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Iodine-catalyzed synthesis of pyrazolo[4,3-*f*]quinoline derivatives via a highly regio-selective Povarov reaction

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Abstract A highly regio-selective Povarov reaction of an aromatic aldehyde, 1*H*-indazol-5-amine, and methyl 3-oxobutanoate catalyzed by iodine is described. This novel reaction selectively gave 3*H*-pyrazolo[4,3-*f*]quinolin-9-yl acetates, in high yield, rather than 3*H*-pyrazolo[4,3-*f*]quinoline-8-carboxylate derivatives. This procedure has the advantages of mild reaction conditions, high yields, metal-free catalyst, and high regio-selectivity.

Keywords Pyrazolo[4,3-*f*]quinoline · 1*H*-indazol-5-amine · Regio-selectivity · Iodine · Synthesis

Introduction

Pyrazoloquinoline and its derivatives are important heterocyclic compounds because of their variety of medicinal properties, for example antimicrobial [1], antifungal [2], antibacterial [3], and antileishmanial activity [4]. They are also promising materials for optoelectronic applications [5–11]. Therefore, preparation of pyrazoloquinolines by use of mild, efficient, and environmentally benign methods is an attractive proposition.

The Povarov reaction [12] is an important method that provides convenient access to quinoline derivatives by use of a Schiff base and an electron-rich

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dienophile as reactants. In 2006, this method was substantially improved by Wang and coworkers who used iodine as catalyst [13] and an aliphatic aldehyde as starting material. In this type of Povarov reaction, iodine is a novel metal-free Lewis-acid catalyst which converts the aliphatic aldehyde to its enol form; this electron-rich dienophile reacts with the Schiff base to give the desired quinolines.

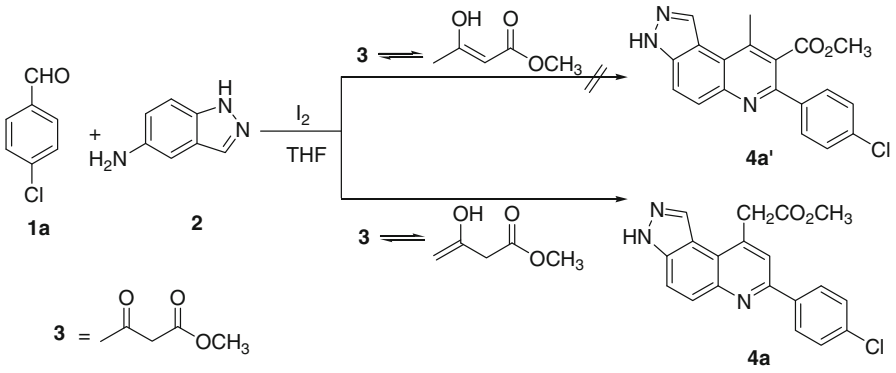
It is well known that 3-oxobutanoate is in equilibrium with its enol form, which is readily formed. Furthermore, the enol usually forms on the methylene side and is, therefore, stabilized by conjugation with the ester carbonyl (Scheme 1). On the basis of this assumption, 3*H*-pyrazolo[4,3-*f*]quinoline-8-carboxylate (**4a′**) might be obtained in high yield by reaction of 4-chlorobenzaldehyde (**1a**), 1*H*-indazol-5-amine (**2**), and methyl 3-oxobutanoate (**3**) as reactants. However, this reaction gave methyl 2-(7-(4-chlorophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl) acetate (**4a**) in 89 % yield and with high regio-selectivity rather than methyl 7-(4-chlorophenyl)-9-methyl-3*H*-pyrazolo[4,3-*f*]quinoline-8-carboxylate (**4a′**) (Scheme 1).

In connection with our continued research on the iodine-catalyzed Povarov reaction [14–16], in this paper, we report an efficient and highly regio-selective synthesis of methyl 2-(7-aryl-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate derivatives catalyzed by iodine.

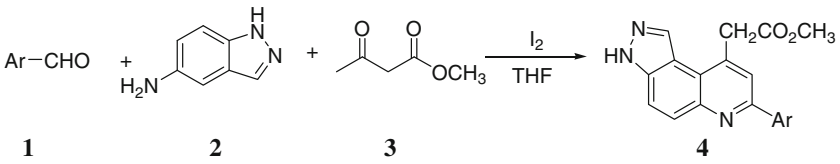
Results and discussion

Reaction of aromatic aldehydes **1a-l**, 1*H*-indazol-5-amine **2**, and methyl 3-oxobutanoate **3** in THF in the presence of 5 mol% iodine under reflux conditions afforded the corresponding methyl 2-(7-aryl-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate derivatives **4a-l** in high yields (Scheme 2).

In our initial study, several conditions, including type and amount of catalyst, reaction temperature, and solvents, were screened for this reaction. The model reaction was conducted using 4-chlorobenzaldehyde (**1a**), 1*H*-indazol-5-amine, and methyl 3-oxobutanoate. The results obtained from screening of the reaction are summarized in Table 1. When different Lewis acids were used, iodine gave the best



Scheme 1 The highly regio-selective model reaction



Scheme 2 Reaction of **1**, **2**, and **3**

results. Except for TsOH the other Lewis acid catalysts tested did not promote this reaction successfully (Table 1, entries 11–15). Subsequently, 1, 5, and 10 mol% iodine were used to mediate the reaction, 5 mol% I_2 under reflux in THF is sufficient to initiate the reaction (Table 1, Entries 4–6). To find the optimum reaction temperature, the reaction was carried out with 5 mol% of I_2 at room temperature, 50 °C, and reflux temperature, resulting in the isolation of **4a** in a trace amount, and 67 % and 89 % yields, respectively (Table 1, entries 2, 3, and 5). In addition, CH_3CN, benzene, DMF, $CHCl_3$ (Table 1, entries 7–10) were also tested as the solvents. Under these conditions, product **4a** was formed in slightly lower yields.

Using these optimized conditions, a variety of aromatic aldehydes **1a-l** were then reacted with **2** and **3** to generate (7-aryl-3*H*-pyrazolo [4,3-*f*]quinolin-9-yl)acetate derivatives **4a-l** (Table 2). For aldehydes **1a-l**, the yields of **4a-l** were not sensitive to the electronic properties of the aromatic ring in the presence of electron-withdrawing groups (for example halide and nitro) or electron-donating groups (for example alkyl or alkoxy) (Table 2).

Table 1 Optimization of yield of **4a** under different conditions

Entry	Temp. (°C)	Cat. (mol%)	Solvent	Yields (%)[a]
1	Reflux	–	THF	0
2	r.t.	I_2(5)	THF	Trace
3	50	I_2(5)	THF	67
4	Reflux	I_2(1)	THF	82
5	Reflux	I_2(5)	THF	89
6	Reflux	I_2(10)	THF	89
7	Reflux	I_2(5)	CH_3CN	83
8	Reflux	I_2(5)	Benzene	78
9	80	I_2(5)	DMF	76
10	Reflux	I_2(5)	$CHCl_3$	80
11	Reflux	CuI(5)	THF	Trace
12	Reflux	TsOH(5)	THF	67
13	Reflux	$Yb(OTf)_3$(5)	THF	Trace
14	Reflux	$Sc(OTf)_3$(5)	THF	Trace
15	Reflux	AgOTf(5)	THF	Trace

Reagents and conditions: 4-chlorobenzaldehyde **1a** (0.281 g, 2.0 mmol), **2** (0.266 g, 2.0 mmol), **3** (0.232 g, 2.0 mmol), solvent (10 mL)

[a] Isolated yields

Table 2 Results from synthesis of **4a-l** catalyzed by iodine in THF

Entry	Ar	Product	Time (h)	Yield (%)[a]
1	4-ClC_6H_4	**4a**	12	89
2	4-BrC_6H_4	**4b**	14	92
3	4-FC_6H_4	**4c**	12	82
4	3,4-$Cl_2C_6H_3$	**4d**	10	86
5	4-MeC_6H_4	**4e**	16	78
6	4-$MeOC_6H_4$	**4f**	16	87
7	3,4-$(MeO)_2C_6H_3$	**4g**	16	90
8	3-ClC_6H_4	**4h**	12	79
9	2,4-$Cl_2C_6H_3$	**4i**	12	84
10	3,4-$Me_2C_6H_3$	**4j**	15	90
11	2-Thienyl	**4k**	12	85
12	4-$NO_2C_6H_4$	**4l**	10	88

Reagents and conditions: **1a-l** (2.0 mmol), **2** (0.266 g, 2.0 mmol), **3** (0.232 g, 2.0 mmol), I_2 (0.1 mmol, 0.026 g), THF (10 mL)

[b] Isolated yields

When **4a-l** were characterized by use of ^{1}H NMR, IR, and HRMS, the results were in good agreement with the proposed structures. For instance, for compounds **4a** (Ar = 4-ClC_6H_4), only a methyl group was observed in ^{1}H NMR; this was identified as a methoxy group at 3.66 ppm (3H), and the corresponding methylene was observed at 4.52 ppm (2H). In addition, total of eight rather than seven aromatic protons also confirmed the structure of **4a**.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer, as KBr pellets. ^{1}H NMR spectra were obtained from solutions in DMSO-d_6 or $CDCl_3$, with Me_4Si as internal standard, by use of a Bruker-400 spectrometer. HRMS analysis was performed with a Bruker-micro-TOF-Q-MS analyzer.

General procedure for synthesis of methyl 2-(7-aryl-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate derivatives **4a-l**

A dry 50 mL flask was charged with aromatic aldehyde (2.0 mmol), 1*H*-indazol-5-amine (0.266 g, 2.0 mmol), methyl 3-oxobutanoate (0.232 g, 2.0 mmol), I_2 (0.026 g, 0.1 mmol), and THF (10 mL). The reaction mixture was stirred at reflux for 10–16 h. After completion of the reaction, as indicated by TLC, small amounts of DMF were added to the mixture until all the yellow solid had dissolved. The mixture was then cooled to room temperature and the powder obtained was isolated by filtration to give the pure product **4**.

Methyl 2-(7-(4-chlorophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4a**

mp: 217–218 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.63 (d, J = 8.0 Hz, 2H, ArH), 7.95–8.02 (m, 2H, ArH), 8.25 (s, 1H, ArH), 8.30 (d, J = 8.4 Hz, 2H, ArH), 8.43 (s, 1H, ArH), 13.78 (s, 1H, NH). IR (KBr, cm^{-1}): v 3188, 2998, 2949, 1739, 1580, 1566, 1495, 1423, 1334, 1278, 1204, 1185, 1156, 1097, 1012, 991, 934, 837, 793, 746. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}ClN_3O_2$ $[M + H]^+$ 352.0853, found 352.0850.

Methyl 2-(7-(4-bromophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4b**

mp: 249–251 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.77 (d, J = 7.6 Hz, 2H, ArH), 7.95–8.01 (m, 2H, ArH), 8.22–8.24 (m, 3H, ArH), 8.34 (s, 1H, ArH), 13.78 (s, 1H, NH). IR (KBr, cm^{-1}): v 3192, 2949, 1736, 1662, 1578, 1563, 1536, 1492, 1422, 1363, 1333, 1276, 1204, 1185, 1099, 1006, 990, 934, 834, 746, 723. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}BrN_3O_2$ $[M + H]^+$ 396.0348, found 396.0345.

Methyl 2-(7-(4-fluorophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4c**

mp: 194–197 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 7.40 (t, J = 8.8 Hz, 2H, ArH), 7.97 (d, J = 9.6 Hz, 2H, ArH), 8.21 (s, 1H, ArH), 8.30–8.31 (m, 3H, ArH), 13.76 (s, 1H, NH). IR (KBr, cm^{-1}): v 3166, 2954, 1742, 1664, 1601, 1576, 1509, 1435, 1364, 1333, 1281, 1221, 1197, 1158, 1101, 1010, 934, 841, 795, 734. HRMS (ESI, m/z): Calcd for $C_{19}H_{15}FN_3O_2$ $[M + H]^+$ 336.1148, found 336.1151.

Methyl 2-(7-(3,4-dichlorophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4d**

mp: 263–264 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 7.82 (d, J = 8.4 Hz, 1H, ArH), 7.95–8.03 (m, 2H, ArH), 8.26 (d, J = 8.4 Hz, 1H, ArH), 8.31 (s, 1H, ArH), 8.35 (s, 1H, ArH), 8.51 (s, 1H, ArH), 13.79 (s, 1H, NH). IR (KBr, cm^{-1}): v 3286, 2956, 1730, 1577, 1560, 1537, 1473, 1434, 1400, 1356, 1325, 1292, 1207, 1166, 1099, 1026, 989, 936, 898, 846, 815, 739, 715. HRMS (ESI, m/z): Calcd for $C_{19}H_{14}Cl_2N_3O_2$ $[M + H]^+$ 386.0463, found 386.0441.

Methyl 2-(7-(4-methylphenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4e**

mp: 247–249 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 2.40 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.38 (d, J = 8.0 Hz, 2H, ArH), 7.97 (s, 2H, ArH), 8.16–8.18 (m, 3H, ArH), 8.35 (s, 1H, ArH), 13.72 (s, 1H, NH). IR (KBr, cm^{-1}): v 3147, 3097, 2921, 1740, 1605, 1580, 1514, 1434, 1367, 1329, 1279, 1229, 1201, 1163, 1008, 985, 931, 895, 800, 729. HRMS (ESI, m/z): Calcd for $C_{20}H_{18}N_3O_2$ $[M + H]^+$ 332.1399, found 332.1396.

Methyl 2-(7-(4-methoxyphenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4f**

mp: 212–214 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 7.12 (d, J = 8.0 Hz, 2H, ArH), 7.93–7.99 (m, 2H, ArH), 8.16 (s, 1H, ArH), 8.23 (d, J = 8.0 Hz, 2H, ArH), 8.32 (s, 1H, ArH), 13.70 (s, 1H, NH). IR (KBr, cm^{-1}): *v* 3308, 2955, 2837, 1718, 1605, 1570, 1513, 1458, 1429, 1364, 1337, 1282, 1254, 1212, 1178, 1161, 1026, 981, 930, 903, 837, 795, 744. HRMS (ESI, *m*/*z*): Calcd for $C_{20}H_{18}N_3O_3$ $[M + H]^+$ 348.1348, found 348.1354.

Methyl 2-(7-(3,4-dimethoxyphenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4g**

mp: 238–240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.50 (s, 2H, CH_2), 7.13 (d, J = 8.4 Hz, 1H, ArH), 7.83 (d, J = 7.6 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 7.90–8.00 (m, 2H, ArH), 8.20 (s, 1H, ArH), 8.32 (s, 1H, ArH), 13.71 (s, 1H, NH). IR (KBr, cm^{-1}): *v* 3299, 2956, 1719, 1597, 1572, 1519, 1459, 1421, 1361, 1319, 1275, 1219, 1174, 1119, 1021, 983, 927, 866, 811, 747, 714. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{20}N_3O_4$ $[M + H]^+$ 378.1454, found 378.1459.

Methyl 2-(7-(3-chlorophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4h**

mp: 242–245 °C;^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.55–7.61 (m, 2H, ArH), 8.00 (s, 2H, ArH), 8.23 (d, J = 6.8 Hz, 1H, ArH), 8.29 (s, 1H, ArH), 8.33 (s, 1H, ArH), 8.37 (s, 1H, ArH), 13.78 (s, 1H, NH). IR (KBr, cm^{-1}): *v* 3286, 3069, 2953, 1733, 1578, 1568, 1540, 1474, 1433, 1363, 1328, 1290, 1259, 1203, 1166, 1101, 1009, 988, 935, 900, 848, 797, 779, 711. HRMS (ESI, *m*/*z*): Calcd for $C_{19}H_{15}ClN_3O_2$ $[M + H]^+$ 352.0853, found 352.0833.

Methyl 2-(7-(2,4-dichlorophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4i**

mp: 224–226 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.61 (d, J = 8.4 Hz, 1H, ArH), 7.75 (d, J = 8.0 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.87 (s, 1H, ArH), 7.96–8.02 (m, 2H, ArH), 8.39 (s, 1H, ArH), 13.80 (s, 1H, NH). IR (KBr, cm^{-1}): *v* 3157, 2961, 1736, 1588, 1576, 1537, 1474, 1435, 1337, 1282, 1230, 1152, 1100, 1047, 1010, 989, 936, 898, 814, 798, 756. HRMS (ESI, *m*/*z*): Calcd for $C_{19}H_{14}Cl_2N_3O_2$ $[M + H]^+$ 386.0463, found 386.0465.

Methyl 2-(7-(3,4-dimethylphenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4j**

mp: 262–265 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 2.31 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.33 (d, J = 7.2 Hz, 1H, ArH), 7.94–7.98 (m, 3H, ArH), 8.07 (s, 1H, ArH), 8.18 (s, 1H, ArH), 8.33 (s, 1H, ArH), 13.73 (s, 1H, NH). IR (KBr, cm^{-1}): *v* 3161, 3096, 3053, 2949, 1738, 1579, 1506, 1437, 1372, 1331, 1278, 1234, 1197, 1169, 1009, 927, 893, 835, 802, 726. HRMS (ESI, *m*/*z*): Calcd for $C_{21}H_{20}N_3O_2$ $[M + H]^+$ 346.1556, found 346.1559.

Methyl 2-(7-(2-thienyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4k**

mp: >300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.66 (s, 3H, CH_3), 6.77 (s, 2H, CH_2), 7.44 (s, 1H, ArH), 7.68 (s, 1H, ArH), 8.14 (d, $J = 9.6$ Hz, 2H, ArH), 8.25 (m, 3H, ArH), 13.75 (s, 1H, NH). IR (KBr, cm^{-1}): *v* 3125, 2923, 1644, 1594, 1541, 1465, 1375, 1337, 1303, 1227, 1187, 1156, 1124, 1083, 1017, 947, 930, 853, 795, 768, 734. HRMS (ESI, *m*/*z*): Calcd for $C_{17}H_{14}N_3O_2S$ $[M + H]^+$ 324.0827, found 324.0800.

Methyl 2-(7-(4-nitrophenyl)-3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate **4l**

mp: 269–271 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 3.67 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 7.99–8.06 (m, 2H, ArH), 8.37 (s. 2H, ArH), 8.41 (s. 2H, ArH), 8.52–8.56 (m, 2H, ArH), 13.83 (s, 1H, NH). IR (KBr, cm^{-1}): *v* 3111, 2952, 1737, 1663, 1593, 1575, 1511, 1433, 1389, 1344, 1289, 1166, 1108, 1027, 1009, 941, 892, 851, 793, 733. HRMS (ESI, *m*/*z*): Calcd for $C_{19}H_{15}N_4O_4$ $[M + H]^+$ 363.1093, found 363.1094.

Conclusion

In conclusion, we have found a mild and highly regio-selective method for synthesis of 3*H*-pyrazolo[4,3-*f*]quinolin-9-yl)acetate derivatives via three-component reaction of an aromatic aldehyde, 1*H*-indazol-5-amine, and methyl 3-oxobutanoate, catalyzed by iodine. The features of this procedure are mild reaction conditions, high yields, operational simplicity, metal-free catalyst, and high regio-selectivity.

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References and notes

1. P. Muthumani, S. Venkataraman, R. Meera, G. Nayak, N. Chidambaranathan, P. Devi, B. Kameswari, Pharm. Chem. **2**, 385 (2010)
2. J. Nayak, K.S. Girish, M. Babu, B. Kalluraya, Indian J. Heterocycl. Chem. **19**, 105 (2009)
3. S.F. Thakor, D.M. Patel, M.P. Patel, R.G. Patel, Saudi Pharm. J. **15**, 48 (2007)
4. A. Al-Qahtani, Y.M. Siddiqui, A.A. Bekhit, O.A. El-Sayed, H.Y. Aboul-Enein, M.N. Al-Ahdal, Arch. Pharm. **338**, 484 (2005)
5. A. Danel, E. Gondek, I. Kityk, Opt. Mater. **32**, 267 (2009)
6. E. Gondek, A. Danel, B. Kwiecien, J. Sanetra, A.V. Kityk, Spectrochim. Acta A. **74A**, 685 (2009)
7. I. Fuks-Janczarek, R. Miedzinski, E. Gondek, P. Szlachcic, I.V. Kityk, J. Mater. Sci. **19**, 434 (2008)
8. I. Fuks-Janczarek, K. Danel, I.V. Kityk, B. Kwiecien, Mater. Chem. Phys. **111**, 69 (2008)
9. E. Gondek, A. Danel, I.V. Kityk, J. Lumin. **128**, 348 (2008)
10. E. Gondek, J. Sanetra, M. Mac, A. Danel, I. Fuks-Janczarek, Opt. Mater. **30**, 939 (2008)
11. L.S. Povarov, Russ. Chem. Rev. **36**, 65 (1967)
12. V.V. Kouznetsov, Tetrahedron **65**, 2721 (2009)
13. X.F. Lin, S.L. Cui, Y.G. Wang, Tetrahedron Lett. **47**, 3127 (2006)
14. X.S. Wang, Q. Li, J.R. Wu, S.J. Tu, J. Comb. Chem. **11**, 433 (2009)
15. X.S. Wang, Q. Li, J.R. Wu, Y.L. Li, C.S. Yao, S.J. Tu, Synthesis 1902 (2008)
16. X.S. Wang, J. Zhou, M.Y. Yin, K. Yang, S.J. Tu, J. Comb. Chem. **12**, 266 (2010)