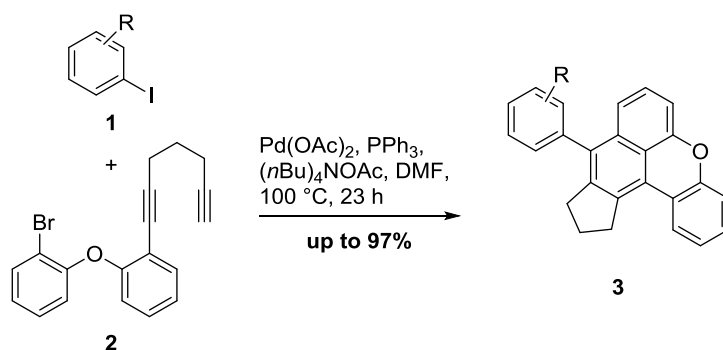
Abstract – A facile synthesis of fluorescent polycyclic aromatic hydrocarbons through a highly productive palladium-catalyzed fourfold domino Sonogashira/double carbopalladation/C–H-activation process was developed.

Dedicated to Professor Isao Kuwajima on the occasion of his birthday

INTRODUCTION

Domino reactions allow the transformation of simple organic building blocks into complex functional structures within few steps.¹ Beside this compelling characteristic of efficiency the concept is also reassuring due to its economic and environmental sustainability, since two or more reactions are included in one process without the need of any intermediate purification. Moreover, domino reactions can proceed via unstable intermediates, which is usually not possible in a step-wise approach. In addition to the development of domino Knoevenagel/hetero-Diels-Alder reactions,² domino imine formation/hydride shift/alkylation reactions,³ domino amidation/spirocyclization/electrophilic aromatic substitution reactions⁴ and domino acetalization/allylation reactions,⁵ in the last years we have focused especially on palladium-catalyzed domino processes.⁶ In this aspect, it was one of our goals to include C–H-activation reactions⁷ in domino processes for the synthesis of natural products and functional materials. C–H activation reactions that are part of palladium-catalyzed domino processes have persuading advantages compared to typically used transition-metal catalyzed cross-coupling reactions, as no functionalization of the precursors is necessary.

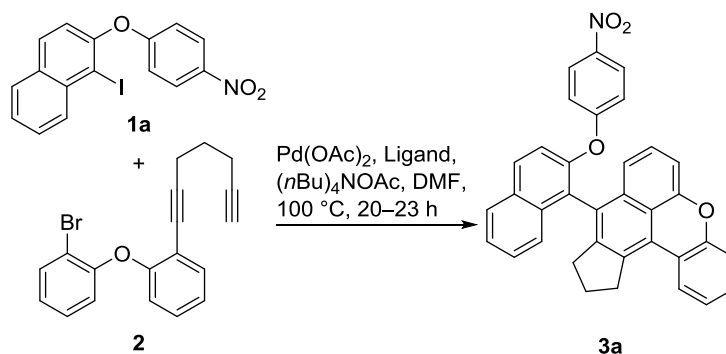
Quite recently, we have developed a domino Sonogashira/carbopalladation/C–H-activation reaction for the synthesis of tetra-substituted helical alkenes as potential switches⁸ and domino Sonogashira/double carbopalladation/C–H-activation reactions for the preparation of condensed aromatic systems.⁹ Herein we report even more productive domino Sonogashira/double carbopalladation/C–H activation reactions that convert aryl iodides **1** and dialkyne **2** into polycyclic aromatic hydrocarbons **3** in up to 97% yield (Scheme 1).



Scheme 1. Domino Sonogashira/double carbopalladation/C–H-activation reactions

RESULTS AND DISCUSSION

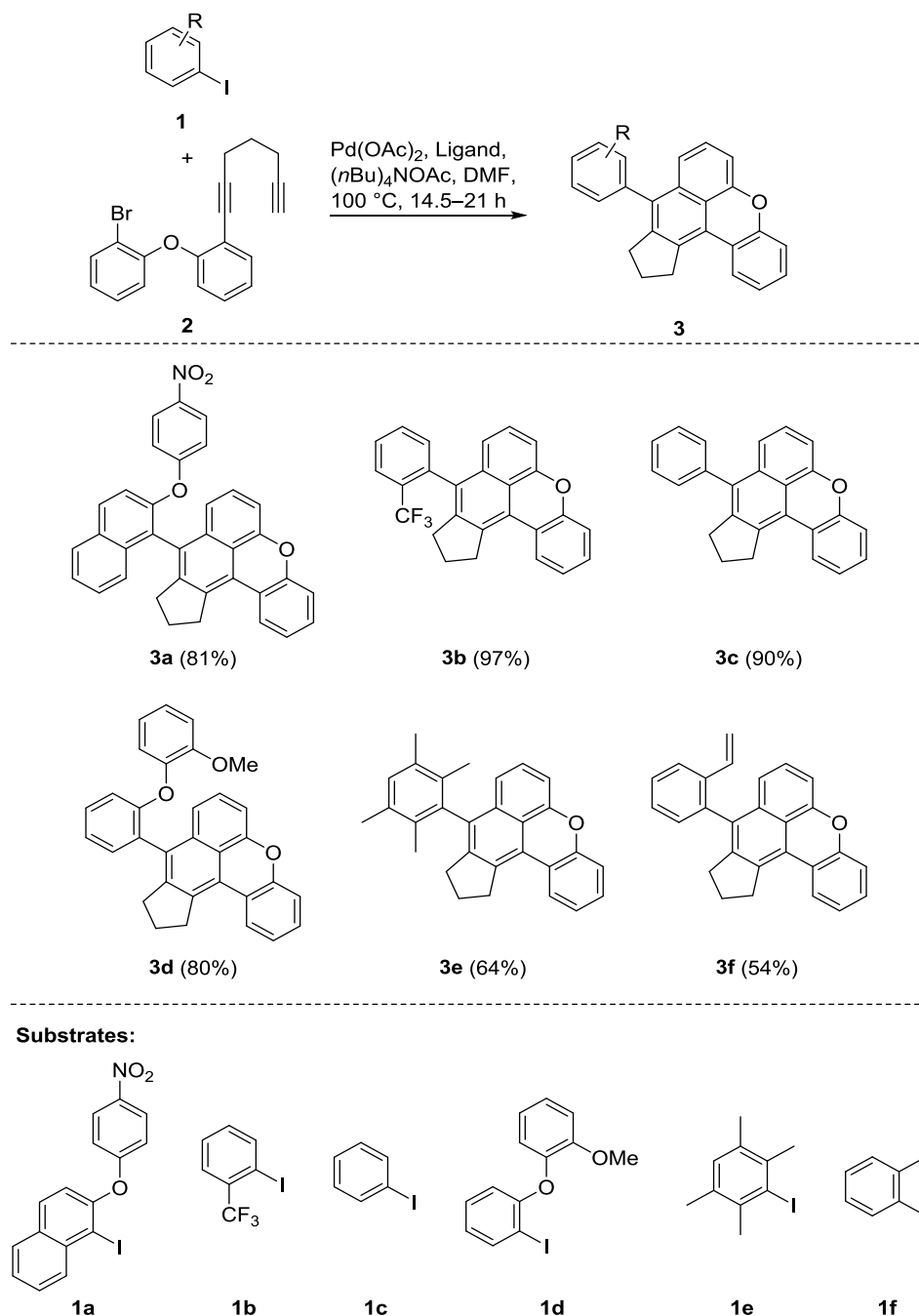
For the optimization of the reaction conditions, we investigated the domino reaction of **1a** and **2** as coupling partners in the presence of a combination of Pd(OAc)₂ and PPh₃ in a ratio of 1:5 as catalytic system and (nBu)₄NOAc as base in DMF at 100 °C. A catalyst loading of 10 mol% Pd(OAc)₂ furnished the domino product **3a** in 81% yield as the best result for this system (Table 1, Entry 1). Reduction of the catalyst loading to 5 mol% of Pd(OAc)₂ led to **3a** in 67% yield while 1 mol% of Pd(OAc)₂ furnished **3a** in 66% yield (Entries 2 and 3). Moreover, a higher catalyst loading of 20 mol% of Pd(OAc)₂ was also not advantageous, since the yield of the domino reaction dropped to 60% (Entry 4). In order to further optimize the reaction conditions, we tested several ligands with a 20 mol% loading of Pd(OAc)₂. Electron rich PCy₃ led to **3a** in 53% yield (Entry 5), while the electron rich and bulky SPhos ligand as well as the ionic species [PtBu₄][BF₄] gave 49% yield (Entries 6 and 7). The use of bidentate dppe furnished **3a** in only 16% (Entry 8). Thus, PPh₃ showed the best results and was used in the further investigations employing different substrates.

Table 1. Optimization of the reaction conditions^[a]

Entry	Pd(OAc) ₂ (mol%)	Ligand	Ligand (mol%)	Yield [%] ^[b]
1	10	PPh ₃	50	81
2	5	PPh ₃	25	67
3	1	PPh ₃	5	66
4	20	PPh ₃	100	60
5	20	PCy ₃	100	53
6	20	SPhos	100	49
7	20	[PtBu ₄][BF ₄]	100	49
8	20	dppe	50	16

[a] **1a** (1.00 equiv.), **2** (1.05 equiv.), Pd(OAc)₂, ligand, (nBu)₄NOAc (6.00 equiv.), DMF, 100 °C, 20–23 h; [b] isolated yields following flash column chromatography.

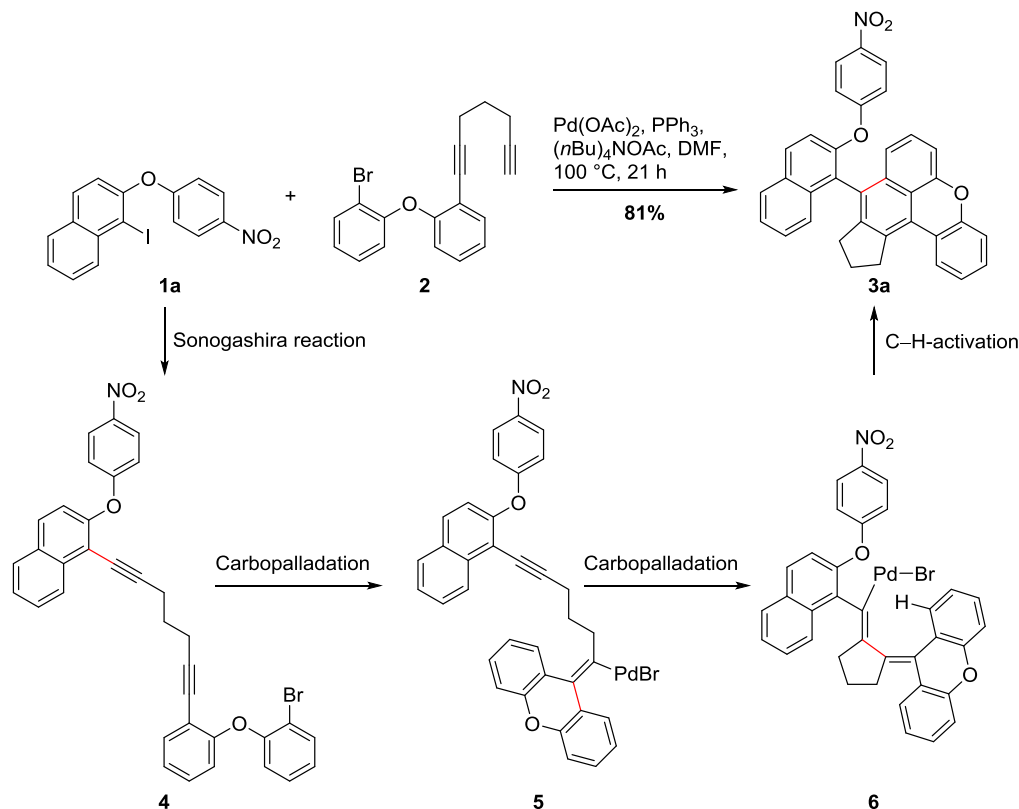
In the following, we extended the scope of the fourfold domino reaction using differently substituted substrates **1b-f**. The corresponding polycyclic aromatic hydrocarbons **3b-f** were obtained highly selectively and in good to excellent yield ranging from 54 – 97% (Scheme 2). Moreover, the results show that functional groups having electron-accepting and electron-donating properties are tolerated. Thus, the already mentioned naphthyl iodide **1a** containing a 4-nitro-phenoxy group in the *ortho* position gave **3a** in 81% yield and the 2-trifluorophenyl iodide **1b** led to **3b** in 97% yield. Excellent yields of 90% and 80%, respectively, were also obtained with the electron neutral **1c** and the phenyl iodide **1d** containing a 2-methoxyphenoxy group in the *ortho* position. Interesting examples are the phenyl iodides **1e** and **1f**. Compound **1e** containing four methyl groups is sterically highly hindered and in **1f** there is a competing vinyl group which might undergo an intermolecular Mizoroki-Heck reaction after the primary oxidative addition. However, the Sonogashira reaction of **1f** with **2** seems to be much faster than the also possible Mizoroki-Heck reaction. Anyhow, in both cases the yields with 64% and 54% were slightly lower.



Scheme 2. Domino Sonogashira/double carbopalladation/C–H activation process of **1a–f** and **2**

The domino Sonogashira/double carbopalladation/C–H activation process as described for the reaction of aryl iodide **1a** and dialkyne **2** starts with a Sonogashira reaction that couples **1a** with **2** to form intermediate **4** (Scheme 3). After an oxidative addition at the C–Br bond in **4**, a first carbopalladation takes place at one of the two triple bonds in **4** to provide vinyl-palladium species **5** which contains a newly generated six-membered heterocycle. The vinyl-palladium species then undergoes a carbopalladation at the second triple bond furnishing dialkene **6** containing another vinyl-palladium

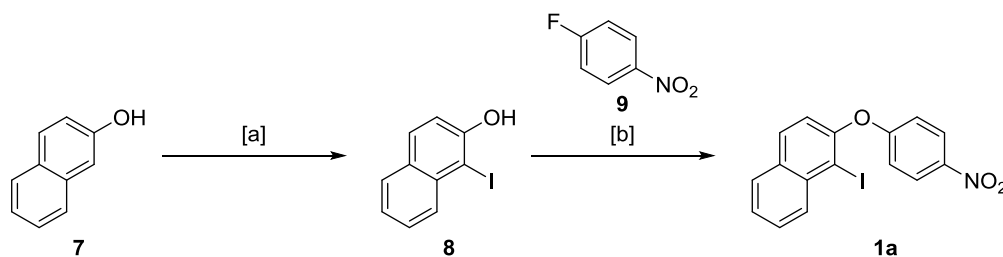
species and a five-membered ring which is built up during the carbopalladation process. Finally, a C–H-activation reaction transforms **6** into the desired polycyclic aromatic hydrocarbon **3a** whereupon the two newly formed double bonds become part of the aromatic naphthalene system in **3a**. This fact might act as a driving force and could explain the smooth and high yielding course of the domino process.



Scheme 3. Postulated mechanism of the domino Sonogashira/double carbopalladation/C–H activation reaction. The ligands at the Pd-atom are omitted for clarity.

The syntheses of the substrates **1** and **2** for the domino reactions either followed literature known protocols^{8–11} or the necessary compounds were commercially available as **1b**, **c** and **e**.

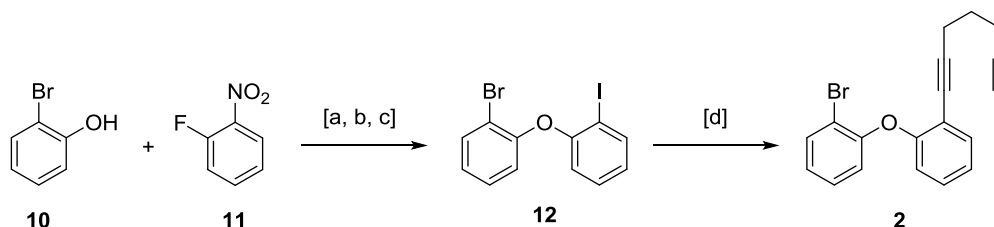
Building block **1a** was prepared through an iodination of naphthol **7** and a subsequent nucleophilic aromatic substitution coupling naphthol **8** with 4-fluoronitrobenzene **9** to give **1a** in 78% yield (Scheme 4).



Scheme 4. Synthesis of **1a**

Reaction conditions: [a] KI, H₂O₂, H₂SO₄, MeOH, 0 °C, 1 h, 72%; [b] **9**, K₂CO₃, DMSO, 95 °C, 24 h, 78%.

The sequence leading to building block **2** started with a nucleophilic aromatic substitution of phenol **10** and 2-fluoronitrobenzene (**11**), which was followed by a reduction of the nitro group and a Sandmeyer reaction to give the aryl iodide **12**. Then, compound **12** was converted into the dialkyne **2** through a Sonogashira reaction using 1,6-heptadiyne as coupling partner (Scheme 5).



Scheme 5. Synthesis of **2**

Reaction conditions: [a] K_2CO_3 , DMSO, 95 °C, 23 h, quant.; [b] Zn, conc. HCl, conc. AcOH, EtOAc, 0 °C \rightarrow rt, 15 min, 86%; [c] $p\text{TsOH}\cdot\text{H}_2\text{O}$, KI, NaNO_2 , MeCN, H_2O , rt, 30 min, 87%; [d] 1,6-heptadiyne, $\text{PdCl}_2(\text{PPh}_3)_2$, CuI, NEt_3 , rt, 17 h, 72%.

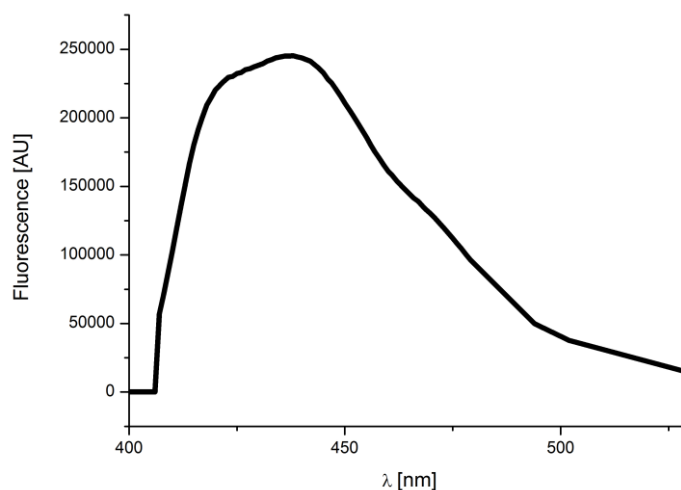


Figure 1. Fluorescence spectrum of **3c** in acetonitrile

Compounds **3b-f** exhibit an interesting fluorescence activity and we investigated molecule **3c** exemplarily by fluorescence spectrometry (Figure 1).¹² Irradiation at a wavelength of 352 nm caused an emission of blue light with a maximum at a wavelength of 436 nm. The fluorescence properties of **3b-f** could be useful for the application of compounds of type **3** as fluorescence dyes or chemical sensors.

In conclusion, we have developed a fourfold domino process with a C–H-activation reaction as the final step to transform simple precursors highly efficiently into polycyclic aromatic hydrocarbons with pronounced fluorescence activity.

EXPERIMENTAL

General method for the domino reaction:

9-[2-(4-Nitrophenoxy)naphthalene-1-yl]-11,12-dihydro-10H-indeno[6,5,4-kl]xanthene (3a):

A mixture of **1a** (73.6 mg, 189 μmol , 1.00 equiv.), **2** (67.1 mg, 198 μmol , 1.05 equiv.), Pd(OAc)₂ (4.22 mg, 18.8 μmol , 0.10 equiv.), PPh₃ (24.7 mg, 94.0 μmol , 0.50 equiv.) and (*n*Bu)₄NOAc (341 mg, 1.13 mmol, 6.00 equiv.) in degassed DMF (5 mL) was stirred at 100 °C for 21 h. The reaction mixture was filtered through SiO₂, flushed with EtOAc and the solvent of the filtrate was removed *in vacuo*. Column chromatography (SiO₂, *n*-pentane/EtOAc 20:1) yielded **3a** as a yellow solid (79.9 mg, 153 μmol , 81%).

R_f = 0.40 (*n*-pentane/EtOAc, 20:1); UV/Vis (MeCN) nm (lg ϵ) = 193 (4.9352), 223 (4.3783), 256 (3.8842), 286 (3.6870), 350 (3.4956), 367 (3.4858); IR (ATR) cm^{-1} = 1580, 1509, 1485, 1463, 1442, 1338, 1307, 1279, 1240, 1166, 1128, 1110, 1066, 1045, 1028, 1012, 958, 860, 852, 836, 821, 808, 768, 761, 750, 734, 703, 688, 667, 645, 629, 618, 530, 522, 514; ¹H-NMR (600 MHz, C₆D₆) δ : 1.58–1.70 (m, 2H, 6''-H₂), 2.33 (ddd, J = 16.2 and 8.4 and 6.2 Hz, 1H), 2.50 (dt, J = 15.9 and 7.9 Hz, 1H), 2.87 (dt, J = 15.6 and 7.5 Hz, 1H, 5''-H_a), 2.94 (ddd, J = 15.8 and 8.2 and 5.9 Hz, 1H, 5''-H_b), 6.37 (d, J = 9.2 Hz, 2H, 2'-H, 6'-H), 6.77 (dd, J = 7.9 and 1.6 Hz, 1H, 10''-H), 6.84–6.92 (m, 3H, 3''-H, 8''-H, 9''-H), 6.97 (ddd, J = 8.3 and 7.3 and 1.4 Hz, 1H, 2''-H), 7.03–7.09 (m, 2H, 3-H, 1''-H), 7.14 (m_C, 1H, 7-H), 7.26 (ddd, J = 8.1 and 6.8 and 1.2 Hz, 1H, 6-H), 7.43 (dd, J = 8.5 and 1.1 Hz, 1H, 8-H), 7.59 (d, J = 9.2 Hz, 2H, 3'-H, 5'-H), 7.67 (d, J = 8.9 Hz, 1H, 4-H), 7.71 (d, J = 8.4 Hz, 1H, 4''-H), 7.73 (d, J = 8.4 Hz, 1H, 5-H); ¹³C-NMR (126 MHz, C₆D₆) δ : 25.5 (C-6''), 32.2 (C-7''), 35.3 (C-5''), 108.1 (C-8''), 117.0 (C-2', C-6'), 117.2 (C-1''), 118.2 (C-10''), 120.7 (C-3), 122.4, 122.6 (C-4''a), 123.1 (C-3''), 123.3 (C-4''b), 125.5 (C-3', C-5'), 125.7, 126.1 (C-6, C-8), 127.0, 127.1, 127.6 (C-7, C-4'', C-9''), 127.9 (C-1), 128.3, 128.6 (C-5), 129.6 (C-2''), 130.2 (C-4), 132.0 (C-4a), 133.9 (C-8a, C-4''c/C-7''a), 134.1 (C-7''d), 143.0 (C-1'), 146.4 (C-4''c/C-7''a), 150.2 (C-2), 151.7 (C-10a), 153.4 (C-10''b), 162.7 (C-1'') (Further signals could not be assigned); MS (ESI): 544.2 (41) (M+Na⁺); HRMS (ESI): calcd for C₃₅H₂₃NO₄+Na⁺: 544.1519. Found: 544.1505.

ACKNOWLEDGEMENTS

We thank the Bundesland Niedersachsen, the Deutsche Forschungsgemeinschaft and the Volkswagen-Stiftung for their generous support.

REFERENCES AND NOTES

1. L. F. Tietze (Ed), ['Domino Reactions', Wiley-VCH, Weinheim, 2014](#); L. F. Tietze, S.-C. Dufert, and J. Hierold, ['Domino Reactions in the Total Synthesis of Natural Products' in "Domino Reactions: Concepts for Efficient Organic Synthesis", ed. by L. F. Tietze, Wiley-VCH, Weinheim, 2014, pp. 523–578](#); L. G. Voskressensky, A. A. Festa, and A. V. Varlamov, [Tetrahedron, 2014, 70, 551](#); C. M. R. Chandra, I. Atodiresei, and M. Rueping, [Chem. Rev., 2014, 114, 2390](#); J. Muzart, [Tetrahedron, 2013, 69, 6735](#); L. F. Tietze and A. Dufert in 'Modern Tools for the Synthesis of Complex Bioactive Molecules', Wiley, Hoboken, NJ, 2012; H. Pellissier, [Adv. Synth. Catal., 2012, 48, 5889](#); L. F. Tietze and A. Dufert in ['Catalytic Asymmetric Conjugate Reactions', Wiley-VCH, Weinheim, 2010, pp. 321-350](#); L. F. Tietze, G. Brasche, and K. M. Gericke in ['Domino Reactions in Organic Synthesis', WILEY-VCH, Weinheim, 2006](#); L. F. Tietze, [Chem. Rev., 1996, 96, 115](#); L. F. Tietze, S. Dietz, N. Böhnke, M. A. Dufert, I. Objartel, and D. Stalke, [Eur. J. Org. Chem., 2011, 6574](#).
2. L. F. Tietze, S. Dietz, N. Böhnke, M. A. Dufert, I. Objartel, and D. Stalke. [Eur. J. Org. Chem., 2011, 6574](#).
3. J. Wölfling, E. Frank, G. Schneider, and L. F. Tietze, [Eur. J. Org. Chem., 2004, 90](#).
4. L. F. Tietze, N. Tölle, D. Kratzert, and D. Stalke, [Org. Lett., 2009, 11, 5230](#).
5. L. F. Tietze, T. Kinzel, and C. Brazel, [Acc. Chem. Res., 2009, 42, 367](#).
6. L. F. Tietze, S. Jackenkroll, J. Hierold, L. Ma, and B. Waldecker, [Chem. Eur. J., 2014, 20, 8628](#); M. Sickert, H. Weinstabl, B. Peters, X. Hou, and M. Lautens, [Angew. Chem. Int. Ed., 2014, 53, 5147](#); E. Elboray, M. F. Aly, H. H. Abbas-Temirek, G. H. Churchill, and R. Grigg, [Tetrahedron, 2014, 70, 110](#); C. Zheng, J. J. Chen, and R. Fan, [Org. Lett., 2014, 16, 816](#); S. R. Walker, M. L. Czyz, and J. C. Morris, [Org. Lett., 2014, 16, 708](#); L. F. Tietze, S.-C. Dufert, J. Clerc, M. Bischoff, C. Maaß, and D. Stalke, [Angew. Chem. Int. Ed., 2013, 52, 3191](#); L. F. Tietze, S. Jackenkroll, C. Raith, D. A. Spiegl, J. R. Reiner, and M. C. Ochoa Campos, [Chem. Eur. J., 2013, 19, 4876](#); L. F. Tietze, T. Hungerland, J. Ammermann, C. Eichhorst, S. O. Reichmann, and D. Stalke, [J. Indian Chem. Soc., 2013, 90, 1537](#); Q. Liu, L. Wu, H. Jiao, X. Fang, R. Jackstell, and M. Beller, [Angew. Chem. Int. Ed., 2013, 52, 8064](#); R. Y. Nimje, M. V. Leskinen, and P. M. Pihko, [Angew. Chem. Int. Ed., 2013, 52, 4818](#); E. Kaneko, Y. Matsumoto, and K. Kamikawa, [Chem. Eur. J., 2013, 19, 11837](#); N. M. Groome, E. E. Elboray, M. W. Imman, H. Ali Dondas, R. M. Phillips, C. Kilner, and R. Grigg, [Chem. Eur. J., 2013, 19, 2180](#); M. Leibelng and D. B. Werz, [Chem. Eur. J., 2012, 18, 6138](#); M. Leibelng, M. Pawliczek, D. Kratzert, D. Stalke, and D. B. Werz, [Org. Lett., 2012, 14, 346](#); X. Jia, D. A. Petrone, and M. Lautens, [Angew. Chem. Int. Ed., 2012, 51, 9870](#); H. Liu, M. El-Salfiti, and M. Lautens, [Angew. Chem. Int. Ed., 2012, 51, 9846](#); L. F. Tietze, T. Hungerland, M. A. Dufert, I. Objartel, and D. Stalke, [Chem. Eur. J., 2012, 18, 3286](#); L. F. Tietze, T. Hungerland, C. Depken, C. Maaß, and D. Stalke,

- [Synlett, 2012, 2516](#); L. F. Tietze, M. A. Dufert, T. Hungerland, K. Oum, and T. Lenzer, [Chem. Eur. J., 2011, 17, 8452](#); J. E. Rixson, T. Chaloner, C. H. Heath, L. F. Tietze, and S. G. Stewart, *Eur. J. Org. Chem.*, 2011, 544; L. F. Tietze, A. Dufert, F. Lotz, L. Sölter, K. Oum, T. Lenzer, T. Beck, and R. Herbst-Irmer, [J. Am. Chem. Soc., 2009, 131, 17879](#); L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith, and C. Grosse, [Chem. Eur. J., 2008, 14, 8956](#); L. F. Tietze, K. M. Sommer, J. Zinngrebe, and F. Stecker, [Angew. Chem., Int. Ed., 2005, 44, 257](#).
7. K. Gao and N. Yoshikai, [Acc. Chem. Res., 2014, 47, 1208](#); A. R. Kapdi, [Dalton Trans., 2014, 43, 3021](#); E. M. Ferreira, [Nat. Chem., 2014, 6, 94](#); N. Yoshikai and Y. Wei, *Asian J. Org. Chem.*, 2013, 2, 466; J. Wencel-Delord and F. Glorius, [Nat. Chem., 2013, 5, 369](#); M. Garcia-Melchior, A. A. C. Braga, A. Lledos, G. Ujaque, and F. Maseras, [Acc. Chem. Res., 2013, 46, 2626](#); J. J. Mousseau and A. B. Charette, [Acc. Chem. Res., 2013, 46, 412](#); L. Ackermann, A. R. Kapdi, H. Potukuchi, and S. I. Kozhushkov, in 'Handbook of Green Chemistry', Wiley-VCH, Weinheim 2012, p. 259; A. Facchetti, L. Vaccaro, and A. Marrocchi, [Angew. Chem. Int. Ed., 2012, 51, 3520](#); S. R. Neufeldt and M. S. Sanford, [Acc. Chem. Res., 2012, 45, 936](#).
8. L. F. Tietze, T. Hungerland, C. Eichhorst, A. Dufert, C. Maaß, and D. Stalke, [Angew. Chem. Int. Ed., 2013, 52, 3668](#).
9. L. F. Tietze, C. Eichhorst, T. Hungerland, and M. Steinert, *Chem. Eur. J.*, 2014, 20, early view.
10. J. A. De la Fuente, [J. Med. Chem., 2003, 46, 5208](#); F. Wen, H. Zhang, Z. Yu, H. Jin, Q. Yang, and T. Hou, [Pestic. Biochem. Physiol., 2010, 98, 248](#).
11. D. Sun, P. Lai, W. Xie, J. Deng, and Y. Jiang, [Synth. Commun., 2007, 37, 2989](#); M. R. Acheson and G. C. M. Lee, [J. Chem. Soc., Perkin Trans. 1, 1987, 11, 2321](#).
12. Fluorescence spectrum: The spectrum was recorded on a fluorimeter FP 6500 by JASCO. Light source: 150 W, Xe lamp; photometric system: monochromatic light; monochromator: signal-to-noise ratio (Raman-band of water, 350 nm excitation wavelength, 2 sec response time, 5 nm bandwidth) of 200:1 (excitation and emission monochromator), measuring wavelength range: zero order, 220–750 nm; resolution: 1 nm (excitation and emission), wavelength accuracy: +/- 1.5 nm (excitation and emission); wavelength reproducibility: +/- 0.3 nm (excitation and emission); detector: photomultiplier tube (excitation and emission).