Enantioselective Access to 1*H*-Isoindoles with Quaternary Stereogenic Centers by Pd(0)-Catalyzed C–H Functionalization

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Abstract: A catalytic enantioselective method for the synthesis of chiral 1*H*-isoindoles bearing quaternary stereogenic centers is reported. Powered by readily accessible phosphoramidite ligands, the presented Pd(0)-catalyzed C–H functionalization uses trifluoroacetimidoyl chlorides as electrophilic components. It delivers previously inaccessible perfluoroalkylated 1*H*-isoindoles in high yields and enantioselectivities. The subsequent diastereoselective addition of nucleophiles provides access to densely substituted and sterically hindered isoindolines.

The isoindole scaffold is a frequently occurring motif in natural products and pharmaceuticals (Figure 1).^[1] As well, the structurally related thienopyrrole moiety is found in several biologically active compounds.^[2] While a variety of catalytic enantioselective methods have been developed to access reduced^[3] or oxidized^[4] derivatives of the isoindole skeleton, synthetic approaches to 1*H*-isoindoles are limited to conventional methods.^[5] Only few catalytic approaches, implemented in a racemic fashion, have been reported.^[6] Therefore, catalytic enantioselective strategies toward synthesis of chiral 1*H*-isoindoles would fill a gap in synthetic methodology and would be a desirable goal.

Figure 1. Biologically active molecules with an isoindole or thienopyrrole core.

Metal-catalyzed C–H functionalizations have developed over the last decade as powerful tools for the rapid generation of structural complexity from simple precursors.^[7, 8] For instance, the enantioselective synthesis of nitrogen-containing heterocycles by Pd(0)-catalyzed intramolecular cyclizations has emerged as an

attractive strategy. There is a wide range of examples employing aryl (pseudo)halides as electrophiles.^[9] Related asymmetric C–H alkenylation,^[10] alkylation^[11] and imidoylation^[12] methods are significantly less developed, despite their potential to access synthetically valuable building blocks. Recently, we have shown that trifluoroacetimidoyl chlorides are competent electrophiles for Pd(0)-catalyzed C(sp³)–H functionalizations.^[12b, 13]

Herein, we report an enantioselective C–H functionalization approach for chiral 1*H*-isoindoles bearing a quaternary stereogenic center (Scheme 1). The quaternary stereogenic center not only provides a three-dimensional structure with functional exit vectors but also prevents isomerization of the 1*H*-isoindole to the highly labile 2*H*-isoindole. The usage of trifluoromethyl-substituted imidoyl chlorides as electrophilic component results in the introduction of perfluoroalkyl substituent on the product. Due to the relevance of fluorine-containing compounds in active ingredient discovery,^[14] such pattern is an additional attractive feature of the approach. Moreover, while methods for perfluoroalkylated isoindolines are reported,^[15] this relevant substitution type fails in conventional methods and does not deliver the corresponding 1*H*-isoindoles.^[5a]

Scheme 1. Enantioselective C–H functionalization strategy for chiral 1*H*-isoindoles.

The envisaged cyclization was initially investigated and optimized with trifluoroacetimidoyl chloride **1a** as the prototype substrate (Table 1). In contrast to its success for a range of enantioselective C–H functionalizations,^[9a, 16] Taddol-derived phosphoramidite **L1** delivered isoindole **2a** only with a modest level of enantioselectivity of 68.5:31.5, albeit excellent chemical yield (entry 1). Related phosphonite ligand **L2** provided even lower enantioselectivity (entry 2). An increase of the steric bulk of flanking aryl groups of the Taddol framework had no beneficial influence for the enantioselectivity (entries 3 and 4). In contrast, the use of phosphoramidite ligand **L5**^[17] resulted in a very efficient reaction proceeding with high enantioselectivity (entry 5). Lowering the temperature from 70 °C to 40 °C, increased the

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selectivity to 95:5 er while the high reactivity of the catalytic system was maintained (entries 5–7). Explored modifications of the *P*-substituent of the diazophospholane or its chiral side-arms did not increase the level of enantiocontrol (entries 8–10). CsOAc was the base of choice among the screened carboxylates and counter ions (entry 6, 11–12). Employing Pd(allyl)Cp as the palladium source instead of Pd(dba)₂ resulted in a significantly slower reaction, presumably due to a sluggish formation of the active catalyst (entry 13). The catalyst loading could be lowered to 5 mol% (entry 14). The transformation proceeded smoothly on a 20-fold increased reaction scale (1 mmol), and isoindole **2a** was obtained in similarly high yield and enantioselectivity with a further reduced catalyst loading of 2.5 mol% Pd (Entry 15).

Table 1. Optimization of the enantioselective 1*H*-isoindole synthesis.^[a]

Entry	L*	Base	T	2a ^[b]	er
1	L1	CsOAc	70 °C	97%	68.5:31.5
2	L2	CsOAc	70 °C	99%	55:45
3	L3	CsOAc	70 °C	73%	50.5:49.5
4	L4	CsOAc	70 °C	68%	56:47
5	L5	CsOAc	70 °C	98%	93:7
6	L5	CsOAc	40 °C	91%	95:5
7	L5	CsOAc	23 °C	42%	95.5:4.5
8	L6	CsOAc	40 °C	78%	93.5:6.5
9	L7	CsOAc	40 °C	53%	55.5:44.5
10	L8	CsOAc	40 °C	99%	51.5:48.5
11	L5	KOAc	40 °C	95%	94.5:5.5
12	L5	CsOPiv	40 °C	96%	93.5:6.5
13 ^[c]	L5	CsOAc	40 °C	22%	95:5
14 ^[d]	L5	CsOAc	40 °C	93%	95.5:4.5
15 ^[e]	L5	CsOAc	40 °C	88% ^[f]	94.5:5.5

[a] Conditions: 0.05 mmol **1a**, 10 mol% Pd(dba)₂, 20 mol% L*, 1.5 equiv base, 0.1 M in toluene for 14 h at indicated temperature. [b] Determined by ¹H-NMR with an internal standard. [c] Pd(allyl)Cp instead of Pd(dba)₂. [d] With 5 mol% Pd(dba)₂ and 10 mol% L5 for 36 h. [e] 1 mmol **1a** (0.34 g), 2.5 mol% Pd(dba)₂, 5 mol% L5, 1.5 mmol CsOAc, 0.1 M in toluene, 60 h. [f] Isolated yield.

Having established optimal reaction conditions, we investigated the scope of the developed transformation (Scheme 2). A variety of *para*-substituted arene substrates underwent efficient C–H functionalization and allowed for the synthesis of

isoindoles **2** in a highly enantioselective fashion. Both electron-rich and electron-poor substrates reacted well. In accordance with the CMD-type activation mechanism,^[7a, 18] electron-rich substrate **1d** reacted slower and hence required longer reaction time. Notably, the reaction tolerated aryl chlorides (substrate **1f**) opening possibilities for subsequent orthogonal Pd-catalyzed functionalizations. Cyclization of naphthyl-derived trifluoroacetimidoyl chloride **1g** allowed for the selective construction of the 1*H*-benzo[*f*]isoindole aromatic system of **2g**. Substrate **1h** bearing electron-rich thienyl substituents underwent efficient cyclization. The corresponding thienopyrrole was obtained in high yield and excellent enantioselectivity. Furthermore, X-Ray crystallographic analysis of thienopyrrole **2h** allowed the assignment of the absolute configuration to be (S).^[19] Different imidoyl chlorides with longer perfluoroalkylated chains reacted well and provided comparable levels of enantioselectivity (**2i** and **2j**). With substrates that bear smaller substituents R such as **1k** (R=Me) and **1l** (R=CH₂CH₂OTBS), the transformation was still highly efficient, albeit with a lower enantioselectivity. In contrast, cyclopropyl-substituted isoindole **2m** was obtained with a high level of enantioselectivity. Notably, no product of the facile cyclopropyl C(sp³)–H activation^[12b] was observed in this case. Functionalized substituents R are well tolerated in the cyclization. Both azetidiny- and piperidiny-substituted isoindoles **2n** and **2o** were obtained in high yields and good enantioselectivities.

Scheme 2. Scope of the enantioselective 1*H*-isoindole synthesis. Conditions: 0.1 mmol **1**, 5 μmol Pd(dba)₂, 10 μmol L5, 0.15 mmol CsOAc, 0.1 M in toluene for 36 h at 40 °C; isolated yields. [a] for 80 h. [b] With 10 mol% Pd(dba)₂ and 20 mol% L5. 2-Np = 2-naphthyl, Ts = *p*-toluenesulfonyl.

The discovery of conditions for improved enantioselectivity for substrates with small substituents R was challenging and required substantial additional screening efforts (see ESI for the extensive set of optimization reactions). In essence, the parent Taddol-phosphoramidite ligand **L1** was the best performer. Its

combination with the cesium salt of *ortho*-anisic acid as the base allowed for high enantioselectivity of this important substrate subset (Scheme 3). As previously, the reaction outcome remains largely unaffected by electronic modifications of the aryl group. Electron-rich and electron-poor arenes were efficiently cyclized to products **2k**, **2p** and **2q**. Moreover, a benzothiophene substituent reacts well, providing benzothienopyrrole heterocycle **2r** in good yield and high enantioselectivity. The re-optimized conditions were equally applicable for other small groups R. For instance, benzyl ether and alkyl chains have no negative influence on the selectivity of the transformation and *1H*-isindoles **2s** and **2t** were obtained in good enantioselectivity.

Scheme 3. Scope of the enantioselective cyclization for *1H*-isindoles **2** with small substituents R. Conditions: 0.1 mmol **1**, 10 μ mol Pd(allyl)Cp, 20 μ mol **L1**, 0.15 μ mol cesium *o*-anisate, 0.1 M in toluene for 36 h at 50 °C; isolated yields.

While the *1H*-isindole products are very stable, the CF₃-substituted imine moiety retains some moderate electrophilic character. For instance, a reduction of **2t** with Red-Al delivered tri-substituted isoindoline **3** in good yield and 6.3:1 diastereoselectivity (Scheme 4). The ether side chain directs the approach of the hydride from the same face. The addition of methyl lithium to compound **2a** occurred with excellent diastereoselectivity from the same face as the less bulky phenyl group, leading to hindered tetra-substituted isoindoline **4**.

Scheme 4. Diastereoselective additions of hydride and MeLi across the imine of *1H*-isindoles **2**. Red-Al=sodium bis(2-methoxyethoxy)aluminum hydride.

In conclusion, we have developed a highly enantioselective approach to CF₃-substituted chiral *1H*-isindoles. The Pd(0)-catalyzed C–H functionalization is enabled by readily accessible and bench-stable diazaphospholane or TADDOL-phosphoramidite ligands. In addition to a perfluoroalkyl group, the

obtained *1H*-isindoles bear a quaternary stereogenic center and feature synthetically attractive functionalities. Furthermore, the diastereoselective additions of nucleophiles allow preparation of hindered and heavily substituted isoindolines.

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- [1] a) K. Speck, T. Magauer, *Beilstein J. Org. Chem.* **2013**, *9*, 2048–2078; b) A. Mertens, H. Zilch, B. Koenig, W. Schaefer, T. Poll, W. Kampe, H. Seidel, U. Leser, H. Leinert, *J. Med. Chem.* **1993**, *36*, 2526–2535; c) T. L. Stuk, B. K. Assink, R. C. Bates, D. T. Erdman, V. Fedij, S. M. Jennings, J. A. Lassig, R. J. Smith, T. L. Smith, *Org. Process Res. Dev.* **2003**, *7*, 851–855; d) B.-M. Swahn *et al.*, *J. Med. Chem.* **2012**, *55*, 9346–9361; e) S. Sharma, Y. Oh, N. K. Mishra, U. De, H. Jo, R. Sachan, H. S. Kim, Y. H. Jung, I. S. Kim, *J. Org. Chem.* **2017**, *82*, 3359–3367; f) J. H. Come *et al.*, *J. Med. Chem.* **2018**, *61*, 5245–5256; g) H. Kamauchi, Y. Shiraishi, A. Kojima, N. Kawazoe, K. Kinoshita, K. Koyama, *J. Nat. Prod.* **2018**, *81*, 1290–1294.
- [2] a) N. P. H. Tan, M. K. Taylor, S. E. Bottle, C. E. Wright, J. Ziogas, J. M. White, C. H. Schiesser, N. V. Jani, *Chem. Commun.* **2011**, *47*, 12083–12085; b) N. V. Jani, J. Ziogas, J. A. Angus, C. H. Schiesser, P. E. Macdougall, R. L. Grange, C. E. Wright, *Eur. J. Pharmacol.* **2012**, *695*, 96–103; c) G. Rai, V. N. Vyjayanti, D. Dorjsuren, A. Simeonov, A. Jadhav, D. M. Wilson, D. J. Maloney, *J. Med. Chem.* **2012**, *55*, 3101–3112.
- [3] a) D. Enders, A. Narine Arun, F. Toulgoat, T. Bisschops, *Angew. Chem. Int. Ed.* **2008**, *47*, 5661–5665; b) S. Takizawa, N. Inoue, S. Hirata, H. Sasai, *Angew. Chem. Int. Ed.* **2010**, *49*, 9725–9729; c) C. Wang, X.-H. Chen, S.-M. Zhou, L.-Z. Gong, *Chem. Commun.* **2010**, *46*, 1275–1277; d) F. J. Williams, E. R. Jarvo, *Angew. Chem. Int. Ed.* **2011**, *50*, 4459–4462; e) Z. He, T. Liu, H. Tao, C.-J. Wang, *Org. Lett.* **2012**, *14*, 6230–6233.
- [4] a) Y. Suzuki, M. Kanai, S. Matsunaga, *Chem. Eur. J.* **2012**, *18*, 7654–7657; b) B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 7896–7899; c) M. Nagamoto, D. Yamauchi, T. Nishimura, *Chem. Commun.* **2016**, *52*, 5876–5879; d) C.-Q. Wang, L. Ye, C. Feng, T.-P. Loh, *J. Am. Chem. Soc.* **2017**, *139*, 1762–1765; e) L. Teng, Z. Chao, Y. Xiaoqiang, W. Jun, *Angew. Chem. Int. Ed.* **2018**, *57*, 4048–4052.
- [5] a) C. G. Savarin, C. Grisé, J. A. Murry, R. A. Reamer, D. Hughes, *Org. Lett.* **2007**, *9*, 981–983; b) K. Kobayashi, M. Horiuchi, S. Fukamachi, H. Konishi, *Heterocycles* **2009**, *78*, 669–677; c) B. Hatano, K. Miyoshi, H. Sato, T. Ito, T. Ogata, T. Kijima, *Tetrahedron Lett.* **2010**, *51*, 5399–5401; d) M. Kuroda, K. Kobayashi, *Helv. Chim. Acta* **2015**, *98*, 279–286.
- [6] a) Q. Wang, Y. Li, Z. Qi, F. Xie, Y. Lan, X. Li, *ACS Catal.* **2016**, *6*, 1971–1980; b) Y. Yi, H. Lee, C.-H. Jun, *Chem. Commun.* **2016**, *52*, 10171–10174; c) S. Tang, S.-W. Yang, H. Sun, Y. Zhou, J. Li, Q. Zhu, *Org. Lett.* **2018**, *20*, 1832–1836.
- [7] Selected recent reviews: a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; b) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, *Chem. Rev.* **2017**, *117*, 9333–9403; c) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754–8786; d) J. R. Hummel, J. A. Boerth, J. A. Ellman, *Chem. Rev.* **2017**, *117*, 9163–9227; e) D.-S. Kim, W.-J. Park, C.-H. Jun, *Chem. Rev.* **2017**, *117*, 8977–9015; f) K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302–9332.
- [8] Selected reviews on enantioselective C–H functionalizations: a) J. Wencel-Delord, F. Colobert, *Chem. Eur. J.* **2013**, *19*, 14010–14017; b) C.

- Zheng, S.-L. You, *RSC Advances* **2014**, *4*, 6173-6214; c) D.-W. Gao, J. Zheng, K.-Y. Ye, C. Zheng, S.-L. You in *Asymmetric Functionalization of C-H Bonds*, (Ed.: S.-L. You), Royal Society of Chemistry, Cambridge, U. K., **2015**, p. 141. d) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908-8976; e) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, *Science* **2018**, *359*, 759.
- [9] a) S. Anas, A. Cordi, H. B. Kagan, *Chem. Commun.* **2011**, *47*, 11483-11485; b) M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Angew. Chem. Int. Ed.* **2011**, *50*, 7438-7441; c) D. Katayev, M. Nakanishi, T. Burgi, E. P. Kündig, *Chem. Sci.* **2012**, *3*, 1422-1425; d) T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 2238-2242; e) T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12842-12845; f) E. Larionov, M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Chem. Sci.* **2013**, *4*, 1995-2005; g) T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2013**, *52*, 7865-7868; h) D. Katayev, E. Larionov, M. Nakanishi, C. Besnard, E. P. Kündig, *Chem. Eur. J.* **2014**, *20*, 15021-15030; i) L. Liu, A.-A. Zhang, R.-J. Zhao, F. Li, T.-J. Meng, N. Ishida, M. Murakami, W.-X. Zhao, *Org. Lett.* **2014**, *16*, 5336-5338; j) X. Ma, Z. Gu, *RSC Advances* **2014**, *4*, 36241-36244; k) Z.-Q. Lin, W.-Z. Wang, S.-B. Yan, W.-L. Duan, *Angew. Chem. Int. Ed.* **2015**, *54*, 6265-6269; l) J. Pedroni, T. Saget, P. A. Donets, N. Cramer, *Chem. Sci.* **2015**, *6*, 5164-5171; m) C. He, M. Hou, Z. Zhu, Z. Gu, *ACS Catal.* **2017**, *7*, 5316-5320; n) L. Yang, R. Melot, M. Neuburger, O. Baudoin, *Chem. Sci.* **2017**, *8*, 1344-1349; o) L. Yang, M. Neuburger, O. Baudoin, *Angew. Chem. Int. Ed.* **2018**, *57*, 1394-1398; p) R. Rocaboy, D. Dailler, O. Baudoin, *Org. Lett.* **2018**, *20*, 772-775; q) C. G. Newton, E. Braconi, J. Kuziola, M. D. Wodrich, N. Cramer, *Angew. Chem. Int. Ed.* **2018**, DOI:10.1002/anie.201806527.
- [10] Alkenylations: a) M. R. Albicker, N. Cramer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9139-9142; b) C. L. Ladd, A. B. Charette, *Org. Lett.* **2016**, *18*, 6046-6049; c) P. M. Holstein, D. Dailler, J. Vantourout, J. Shaya, A. Millet, O. Baudoin, *Angew. Chem. Int. Ed.* **2016**, *55*, 2805-2809; c) D. Grosheva, N. Cramer, *ACS Catal.* **2017**, *7*, 7417-7420.
- [11] Alkylations: a) J. Pedroni, M. Boghi, T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9064; b) J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 11826.
- [12] Imidoylations and carbamoylations: a) J. Wang, D.-W. Gao, J. Huang, S. Tang, Z. Xiong, H. Hu, S.-L. You, Q. Zhu, *ACS Catal.* **2017**, *7*, 3832-3836; b) J. Pedroni, N. Cramer, *J. Am. Chem. Soc.* **2017**, *139*, 12398-1240; c) D. Dailler, R. Rocaboy, O. Baudoin, *Angew. Chem. Int. Ed.* **2017**, *56*, 7218-7222; d) S. Luo, Z. Xiong, Y. Lu, Q. Zhu, *Org. Lett.* **2018**, *20*, 1837-1840.
- [13] Trifluoroacetimidoyl chlorides in achiral functionalizations: a) H. Amii, Y. Kishikawa, K. Uneyama, *Org. Lett.* **2001**, *3*, 1109-1112; b) M. Zhu, W. Fu, G. Zou, C. Xu, Z. Wang, *J. Fluorine Chem.* **2014**, *163*, 23-27; c) J. Pedroni, N. Cramer, *Org. Lett.* **2016**, *18*, 1932-1935.
- [14] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330; b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214-8264; c) E. Prchalová, O. Štěpánek, S. Smrček, M. Katora, *Future Medicinal Chemistry* **2014**, *6*, 1201-1229; d) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315-8359.
- [15] a) G. T. Shchetnikov, S. N. Osipov, C. Bruneau, P. H. Dixneuf, *Synlett* **2008**, 578-582; b) S. Fustero, J. Moscardo, M. Sánchez-Roselló, E. Rodríguez, P. Barrio, *Org. Lett.* **2010**, *12*, 5494-5497; c) S. Fustero, I. Ibáñez, P. Barrio, M. A. Maestro, S. Catalán, *Org. Lett.* **2013**, *15*, 832-835; d) S. Fustero, L. Herrera, R. Lázaro, E. Rodríguez, M. A. Maestro, N. Mateu, P. Barrio, *Chem. Eur. J.* **2013**, *19*, 11776-11785.
- [16] J. Pedroni, N. Cramer, *Chem. Commun.* **2015**, *51*, 17647-17657.
- [17] P. A. Donets, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 11772-11775.
- [18] S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.*, **2010**, *132*, 10692-10705.
- [19] CCDC 1860949 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.

Daria Grosheva, Nicolai Cramer*

Page No. – Page No.
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A catalytic enantioselective method for the synthesis of chiral 1*H*-isoindoles bearing quaternary stereogenic centers is reported. Powered by readily accessible phosphordiamidite ligands, the Pd(0)-catalyzed C–H functionalization uses trifluoroacetimidoyl chlorides as electrophilic components and delivers perfluoroalkylated 1*H*-isoindoles in high yields and enantioselectivities. Subsequent diastereoselective additions of nucleophiles provide access to densely substituted isoindolines.