Pyrrole Alkylation

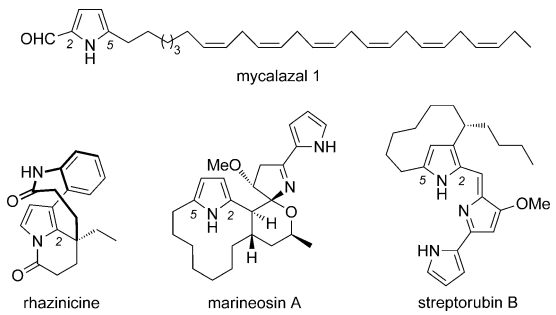
DOI: 10.1002/ange.201301154

Palladium-Catalyzed Direct C–H Alkylation of Electron-Deficient Pyrrole Derivatives**

*Lei Jiao and Thorsten Bach**

Dedicated to Dr. Toni Dockner on the occasion of his 75th birthday

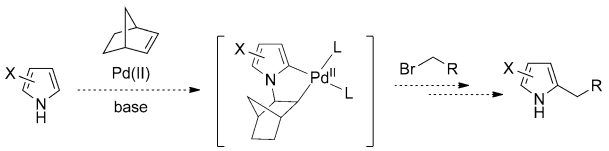
Pyrroles represent an important class of nitrogen-containing heterocycles. The pyrrole core exists abundantly in biologically active compounds, and many pyrrole derivatives have been employed as versatile synthetic intermediates and building blocks.[1,2] Among them, C2,C5-alkyl-substituted pyrroles have attracted much research interest, because they are a key structural element in several biologically active natural products (Scheme 1).[3]



Scheme 1. Biologically active natural products containing a C2,C5-alkyl substituted pyrrole framework.

There is great interest in new synthetic methods that provide selective access to substituted pyrrole derivatives.[4,5] With regard to the alkylation of free-NH pyrroles there has been only limited success so far. The traditional nucleophilic alkylation reaction of metal pyrrolides usually results in a mixture of regioisomeric alkylation products.[6] The oxidative radical aromatic substitution of pyrroles with in situ generated α-carbonyl radical intermediates produces alkyl pyrroles regioselectively, although with limited scope.[7] The Friedel–Crafts alkylation of pyrroles with α,β-unsaturated carbonyl compounds[8] and the transition-metal-catalyzed allylic alkylation of pyrroles[9] enable the installation of a functionalized alkyl group to the C2-position of pyrrole. However, these methods are restricted regarding the choice of electrophile, and an introduction of simple alkyl groups is impossible. The recently reported C2,C5-alkylation of a pyrrole in an ionic liquid is the only regioselective pyrrole alkylation method that works with simple alkyl halides,[10] but only a limited number of electron-rich pyrroles can be employed and they have to be used in large excess (10 equiv). Thus, methods enabling a regioselective C-alkylation of pyrroles with simple alkyl halides are still in a high demand. Herein, we report a regioselective pyrrole alkylation reaction employing electron-deficient pyrrole derivatives and common primary alkyl bromides as substrates; this method complements the established protocols.

Apart from the above-mentioned reasons, an additional motivation for studying the pyrrole alkylation arose from our earlier discovery of an NH indole alkylation with alkyl bromides.[11] This reaction involves the use of a Pd^{II} catalyst and norbornene as a transpositional co-catalyst, in which an indole- and norbornyl-fused palladaheterocycle forms as the key intermediate[11b] and an alkyl bromide reacts with this intermediate[12] to achieve regioselective alkylation at the C2-position of indole. Following this success, we hoped to establish a regioselective direct alkylation method for pyrroles, involving the Pd^{II}/norbornene-co-catalyzed process (Scheme 2).



Scheme 2. Design of a Pd^{II}-catalyzed norbornene-mediated pyrrole alkylation reaction.

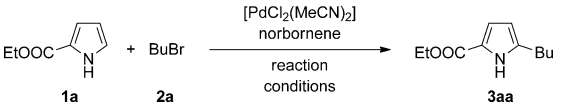
Disappointingly, preliminary attempts towards alkylation of electron-rich pyrroles, such as pyrrole and 2-phenylpyrrole, were largely unsuccessful. Given that pyrrole is more electron rich and less acidic ($pK_a = 23$)[13] than indole ($pK_a = 20.95$),[13] we supposed that pyrrole derivatives with an electron-withdrawing substituent might better meet the electronic requirements of this reaction. Therefore, we studied the alkylation of the readily available and versatile building block ethyl-1*H*-pyrrole-2-carboxylate (**1a**) with *n*-butyl bromide (Table 1). Under reaction conditions identical to the previously established indole alkylation method,[11] the 5-alkylation product **3aa** was obtained as a minor product, in addition to a major amount of N-alkylation product (entry 1). This finding indicated that the electron-deficient pyrrole derivative par-

[*] Dr. L. Jiao, Prof. Dr. T. Bach
Lehrstuhl für Organische Chemie I and Catalysis Research Center (CRC), Technische Universität München
Lichtenbergstr. 4, 85747 Garching (Germany)
E-mail: thorsten.bach@ch.tum.de
Homepage: http://www.oc1.ch.tum.de/home_en/

[**] L.J. acknowledges the Alexander von Humboldt Foundation for a postdoctoral fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301154.

Table 1: Optimization of the reaction conditions for the butylation of ethyl 1*H*-pyrrole-2-carboxylate (**1a**) with butyl bromide (**2a**).[a]



1a **2a** **3aa**

Entry	Base (equiv)	Solvent	Conc. [M][b]	*T* [°C]	*t* [h]	Conv. [%][c]	Yield [%][d]
1	K_2CO_3 (2)	DMA[e]	0.2	70	43	(62)	(13)[f]
2	$KHCO_3$ (3)	DMA[e]	0.2	70	24	61	49
3	$KHCO_3$ (3)	DMA	0.2	80	21	99	70
4	$KHCO_3$ (3)	DMA[e]	0.2	90	21	97	81
5	$KHCO_3$ (3)	DMA	0.2	90	19	99	75 (73)[g]
6	$KHCO_3$ (3)	DMF[e]	0.2	90	19	83	67
7	$KHCO_3$ (3)	MeCN[e]	0.2	90	19	68	48
8	$KHCO_3$ (3)	MeCN	0.2	90	19	74	58
9	$KHCO_3$ (3)	DMA	1	90	22	97	89 (83)[h]

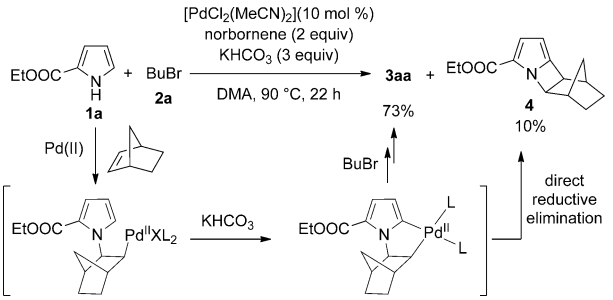
[a] Pyrrole **1a** (1 equiv), bromide **2a** (2 equiv), $[PdCl_2(MeCN)_2]$ (10 mol%), and norbornene (2 equiv) were heated in the indicated solvent for the indicated temperature *T* under argon. [b] Concentration with respect to the pyrrole substrate. [c] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. The conversion based on isolated starting material is given in brackets. [d] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. The yields after column chromatography are given in brackets. [e] With 0.5 M H_2O as additive. [f] Isolated together with 23% of ethyl *N*-butylpyrrol-2-carboxylate. [g] Reaction time = 22 h. [h] Under air. DMF = *N*,*N*-dimethylformamide.

ticipates in the proposed alkylation process, although further optimization was clearly necessary. Upon using $KHCO_3$ as base instead of K_2CO_3, formation of the N-alkylation by-product was suppressed and 5-alkylpyrrole **3aa** was formed in an increased yield (entry 2). An elevated reaction temperature (90 °C) improved both conversion and yield (entries 2–5).

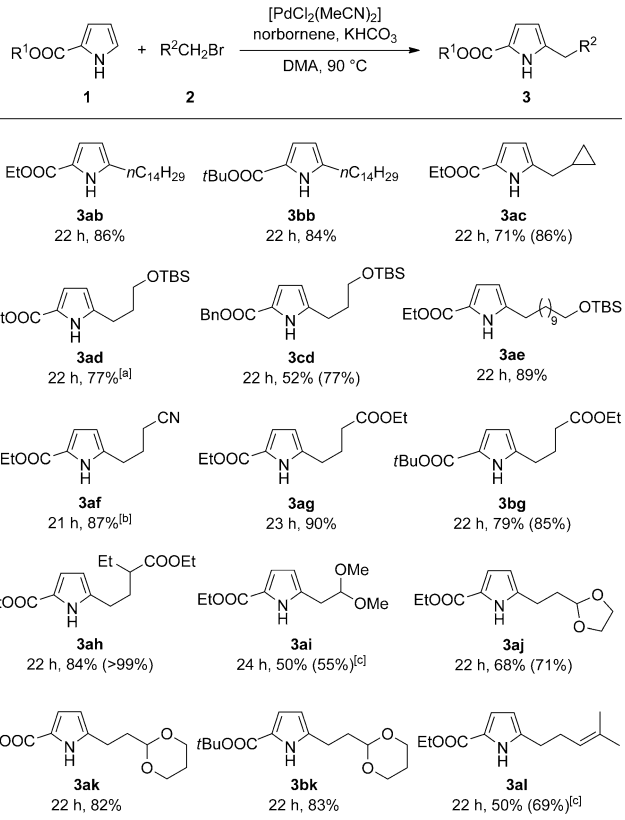
A screen of solvents indicated that *N*,*N*-dimethylacetamide (DMA) was the optimal solvent among those tested (entries 4–8), and, unlike in the corresponding indole alkylation reaction,[11] H_2O as additive did not bring about a significant beneficial effect (entries 4 vs. 5 and 7 vs. 8). Running the reaction at high concentration ($c = 1$ M) resulted in a further improvement in yield, and a reaction at synthetic scale (1 mmol) afforded product **3aa** in an 83% yield (entry 9). Notably, the reaction does not require an inert atmosphere and proceeds well under air (entry 9).[14]

Control experiments indicated that the C5-alkylation of pyrrole **1a** did not proceed in the absence of either the Pd^{II} catalyst or norbornene;[14] this result is consistent with the proposed Pd^{II}-catalyzed norbornene-mediated mechanism (Scheme 2). The formation of the norbornane-fused azacyclobutane by-product **4**, observed during the optimization study, also sheds light on the reaction mechanism (Scheme 3). This compound is assumed to be the direct reductive elimination product from a potential norbornene-containing palladacycle intermediate, thus providing support for the intermediacy of the proposed palladaheterocycle species in the alkylation process.[15]

Studies on other electron-deficient pyrrole derivatives showed that pyrrole-2-carboxylates are the best suited substrates for this reaction, as compared with 2-cyano-, 2-dimethylaminocarbonyl-, 2-formyl-, and 2-acetyl-substituted 1*H*-pyrroles.[16] Therefore, the scope of this alkylation reaction was explored with the former compound class and various primary alkyl bromides (Scheme 4). The reaction tolerates different functional groups on the alkyl moiety to afford an array of functionalized 2,5-disubstituted pyrrole derivatives in good yields. Some alkyl bromides (i.e., **2f**, **2i**, and **2l**) showed diminished reactivity and slightly modified



Scheme 3. Isolation of azacyclobutane by-product **4** in the butylation of substrate **1a** ($c = 0.2$ M).

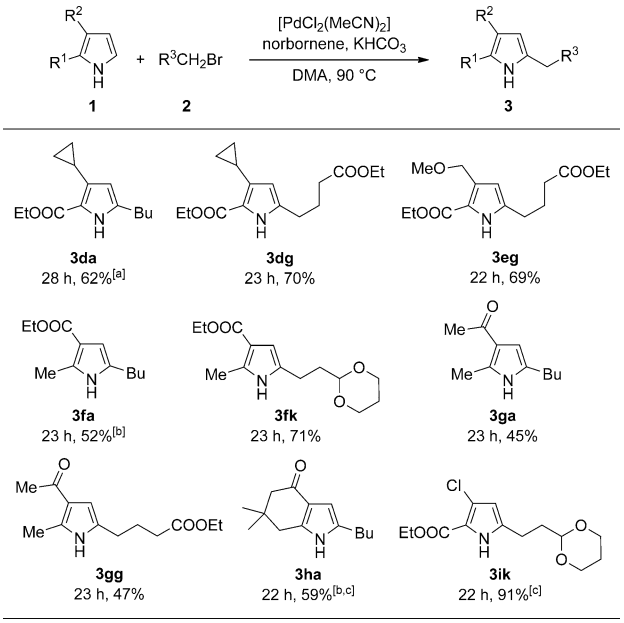


Scheme 4. Reaction times and yields in the direct alkylation of pyrrole-2-carboxylates. Reaction conditions: Pyrrole **1** (1 equiv), bromide **2** (2 equiv), norbornene (2 equiv), $KHCO_3$ (3 equiv) and $[PdCl_2(MeCN)_2]$ (10 mol%) were heated in anhydrous DMA ($c = 1$ M), at 90 °C under air. Yields based on conversion are given in brackets. [a] $c = 0.33$ M. [b] Reaction was conducted under 1 atm O_2 in a solvent mixture of DMA/DMSO 9:1 ($c = 1$ M). [c] 0.5 equiv of 2-bromomesitylene was added.

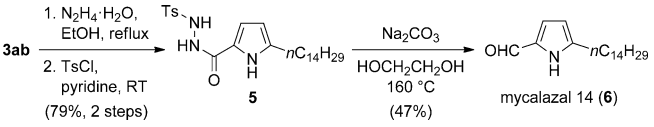
reaction conditions had to be applied. With regard to the pyrrole substrate, ethyl and *tert*-butyl pyrrole-2-carboxylates **1a** and **1b** participated in the alkylation reaction equally efficiently, whereas the corresponding benzyl ester **1c** was less reactive. In all cases, the 5-alkylation product was the only regioisomer obtained. It has been established that the reactive site of pyrrole-2-carboxylates for electrophilic substitution is the C4-position as a result of the directing effect of the electron-withdrawing ester substituent.[17] This intrinsic preference can be overcome by using the present Pd^{II}-catalyzed alkylation reaction to regioselectively introduce an alkyl group at the C5-position.

To explore the potential of the present method for synthesizing more complex alkylpyrrole derivatives, we employed 2,3-disubstituted pyrroles in the alkylation reaction (Scheme 5). Both alkoxycarbonyl and acyl groups can be used as electron-withdrawing substituents on either the C2- or C3-position of pyrrole. A chlorinated pyrrole substrate **3i** underwent the alkylation smoothly to afford chloro-substituted alkylpyrrole **3ik** in high yield. The C–H alkylation reaction always took place at the C5-position[18] to afford a series of 2,3,5-trisubstituted pyrrole products. Since numerous approaches to 2,3-disubstituted electron-deficient pyrroles have been established,[19] the combination of these methods and the present 5-alkylation protocol provides a regioselective route to advanced functionalized pyrrole derivatives.

Synthetic manipulations on the alkylpyrrole products highlight the utility of the present alkylation method. The carboxylate functionality can be removed under either acidic



Scheme 5. Reaction times and yields in the direct alkylation of 2,3-disubstituted pyrroles. Reaction conditions: Pyrrole **1** (1 equiv), bromide **2** (2 equiv), norbornene (2 equiv), $KHCO_3$ (3 equiv), and $[PdCl_2(MeCN)_2]$ (10 mol%) were heated in anhydrous DMA ($c = 1$ M), at 90 °C under air. Yields are based on conversion of pyrrole. [a] 4 equiv of BuBr and 5 equiv of $KHCO_3$ were used. [b] $c = 0.2$ M. [c] K_2HPO_4 (3 equiv) as the base.



Scheme 6. Synthesis of mycalazal 14 (**6**) from alkylation product **3ab**.

(e.g. for **3bg**)[14] or basic decarboxylation conditions (e.g. for **3ak**),[14] thus enabling a formal regioselective alkylation of the pyrrole motif. Another example is the transformation of the carboxylate group in product **3ab** to a formyl group, which was achieved by the formation of *N*-acyl-*N*′-tosylhydrazide **5** and a subsequent McFadyen–Stevens reaction[20] (Scheme 6). This sequence delivered mycalazal 14 (**6**), a lipophilic pyrrole natural product isolated from the lipid extract of the marine sponge *Mycale* sp.[21]

In summary, we have developed a Pd^{II}-catalyzed, norbornene-mediated regioselective C–H alkylation method for electron-deficient pyrroles that uses non-activated primary alkyl bromides as the alkylating reagent. This protocol enables a straightforward approach to multisubstituted alkylpyrrole derivatives and complements the existing pyrrole alkylation methods. The success of this reaction demonstrates the potential of the Pd^{II}/norbornene co-catalyzed reaction system in promoting the *ortho*-selective C–H alkylation on different N–H heterocycles, which remains an ongoing research project in our laboratory.

Experimental Section

Typical procedure for the synthesis of **3aa**: A reaction tube (30 × 190 mm) equipped with a magnetic stirring bar and a rubber septum was charged with pyrrole-2-carboxylate **1a** (140 mg, 1.01 mmol), norbornene (189 mg, 2.01 mmol), $KHCO_3$ (308 mg, 3.08 mmol), $[PdCl_2(MeCN)_2]$ (25.5 mg, 0.098 mmol), and BuBr (**2a**, 285 mg, 2.08 mmol). Anhydrous DMA (1 mL) was added, and the reaction tube was heated in an aluminium block preset to 90 °C, under a balloon pressure of air for 22 h. The reaction mixture was cooled to room temperature, diluted with ether (30 mL), and filtered. The filtrate was washed with water (20 mL) and the organic phase was separated. The aqueous layer was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After evaporation of the solvent the crude product was purified by flash column chromatography on silica gel (eluted with pentane/ether 20:1 to 10:1) to afford ethyl 5-butylpyrrole-2-carboxylate (**3aa**) as a pale yellow oil (163 mg, 83% yield).

Received: February 8, 2013
Published online: April 25, 2013

Keywords: alkylation · C–H activation · heterocycles · homogeneous catalysis · palladium

[1] M. d'Ischia, A. Napolitano, A. Pezzella, *Comprehensive Heterocyclic Chemistry III*: *Pyrroles and their Benzo Derivatives*: *Applications*, *Vol. 3* (Eds: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Amsterdam, **2008**, pp. 353–388.

[2] Selected recent reports on the synthesis of pyrroles: a) I. Schäfer, T. Opatz, *Synthesis* **2011**, 1691–1704; b) X. Xin, D. Wang, X. Li, B. Wan, *Angew. Chem.* **2012**, *124*, 1725–1729; *Angew. Chem. Int.*

Ed. **2012**, *51*, 1693 – 1697; c) W. J. Humenny, P. Kyriacou, K. Sapeta, A. Karadeolian, M. A. Kerr, *Angew. Chem.* **2012**, *124*, 11250 – 11253; *Angew. Chem. Int. Ed.* **2012**, *51*, 11088 – 11091; d) Y.-L. Zhao, C.-H. Di, S.-D. Liu, J. Meng, Q. Liu, *Adv. Synth. Catal.* **2012**, *354*, 3545 – 3550; e) R. Narayan, R. Fröhlich, E.-U. Würthwein, *J. Org. Chem.* **2012**, *77*, 1868 – 1879; f) Y.-Q. Zhang, D.-Y. Zhu, B.-S. Li, Y.-Q. Tu, J.-X. Liu, Y. Lu, S.-H. Wang, *J. Org. Chem.* **2012**, *77*, 4167 – 4170; g) M. Zhao, F. Wang, X. Li, *Org. Lett.* **2012**, *14*, 1412 – 1415; h) F. Chen, T. Shen, Y. Cui, N. Jiao, *Org. Lett.* **2012**, *14*, 4926 – 4929; i) M. Zhang, H. Neumann, M. Beller, *Angew. Chem.* **2013**, *125*, 625 – 629; *Angew. Chem. Int. Ed.* **2013**, *52*, 597 – 601; j) V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Commun.* **2013**, *49*, 591 – 593; k) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140 – 144; l) L. Wang, L. Ackermann, *Org. Lett.* **2013**, *15*, 176 – 179; m) N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Synthesis* **2013**, *45*, 93 – 100.

[3] Isolation of C-alkyl pyrrole natural products: mycalazals: a) M. J. Ortega, E. Zubia, J. L. Carballo, J. Salvá, *Tetrahedron* **1997**, *53*, 331 – 340; rhazinicine: b) T. S. Kam, G. Subramaniam, W. Chen, *Phytochemistry* **1999**, *51*, 159 – 169; marineosins: c) C. Boonlarppradab, C. A. Kauffmann, P. R. Jensen, W. Fenical, *Org. Lett.* **2008**, *10*, 5505 – 5508; streptorubin B: d) H. Laatsch, M. Kellner, H. Weyland, *J. Antibiot.* **1991**, *44*, 187 – 191.

[4] Review on pyrrole substitution by C–H activation: a) E. M. Beck, M. J. Gaunt, *Top. Curr. Chem.* **2010**, *292*, 85 – 121; for selected recent reports, see: b) O. Vakuliuk, B. Koszarna, D. T. Gryko, *Adv. Synth. Catal.* **2011**, *353*, 925 – 930; c) E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* **2011**, *76*, 471 – 483; d) A. M. Wagner, M. S. Sanford, *Org. Lett.* **2011**, *13*, 288 – 291; e) L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332 – 3335; f) C. B. Bheeter, J. K. Bera, H. Doucet, *Tetrahedron Lett.* **2012**, *53*, 509 – 513; g) L. Zhao, C. Bruneau, H. Doucet, *ChemCatChem* **2013**, *5*, 255 – 262.

[5] Review on regioselective cross-coupling reactions of pyrroles: a) M. G. Banwell, T. E. Goodwin, S. Ng, J. A. Smith, D. J. Wong, *Eur. J. Org. Chem.* **2006**, 3043 – 3060; for selected recent reports, see: b) S. Schröter, T. Bach, *Heterocycles* **2007**, *74*, 569 – 594; c) T. Fukuda, E. Sudo, K. Shimokawa, M. Iwao, *Tetrahedron* **2008**, *64*, 328 – 338; d) F. Ullah, T. T. Dang, J. Heinicke, A. Villinger, P. Langer, *Synlett* **2009**, 838 – 842; e) F. Beaumard, P. Dauban, R. H. Dodd, *Synthesis* **2010**, 4033 – 4042.

[6] a) P. S. Skell, G. P. Bean, *J. Am. Chem. Soc.* **1962**, *84*, 4655 – 4660; b) C. E. Griffin, R. Obrycki, *J. Org. Chem.* **1964**, *29*, 3090 – 3092; c) A. J. Castro, J. F. Deck, N. C. Ling, J. P. Marsh Jr., G. E. Means, *J. Org. Chem.* **1965**, *30*, 344 – 350; d) G. P. Bean, *J. Org. Chem.* **1967**, *32*, 228 – 231; e) E. P. Papadopoulos, K. I. Y. Tabello, *J. Org. Chem.* **1968**, *33*, 1299 – 1300; f) M. G. Reinecke, J. F. Sebastian, H. W. Johnson Jr., C. Pyun, *J. Org. Chem.* **1972**, *37*, 3066 – 3068; g) N.-C. Wang, K.-E. Teo, H. J. Anderson, *Can. J. Chem.* **1977**, *55*, 4112 – 4116.

[7] a) J. H. Byers, J. E. Campbell, F. H. Knapp, J. G. Thissell, *Tetrahedron Lett.* **1999**, *40*, 2677 – 2680; b) J. H. Byers, M. P. Duff, G. W. Woo, *Tetrahedron Lett.* **2003**, *44*, 6853 – 6855; c) Y. M. Osornio, R. Cruz-Almanza, V. Jiménez-Montaño, L. D. Miranda, *Chem. Commun.* **2003**, 2316 – 2317; d) J. H. Byers, A. DeWitt, C. G. Nasveschuk, J. E. Swigor, *Tetrahedron Lett.* **2004**, *45*, 6587 – 6590; e) M. A. Guerrero, L. D. Miranda, *Tetrahedron Lett.* **2006**, *47*, 2517 – 2520; f) O. Guadarrama-Morales, F. Méndez, L. D. Miranda, *Tetrahedron Lett.* **2007**, *48*, 4515 – 4518.

[8] a) For a review, see: A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin, *Handbook of Heterocyclic Chemistry*, *Vol. 3*, Elsevier, Oxford, **2010**, pp. 383 – 472; Selected representative reports for asymmetric Friedel – Crafts alkylation of pyrroles: b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370 – 4371; c) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. García, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154 – 4155; d) G. Blay, I. Fernández, J. R. Pedro, C. Vila, *Org. Lett.* **2007**, *9*, 2601 – 2604; e) B. M. Trost, C. Müller, *J. Am. Chem. Soc.* **2008**, *130*, 2438 – 2439; f) N. Yokoyama, T. Arai, *Chem. Commun.* **2009**, 3285 – 3287; g) L. Hong, C. Liu, W. Sun, L. Wang, K. Wong, R. Wang, *Org. Lett.* **2009**, *11*, 2177 – 2180; h) Y.-F. Sheng, Q. Gu, A.-J. Zhang, S.-L. You, *J. Org. Chem.* **2009**, *74*, 6899 – 6901.

[9] a) A. B. Zaitsev, S. Gruber, P. A. Plüss, P. S. Pregosin, L. F. Veiros, M. Wörle, *J. Am. Chem. Soc.* **2008**, *130*, 11604 – 11605; b) H. Yang, L. Fang, M. Zhang, C. Zhu, *Eur. J. Org. Chem.* **2009**, 666 – 672; c) Z. Cao, Y. Liu, Z. Liu, X. Feng, M. Zhuang, H. Du, *Org. Lett.* **2011**, *13*, 2164 – 2167; d) Y. Liu, Z. Cao, H. Du, *J. Org. Chem.* **2012**, *77*, 4479 – 4483.

[10] a) Y. R. Jorapur, C.-H. Lee, D. Y. Chi, *Org. Lett.* **2005**, *7*, 1231 – 1234; b) Y. R. Jorapur, D. Y. Chi, *Bull. Korean Chem. Soc.* **2011**, *32*, 3130 – 3132.

[11] a) L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990 – 12993; b) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563 – 14572.

[12] For reviews on norbornene-mediated *ortho*-alkylation reactions of aryl halides (Catellani reaction), see: a) M. Catellani, *Synlett* **2003**, 298 – 313; b) M. Catellani, *Top. Organomet. Chem.* **2005**, *14*, 21 – 53; c) M. Catellani, E. Motti, N. Della Ca′, *Acc. Chem. Res.* **2008**, *41*, 1512 – 1522; d) A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1 – 33.

[13] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 – 463.

[14] See the Supporting Information for further details.

[15] In the Catellani reaction, direct reductive elimination from the palladacycle intermediate leads to norbornane-fused cyclobutane by-products, see: a) G. Bocelli, M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1985**, *279*, 225 – 232; b) M. Catellani, G. P. Chiusoli, S. Ricotti, *J. Organomet. Chem.* **1985**, *296*, c11 – c15; c) M. Catellani, L. Ferioli, *Synthesis* **1996**, 769 – 772.

[16] The tested electron-deficient pyrroles either underwent only *N*-alkylation (2-cyano-1*H*-pyrrole) or exhibited a low reactivity, indicating that the choice of the pyrrole substituent is critical for the success of the alkylation reaction.

[17] a) H. J. Anderson, L. C. Hopkins, *Can. J. Chem.* **1964**, *42*, 1279 – 1287; b) M. Tani, T. Ariyasu, C. Nishiyama, H. Hagiwara, T. Watanabe, Y. Yokoyama, Y. Murakami, *Chem. Pharm. Bull.* **1996**, *44*, 48 – 54; c) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, *5th ed.*, Wiley, Chichester, **2010**, p. 310.

[18] When methyl 1*H*-pyrrole-3-carboxylate (**1j**) was employed as a substrate, the alkylation expectedly did not proceed in a selective fashion. An attempted butylation reaction afforded a mixture of 5-butylation (minor) and 2,5-dibutylation product (major). For further details, see the Supporting Information.

[19] a) R. C. Cambie, S. C. Moratti, P. S. Rutledge, P. D. Woodgate, *Synth. Commun.* **1990**, *20*, 1923 – 1929; b) T. D. Lash, M. C. Hoehner, *J. Heterocycl. Chem.* **1991**, *28*, 1671 – 1676; c) A. Rolfs, J. Liebscher, *Angew. Chem.* **1993**, *105*, 797 – 799; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 712 – 714; d) J. Boëlle, R. Schneider, P. Gérardin, B. Loubinoux, *Synthesis* **1997**, 1451 – 1456; e) S. H. Hwang, M. J. Kurth, *Tetrahedron Lett.* **2002**, *43*, 53 – 56; f) Y. Aoyagi, T. Mizusaki, M. Shishikura, T. Komine, T. Yoshinaga, H. Inaba, A. Ohta, K. Takeya, *Tetrahedron* **2006**, *62*, 8533 – 8538; g) E. Bellur, P. Langer, *Tetrahedron Lett.* **2006**, *47*, 2151 – 2154; h) A. V. Lygin, O. V. larionov, V. S. Korotkov, A. de Meijere, *Chem. Eur. J.* **2009**, *15*, 227 – 236; i) E. Bellur, M. A. Yawer, I. Hussain, A. Riahi, O. Fatunsin, C. Fischer, P. Langer, *Synthesis* **2009**, 227 – 242; j) R. Hekmatshoar, S. Sadjadi, S. Sadjadi, M. M. Heravi, Y. S. Beheshtiha, F. F. Bamoharram, *Synth. Commun.* **2010**, *40*, 1708 – 1716.

[20] a) J. S. McFadyen, T. S. Stevens, *J. Chem. Soc.* **1936**, 584 – 587; b) D. L. Boger, M. Patel, *J. Org. Chem.* **1988**, *53*, 1405 – 1415.

[21] S.-C. Mao, Y. Liu, J. B. Morgan, M. B. Jekabsons, Y.-D. Zhou, D. G. Nagle, *J. Nat. Prod.* **2009**, *72*, 1927 – 1936.

