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One-Pot Palladium-Catalyzed Synthesis of Selectively Substituted Phenanthridines by Sequential Aryl-Aryl and Heck Couplings, Aza-Michael and Retro-Mannich Reactions

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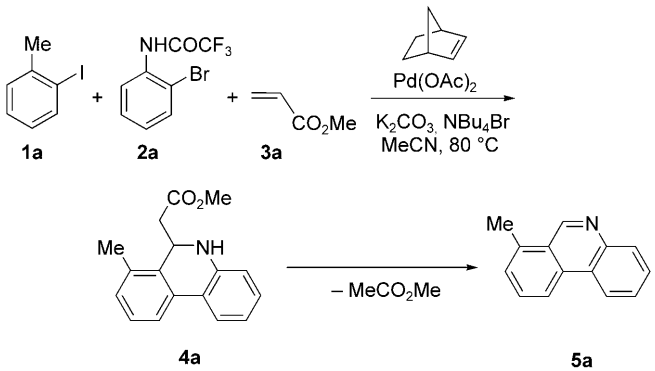
Abstract: A catalytic synthesis of selectively substituted phenanthridines is achieved through a reaction sequence involving palladium/norbornene-catalyzed unsymmetrical aryl-aryl and Heck couplings followed by aza-Michael and retro-Mannich reactions. In spite of the many steps involved the method is very simple and allows the formation of selectively substituted phenanthridines under mild conditions in a straightforward one-pot reaction starting from readily available aryl iodides and bromides.

Keywords: C–C and C–N bond formation; C–H activation; norbornene; palladium; phenanthridine; sequential reactions

Phenanthridines are an important group of natural compounds with a broad range of biological and pharmacological activities.[1] Due to these properties they represent attractive synthetic targets and much attention has been focused to establish simple and efficient methods for their preparation.[2] Palladium-catalyzed sequential reactions have proven very useful since they allow to build up complex structures starting from simple reagents with high selectivity, in one-pot, under mild conditions.[3]

We have previously reported a facile and efficient synthesis of selectively substituted 5-arenesulfonyl-5,6-dihydrophenanthridine derivatives by reaction of an *ortho*-substituted aryl iodide with a sulfonylated *o*-bromoaniline and an activated terminal olefin, in the presence of $Pd(OAc)_2$ and norbornene as catalyst, K_2CO_3 and NBu_4Br in MeCN.[4] On replacing the sulfonylated *o*-bromoaniline with the trifluoroacetylated one, the reaction became very sluggish leading to poor conversion of both aryl halides. For example *o*-iodotoluene (**1a**) reacted with *o*-bromo-*N*-trifluoroacetanilide (**2a**) and methyl acrylate (**3a**), under our previously reported conditions (Scheme 1), to give the corresponding unprotected 5,6-dihydrophenanthridine **4a** in ca.10% yield together with a small amount (*ca.* 4%) of phenanthridine **5a**.

While formation of the unprotected dihydrophenanthridine **4a** could be anticipated in view of an easy hydrolytic cleavage of the *N*-trifluoroacetyl group, that of compound **5a** was quite unexpected. We hypothesized that phenanthridine **5a** derived from a retro-Mannich reaction (*we thank a referee for suggesting the term "retro-Mannich"*) taking place on compound **4a**. Subjecting compound **4a** to the action of a DMF solution of an equimolar amount of potassium carbonate at 105 °C led indeed to the formation of compound **5a** (70% after 24 h) along with the expected methyl acetate. Using the *tert*-butyl ester of acrylic acid for a better analysis we were able to establish by GC and GC-MS analysis that *tert*-butyl acetate was formed in an almost equimolar amount to **5a**. This means that the retro-Mannich is strongly fa-



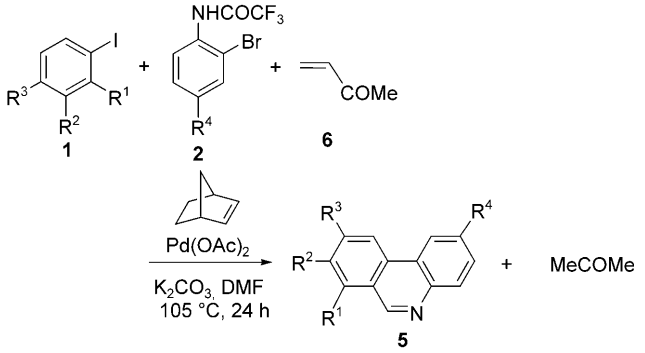
Scheme 1.

vored, as expected in view of the stability of the phenanthridine structure. In respect to the conditions shown in Scheme 1 the increase of the temperature to 105 °C and the use of DMF in place of MeCN were found necessary to obtain the desired results. The preceding steps of the sequence leading to **4a** have also been optimized. This has not been a simple task, however, in view of the many competitive steps involved.[5] We found that lowering the amount of norbornene, was beneficial for the overall process. Potassium carbonate proved to be the base of choice allowing higher selectivity towards compound **5a**. Addition of triphenylphosphine also had a positive effect, while the use of quaternary ammonium salts was found not to be effective.

Thus, when we allowed 1.1 equivalents of *o*-iodotoluene (**1a**) to react with 1.0 equivalent of *o*-bromo-*N*-trifluoroacetanilide (**2a**) and 4 equivalents of methyl acrylate (**3a**) in the presence of 5% of $Pd(OAc)_2$, 10% of PPh_3, 1 equivalent of norbornene and 2.2 equivalents of K_2CO_3 in DMF at 105 °C for 18 h, the desired compound **5a** was isolated in 50% yield together with compound **4a** in 12% yield. The main by-product (34%) was methyl *o*-methylcinnamate resulting from a Heck reaction of *o*-iodotoluene with methyl acrylate. When methyl vinyl ketone was employed in place of methyl acrylate, compound **5a** was obtained in 71% yield (Table 1, entry 1). We thus examined the scope and limitations of the process using methyl vinyl ketone as activating olefin. This ketone, which sacrifices three out of its four carbon atoms as acetone, appears to be the more efficient and convenient partner. Several selectively substituted phenanthridines (**5**) could be prepared in moderate to satisfactory yields from readily available *ortho*-substituted aryl iodides, *ortho*-bromo-*N*-trifluoroacetanilides and methyl vinyl ketone. As in the example reported above with methyl acrylate, the main by-products constantly resulted from the Heck reaction between the aryl iodide and methyl vinyl ketone. Most of the unreacted aryl bromide is recovered. Our results are summarized in Table 1.

ortho-Alkyl-substituted aryl iodides such as methyl, isopropyl and *sec*-butyl efficiently react with *ortho*-bromo-*N*-trifluoroacetanilide and methyl vinyl ketone (entries 1, 4 and 5) to give the corresponding phenanthridine in satisfactory yields. The presence of an additional methyl group in the aryl iodide (entries 2 and 3) is beneficial or innocuous, while the methoxy as well as the methoxycarbonyl groups negatively affect the reaction outcome (entries 7–9). Both the methyl and the methoxy groups in the ring of the trifluoroacetylated *ortho*-bromoaniline (entries 10, 11 and 13) are detrimental to the yield of the reaction, while the joint presence of the chloride substituent in **2** and of the isopropyl one in **1** (entries 12 and 14) has a remarkable positive effect. As in the case of the reaction of *ortho*-iodotoluene with methyl acrylate reported above, the main by-product (from 7 up to 37% yield) appears to be the one resulting from Heck reaction of the aryl iodide with methyl vinyl ketone. Other by-products containing norbornene[6] are also present in variable amount.

Table 1. Synthesis of phenanthridines.[a]



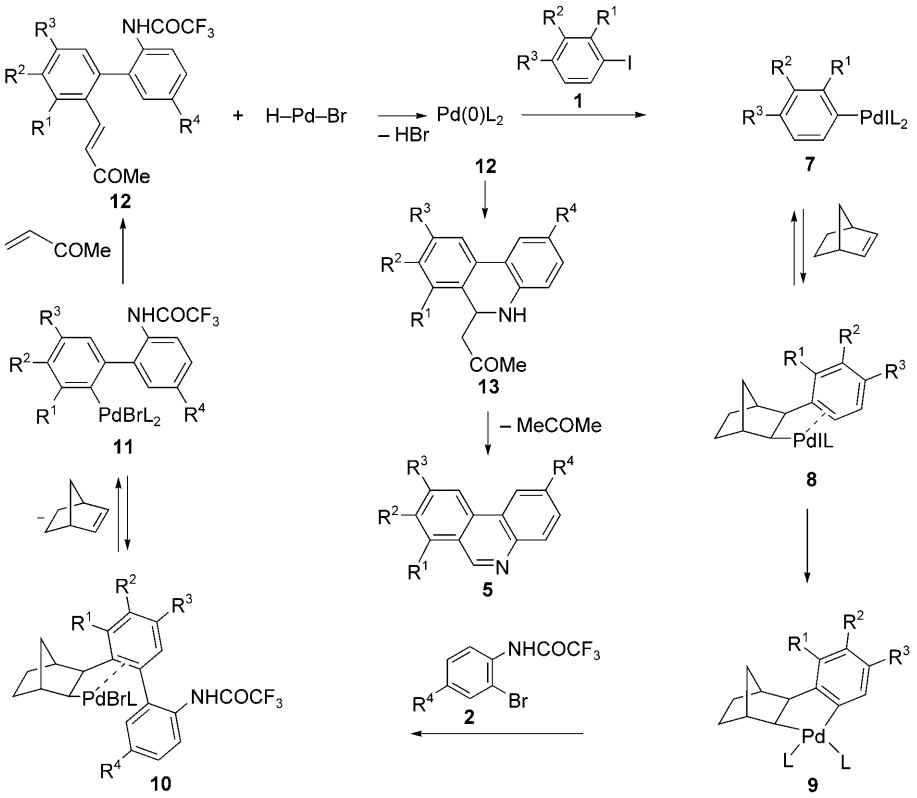
Entry	R^1	R^2	R^3	R^4	**5** Yield [%][b]
1	Me	H	H	H	**5a**, 71
2	Me	Me	H	H	**5b**, 82
3	Me	H	Me	H	**5c**, 72
4	*i*-Pr	H	H	H	**5d**, 84
5	*s*-Bu	H	H	H	**5e**, 66
6	-(CH)$_4$-		H	H	**5f**, 66
7	Me	H	OMe	H	**5g**, 51
8	Me	OMe	OMe	H	**5h**, 63
9	Me	H	CO_2Me	H	**5i**, 49
10[c]	Me	H	H	Me	**5j**, 54
11	Me	H	H	OMe	**5k**, 40
12[c]	Me	H	H	Cl	**5l**, 78
13[c]	*i*-Pr	H	H	Me	**5m**, 73
14[c]	*i*-Pr	H	H	Cl	**5n**, 93

[a] Reactions were carried out with aryl iodide (1.1 equiv.), aryl bromide (1.0 equiv.), methyl vinyl ketone (2.0 equiv.), norbornene (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (2.2 equiv.) in DMF at 105 °C under N_2 for 24 h; $0.2 \cdot 10^{-2}$ mmol $Pd(OAc)_2$/mL DMF.

[b] Isolated yield based on the charged amount of aryl bromides.

[c] Methyl vinyl ketone (4.0 equiv.).

The proposed reaction pathway is reported in Scheme 2. The catalytic cycle is initiated by the oxidative addition of the aryl iodide to palladium(0),[7] formed *in situ* from $Pd(OAc)_2$. Owing to steric strain release, norbornene insertion into the arylpalladium bond of complex **7** readily occurs.[8] The *cis*,*exo*-arylnorbornylpalladium iodide species (**8**), resulting from stereoselective norbornene insertion, is rather stable towards β-hydrogen elimination but prone to undergo ring closure, by C–H activation,[9] to give palladacycle **9**.[10] *ortho*-Bromo-*N*-trifluoroacetanilide reacts at the aryl site of palladacycle **9**,[11] possibly through the intermediacy of a palladium(IV) species,[12] to generate the aryl-aryl bond of complex **10**. Likely due to steric



Scheme 2. Proposed reaction pathway to phenanthridines.

hindrance, norbornene deinsertion then takes place, leading to the formation of the biphenylylpalladium intermediate **11**[13] which, in its turn, undergoes a Heck-type reaction. The organic product **12** and palladium(0) are thus formed; the latter becomes available for a new catalytic cycle, while the former undergoes further transformation. The open precursor **12** cyclizes through an intramolecular aza-Michael reaction by attack of the *ortho*-amido group to the activated double bond to give the deprotected 5,6-dihydrophenanthridine **13**. In agreement with the course of the Michael reaction[14] the cyclization step is catalyzed by the basicity of the medium. On the other side compound **13** undergoes a retro-Mannich-type reaction to form phenanthridine **5** and acetone. Formation of phenanthridine **5** must occur very fast since both compounds **12** and **13** could not be isolated using methyl vinyl ketone as activated olefin. As mentioned before, however, compound **4a** (analogue of **13**) could be isolated employing methyl acrylate in place of methyl vinyl ketone.

It is worth noting that compound **13** is not formed through the corresponding forward reaction, namely addition of acetone carbanion to **5**. On its side **13** results from a sequence of steps involving an aza-Michael reaction.

Under the conditions of Table 1, the reaction of *ortho*-iodotoluene and *N*-trifluoroacetyl-*ortho*-bromoaniline with methyl vinyl ketone in the absence of norbornene did not lead to the formation of phenanthridine derivatives, but to products resulting from the Heck reaction of the aryl iodides and bromides with methyl vinyl ketone (97 and 30% yield, respectively). This confirms the key role of norbornene in directing the aryl-aryl coupling of the two aryl halides, in agreement with the proposed reaction pathway shown in Scheme 2.

In conclusion we have been able to achieve the synthesis of selectively substituted phenanthridines starting from readily available reagents. The process involves the palladium/norbornene-catalyzed sequential coupling of an *ortho*-substituted aryl iodide with an *N*-trifluoroacetylated *ortho*-bromoaniline, insertion of an activated olefin, aza-Michael cyclization and retro-Mannich reaction. The latter step occurs with the sacrificial elimination of acetone.

Experimental Section

Typical Procedure; Synthesis of 7-Methylphenanthridine (5a)

A Schlenk-type flask was charged with $Pd(OAc)_2$ (10 mg, 0.044 mmol), PPh_3 (22 mg, 0.088 mmol), norbornene (82 mg, 0.88 mmol), *ortho*-iodotoluene (**1**, 209 mg, 0.96 mmol),

ortho-bromo-*N*-trifluoroacetylaniline (**2**, 235 mg, 0.88 mmol) and methyl vinyl ketone (123 mg, 1.76 mmol) in DMF (20 mL). K_2CO_3 (276 mg, 2.0 mmol) was then added as a solid powder and the resulting mixture was stirred at 105 °C for 24 h. After cooling to room temperature, EtOAc (60 mL) was added and the mixture was treated with brine (3×50 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. GC, GC-MS and ^{1}H NMR analysis of the crude material revealed the presence of compound **5a**, (*E*)-4-(2-methylphenyl)but-3-en-2-one and traces of products containing norbornene together with unreacted *ortho*-bromo-*N*-trifluoroacetylaniline (19% by ^{1}H NMR). The residue was purified by flash silica gel chromatography using a 95:5 mixture of hexane-EtOAc as eluent to obtain 7-methylphenanthridine **5a** as a pale yellow solid (yield: 120 mg, 71%) and (*E*)-4-(2-methylphenyl)but-3-en-2-one as a colorless oil (yield: 28 mg, 20%).

7-Methylphenanthridine (**5a**): mp (hexane) 83–84 °C; ^{1}H NMR: δ = 9.53 (1H, s), 8.57 (1H, dd, J = 8.1, 1.5 Hz), 8.46 (1H, d, J = 8.3 Hz), 8.19 (1H, d further split, J = 8.0 Hz), 7.78–7.63 (3H, m), 7.48 (1H, d further split, J = 7.2 Hz), 2.85 (3H, s); ^{13}C NMR: δ = 150.0, 143.7, 136.5, 132.8, 130.8, 129.7, 128.8, 128.5, 127.0, 124.7, 124.2, 122.3, 119.9, 18.8; IR (KBr): ν = 3049, 2950, 1605, 1592, 1518, 1454, 1383, 1239, 927, 894, 808, 749 cm^{-1}; MS: *m/z* = 193 (100) (M^+), 192 (39), 165 (19); anal. calcd. for $C_{14}H_{11}N$: C 87.01, H 5.74; found: C 87.17, H 5.69.

(E)-4-(2-Methylphenyl)but-3-en-2-one: ^{1}H NMR: δ = 7.84 (1H, d, J = 16.0 Hz), 7.58 (1H, d, J = 7.6 Hz), 7.31 (1H, t, J = 7.6 Hz), 7.27–7.20 (2H, m), 6.67 (1H, d, J = 16.0 Hz), 2.47 (3H, s), 2.41 (3H, s); ^{13}C NMR: δ = 198.2, 140.8, 137.8, 133.3, 130.8, 130.2, 128.0, 126.4, 126.3, 27.7, 19.7; IR (neat): ν = 1692, 1670 cm^{-1}; MS: *m/z* = 160 (8) (M^+), 145 (100), 117 (26), 116 (22), 115 (68), 91 (27); anal. calcd. for $C_{11}H_{12}O$: C 82.46, H 7.55; found: C 82.61, H 7.59.

Acknowledgements

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References

[1] a) A. R. Katritzky, C. W. Rees, E. F. Scriven, (Eds.), *Comprehensive Heterocyclic Chemistry II*, Pergamon, Oxford, **1996**; G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671–2681.

[2] For recent examples: a) D. A. Candito, M. Lautens, *Angew. Chem.* **2009**, *121*, 6841–6844; *Angew. Chem. Int. Ed.* **2009**, *48*, 6713–6716; b) T. Gerfaud, L. Neuville, J. Zhu, *Angew. Chem.* **2009**, *121*, 580–585; *Angew. Chem. Int. Ed.* **2009**, *48*, 572–577; c) D. Shabashov, O. Daugulis, *J. Org. Chem.* **2007**, *72*, 7720–7725; d) C. Xie, Y. Zhang, Z. Huang, P. Xu, *J. Org. Chem.* **2007**, *72*, 5431–5434.

[3] a) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; b) J. Tsuji, (Ed.), *Palladium in Organic Synthesis* Springer, Berlin, **2005**; c) E.-I. Negishi, A. de Meijere, (Eds.), *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, **2002**.

[4] N. Della Ca′, E. Motti, M. Catellani, *Adv. Synth. Catal.* **2008**, *350*, 2513–2516.

[5] a) M. Catellani, E. Motti, N. Della Ca′, *Acc. Chem. Res.* **2008**, *41*, 1512–1522; b) M. Catellani, *Top. Organomet. Chem.* **2005**, *14*, 21–53; c) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; d) M. Lautens, D. Alberico, C. Bressy, Y.-Q. Fang, B. Mariampillai, T. Wilhelm, *Pure Appl. Chem.* **2006**, *78*, 351–361; e) N. Della Ca′, G. Sassi, M. Catellani, *Adv. Synth. Catal.* **2008**, *350*, 2179–2182.

[6] See for example: **5a**, **5b**: a) E. Motti, G. Ippomei, S. Deledda, M. Catellani, *Synthesis* **2003**, 2671–2678; b) M. Catellani, E. Motti, S. Ghelli, *Chem. Commun.* **2000**, 2003–2004.

[7] a) P. Fitton, E. A. Rick, *J. Organomet. Chem.* **1971**, *28*, 287–291; b) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 13944–13945; c) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321.

[8] a) H. Horino, M. Arai, N. Inoue, *Tetrahedron Lett.* **1974**, 647–650; b) C.-S. Li, C.-H. Cheng, F.-L. Liao, S.-L. Wang, *J. Chem. Soc. Chem. Commun.* **1991**, 710–712; c) M. Portnoy, Y. Ben-David, I. Rousso, D. Milstein, *Organometallics* **1994**, *13*, 3465–3479; d) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P. S. Pregosin, *J. Am. Chem. Soc.* **2002**, *124*, 4336–4346.

[9] a) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; c) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463; d) G. Dyker, (Ed.), *Handbook of C-H Transformations*, Wiley-VCH Verlag, Weinheim, Germany, **2005**.

[10] a) I. P. Beletskaya, A. V. Cheprakov, *J. Organomet. Chem.* **2004**, *689*, 4055–4082; b) M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1992**, *425*, 151–154; c) M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1988**, *346*, C27-C30; d) C.-H. Liu, C.-S. Li, C.-H. Cheng, *Organometallics* **1994**, *13*, 18–20.

[11] M. Catellani, E. Motti, *New J. Chem.* **1998**, *22*, 759–761.

[12] a) A. J. Canty, *Acc. Chem. Res.* **1992**, *25*, 83–90; b) M. Catellani, M. C. Fagnola, *Angew. Chem.* **1994**, *106*, 2559–2561; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2421–2422; c) S. R. Whitfield, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 15142–15143.

[13] a) F. Faccini, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2004**, *126*, 78–79; b) R. Ferraccioli, D. Carenzi, O. Rombolà, M. Catellani, *Org. Lett.* **2004**, *6*, 4759–4762; c) B. Mariampillai, J. Alliot, M. Li, M. Lautens, *J. Am. Chem. Soc.* **2007**, *129*, 15372–15379.

[14] R. D. Little, M. R. Masjedizadeh, O. Wallquist, J. I. Mcloughlin, *Org. React.* **1995**, *47*, 315–552.

