Palladium-Catalyzed, Microwave-Enhanced Three-Component Synthesis of Isoquinolines with Aqueous Ammonia

Monica Dell'Acqua, Giorgio Abbiati,* Elisabetta Rossi

Dipartimento di Scienze Molecolari Applicate ai Biosistemi (DISMAB) – Sezione di Chimica Organica 'A. Marchesini', Università degli Studi di Milano, Via G. Venezian 21, 20133 Milano, Italy
Fax +39(02)50314476; E-mail: giorgio.abbiati@unimi.it
Received 2 August 2010

Abstract: A variety of substituted isoquinoline derivatives can be synthesized in moderate yield by a palladium-catalyzed, microwave-assisted MCR starting from *o*-bromoarylaldehydes, terminal alkynes, and aqueous ammonia.

Key words: multicomponent reaction, alkynes, aqueous ammonia, isoquinoline, palladium

Multicomponent reactions (MCRs) are a powerful tool for the synthesis of complex molecules starting from readily available building blocks in a 'well-contrived' one-pot sequential procedure.[1] These approaches allow an overall reduction of the time required to obtain the desired product with an advantageous economy of solvents and energy and an overall reduction of waste production. MCRs have been widely used for the preparation of heterocyclic structures[2] as well as key steps in the total synthesis of natural products.[3] Moreover, the enhancing power of microwaves in MCRs have been recently highlighted.[4]

The isoquinoline nucleus is the core of well-known alkaloids such as papaverine and local anaesthetics such as quinisocaine, whereas saturated, functionalized, and polycyclic derivatives are known to show different important pharmacological properties.[5]

In the literature there are some valuable approaches to isoquinoline[6] and dihydroisoquinoline[7] nuclei starting from 2-acyl-phenylacetylenes[6a–f,7a–i] or from their imine derivatives.[6g–q,7j–o] Some of them are MCRs leading to the dihydroisoquinoline skeleton.[7a–h] Conversely, multicomponent strategies to obtain isoquinolines are still scarce.[6f,8] Moreover, to the best of our knowledge, in the literature there is only one example involving a Sonogashira coupling as a key step[9] whereas some MCRs involving a Sonogashira reaction have been reported for the preparation of pyrazoles,[10] isoxazoles,[11] halofurans,[12] pyridines,[13] pyrimidines,[14] indoles,[15] indolizines,[16] furo[2,3-*b*]pyridones,[17] thiochromen-4-ones,[18] thiopyran-4-ones,[19] and tetrahydro-β-carbolines.[20]

For many years we devoted our studies to the synthesis of nitrogen-containing rings by sequential addition–annulation reactions of γ- and δ-ketoalkynes in the presence of ammonia.[21] In particular, we reported in-depth investigations on the synthesis of pyrazino[1,2-*a*]indole and pyrrolo[1,2-*a*]pyrazine nuclei by sequential imination–annulation reactions of 2-carbonyl-*N*-propargyl-indoles[22] and -pyrroles,[23] respectively; the reactivity of less reactive substrates has been promoted with $TiCl_4$ as multifunctional additive. In this context, we successfully tested microwaves[24] as highly efficient nonconventional energy source able to improve both yields and selectivity, to reduce reaction times and also to enhance the reactivity of more critical substrates. In the last of these papers we also described a selective path to the isoquinoline skeleton by a MW-promoted domino imination–annulation cascade of 2-alkynylbenzaldehydes prepared by a Pd-catalyzed coupling reaction between *o*-bromobenzaldehyde and various alkynes.[23] We were intrigued to further simplify and optimize the approach, so, encouraged by these results, in this paper we present a one-pot, three-component approach to isoquinolines directly starting from simple *o*-bromobenzaldehyde, terminal alkynes, and ammonia in the presence of a suitable catalytic system. The most interesting features of this approach are: a) the double role of ammonia: base for the Sonogashira coupling and amino partner for imination–cyclization step; b) the potential multiactivity of the metal catalyst, involved in the Sonogashira coupling step and in the imination–cyclization sequence. The suitability of ammonia as base in the Sonogashira coupling has been well described by Mori and co-workers,[25] whereas the ability of some late transition metals to activate the triple bond during the cyclization step has been proven on related cyclization of carbonyl groups on alkynes in the presence of palladium/copper,[26] gold/silver,[27] and also ruthenium or tungsten.[28]

We screened the optimal reaction conditions with 2-bromobenzadehyde (**1a**), ammonia solutions, and 1-ethynyl-4-methylbenzene as model system. The results are depicted in Table 1.

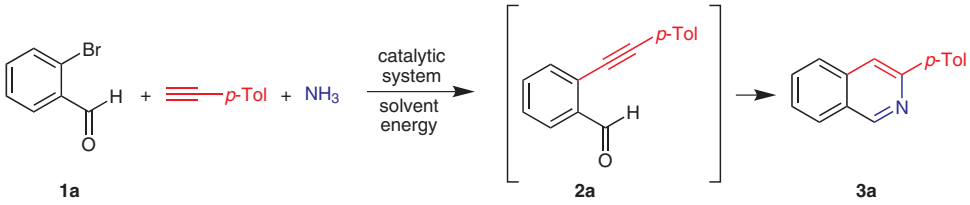
In first instance, we ran the reaction under typical Sonogashira cross-coupling conditions [$PdCl_2(PPh_3)_2$, CuI, 50 °C], under microwave irradiation and in the presence of a solution of ammonia in DMF. After four hours the reaction gave only traces of the desired product **3a**, beside a complex mixture of unidentified products (Table 1, entry 1). At higher temperatures, a modest rise in yields was observed (Table 1, entries 2 and 3). When the reaction was performed in ammonia in methanol, the desired product was obtained in a encouraging 39% yield in one

SYNLETT 2010, No. 17, pp 2672–2676
Advanced online publication: 23.09.2010
DOI: 10.1055/s-0030-1258571; Art ID: G23310ST

hour (Table 1, entry 4). Next, we move our attention to the use of aqueous solution of ammonia.

This readily available and inexpensive reagent has been successfully used in some examples of Sonogashira coupling reactions[25] and the possibility to use it in our MCR could be a further improvement of the method. Nevertheless, probably due to the low water solubility of the reagents, the reaction was sluggish, the yield was still low, and the workup was troublesome (Table 1, entry 5). In the presence of THF as co-solvent and under conventional heating at 100 °C for eight hours the reaction yield jumped to 50% (Table 1, entry 6), whereas under microwave irradiation at the same temperature the reaction gave the same yield in an half time (Table 1, entry 7). By increasing the temperature of microwave oven to 130 °C the desired product was obtained in a satisfying 58% yield in one hour only (Table 1, entry 8). A further reduction of time gave worse results, and a little amount of the *o*-alkynylbenzaldehyde **2a** intermediate was isolated (Table 1, entry 9). Likewise, a rise in temperature to 160 °C resulted in lower yields (Table 1, entry 10). The concentration of ammonia solution was found to be critical in Sonogashira coupling reaction with aqueous ammonia.[25] According to this, an increasing as well as a reduction of the ammonia concentration gave worse results (Table 1, entries 11 and 12). We also tried a different water-soluble co-solvent such as DMF, but also in this case a slightly lowering of the reaction yield was observed (Table 1, entry 13). The studies on copper-free Sonogashira coupling are widely reported in the literature,[29] but when we tested these favorable conditions we observed a reduction of reaction yield (Table 1, entry 14). We also tried a different basic co-catalyst such as silver oxide[30] with scarce results (Table 1, entry 15). Finally, the reaction was performed in

Table 1 Screening of Optimal Reaction Conditions



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

Entry	NH_3, solvent	Catalyst (mol%)	Co-catalyst/ additive	Energy	Temp (°C)	Time (h)[a]	Yield (%)[b] of **3a**	Yield (%)[b] of **2a**
1	2.3 M in DMF[c]	$PdCl_2(PPh_3)_2$ (0.02)	CuI (0.02 mol%)	MW	50	4	trace	–
2	2.3 M in DMF	$PdCl_2(PPh_3)_2$ (0.02)	CuI (0.02 mol%)	MW	80	0.5	10	–
3	2.3 M in DMF	$PdCl_2(PPh_3)_2$ (0.02))	CuI (0.02 mol%)	MW	130	2	26	trace
4	2.0 M in MeOH[d]	$PdCl_2(PPh_3)_2$ (0.02)	CuI (0.02 mol%)	MW	130	1	39	–
5	2.5 M in H_2O[e]	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	oil bath	100	16	30	–
6	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	oil bath	100	8	50	–
7	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	MW	100	4	50	–
8	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	MW	130	1	58	–
9	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	MW	130	0.5	48	10
10	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	MW	160	0.34	48	–
11	5 M in H_2O[f]–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	MW	130	1	47	–
12	1.25 M in H_2O–THF[g] (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	MW	130	2.5	44	20
13	2.5 M in H_2O–DMF (3:1)	$PdCl_2(PPh_3)_2$ (0.01)	CuI (0.02 mol%)	MW	130	1	46	–
14	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.02)	–	MW	130	1	39	11
15	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.02)	Ag_2O (0.2 mol%)	MW	130	1	25	20
16	2.5 M in H_2O–THF (3:1)	$PdCl_2(PPh_3)_2$ (0.02)	KOH (5 equiv)	MW	130	1.5	30	15

[a] Not including 10 min 'ramp time' (10 °C/min).
[b] Yields refer to pure isolated product.
[c] Molar ratio **1**/NH_3 = 1:10.
[d] Molar ratio **1**/NH_3 = 1:16.
[e] Molar ratio **1**/NH_3 = 1:7.5.
[f] Molar ratio **1**/NH_3 = 1:15.
[g] Molar ratio **1**/NH_3 = 1:3.75.

the presence of a stronger water-soluble base such as KOH to restrict the role of ammonia to a simple amino partner for the imination–annulation process, nevertheless the result was still unsatisfactory (Table 1, entry 16).

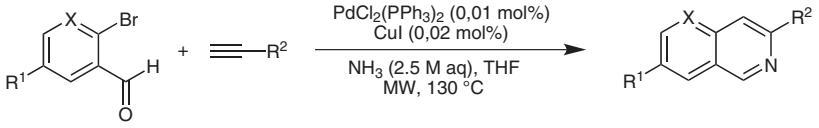
With the best conditions in hand[31] (Table 1, entry 8), we briefly investigated the scope and the limitation of the approach by changing the substitution pattern on the alkyne, on the benzaldehyde framework, and modifying the nature of the aromatic aldehyde. The reactions proceeded with complete 6-*endo*-dig regioselectivity, leading to the formation of the corresponding isoquinolines in moderate yields. It is interesting to note that, although also under the best reaction conditions the yields are not excellent, the overall yields of this multicomponent process are in most cases better than those obtained in the two-step domino sequence.[23] The results are depicted in the Table 2.

Electron-rich phenylacetylenes gave the corresponding isoquinolines in good yields (Table 2, entries 2–4), also when the substituent is in a sterically demanding *ortho* position (Table 2, entries 2 and 4), but in extended reaction times. The presence of an acetal group on the triple bond is tolerated too (Table 2, entry 5). Conversely, in the presence of an electron-withdrawing group on the phenylacetylene, despite a quantitative conversion of **1** in one hour only, the reaction yields are slightly lower (Table 2, entry 6 and 7). Unfortunately, the reaction failed in the presence of aliphatic linear alkynes (Table 2, entries 8 and 9) giving rise to a complex mixture of unidentified byproducts. Then, the effect of the presence of electron-withdrawing and electron-donating groups on the 2-bromobenzaldehyde was briefly investigated (Table 2, entries 10 and 11). In the first trial the reaction yield was satisfying under standard conditions (Table 2, entry 10), whereas in the presence of EDG best results were obtained in a twofold reaction time (Table 2, entry 11). Finally, starting from the electron-poor 2-bromonicotinaldehyde (**1d**) the approach demonstrated to be a little less effective (Table 2, entry 12).

The suggested reaction mechanism involves a well-ordered set of three different events: a) an imination step, b) a Sonogashira coupling (these two steps could also occur simultaneously), c) a final intramolecular annulation reaction. As mentioned above, the ammonia play the double role of base in the cross-coupling and amino partner in the addition–cyclization sequence. Regarding the role of the metals (Pd and Cu), obviously involved in the cross-coupling between the *o*-bromobenzaldehyde and the alkyne, we cannot 'a priori' exclude their involvement as Lewis acids in the imination and in the cyclization steps.[32] This fact could explain the higher overall yields observed in this multicomponent approach, with respect to the domino synthesis.[23]

In summary, we developed an unprecedented multicomponent synthesis of isoquinoline skeleton starting from

Table 2 Scope and Limitation of the Three-Component Approach to Isoquinolines



1 **3**

Entry	X	R^1	Aldehyde	R^2	Time (h)[a]	Product	Yield (%)[b]
1	C	H	**1a**	Ph	1	**3b**	50
2	C	H	**1a**	2-$MeOC_6H_4$	2	**3c**	46
3	C	H	**1a**	4-$MeOC_6H_4$	2	**3d**	56
4	C	H	**1a**	4-MeO-2-MeC_6H_4	3	**3e**	64
5	C	H	**1a**	$(EtO)_2CH$	1	**3f**	42
6	C	H	**1a**	3-$F_3CC_6H_4$	1	**3g**	32
7	C	H	**1a**	3-FC_6H_4	1	**3h**	33
8	C	H	**1a**	C_5H_{11}	3	**3i**	–[c]
9	C	H	**1a**	$SiMe_3$	3	**3j**	–[c]
10	C	F	**1b**	4-MeC_6H_4	1	**3k**	59
11	C	OMe	**1c**	4-MeC_6H_4	2	**3l**	57
12	N	H	**1d**	4-MeC_6H_4	1	**3m**	35

[a] Not including 10 min 'ramp time' (ca. 10 °C/min).
[b] Yields refer to pure isolated product.
[c] Complex mixture of unidentified byproducts.

simple *o*-bromoarylaldehydes, alkynes, and aqueous ammonia. The strategy tolerate a selection of substituents on both alkynyl and aldehyde partners. Moreover, the approach was briefly tested for the synthesis of related 1,6-naphthyridines. With respect to the reported domino approach,[23] this MCR allow a general increase of the overall yields and a reduction of operative steps, reaction times, energy, and solvent consumption. Moreover, the possibility to use aqueous ammonia represents a remarkable improvement of the approach. Further work will be done to in-depth clarify the reaction mechanism and to overcome the breakdown obtained with aliphatic alkynes.

Acknowledgment

This work was supported by Ministero dell'Istruzione, Università e Ricerca, Roma.

References and Notes

(1) (a) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-WCH: Weinheim, **2006**. (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.
(2) (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (b) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (c) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300.
(3) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.
(4) (a) de Boer, T.; Amore, A.; Orru, R. V. A. In *Microwaves in Organic Synthesis*, 2nd ed., Vol. 2; Loupy, A., Ed.; Wiley-VCH: Weinheim, **2006**, 788. (b) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325.
(5) *The Chemistry of Heterocyclic Compounds: Isoquinolines*, Part 3, Vol. 38; Coppola, G. M.; Schuster, H. F., Eds.; John Wiley and Sons: New York, **1981**.
(6) Isoquinoline synthesis: (a) Ghorai, B. K.; Duan, S.; Jiang, D.; Herndon, J. W. *Synthesis* **2006**, 3661. (b) Ghorai, B. K.; Jiang, D.; Herndon, J. W. *Org. Lett.* **2003**, *5*, 4261. (c) Shvartsberg, M. S.; Ivanchikova, I. D.; Vasilevsky, S. F. *Tetrahedron Lett.* **1994**, *35*, 2077. (d) Sakamoto, T.; Numata, A.; Kondo, Y. *Chem. Pharm. Bull.* **2000**, *48*, 669. (e) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499. (f) Ohta, Y. S.; Oishi Fujii, N.; Ohno, H. *Chem. Commun.* **2008**, 835. (g) Magnus, P.; Matthews, K. S.; Lynch, V. *Org. Lett.* **2003**, *5*, 2181. (h) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980. (i) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557. (j) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920. (k) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (l) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042. (m) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. (n) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (o) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (p) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. (q) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.
(7) Dihydroisoquinolines synthesis: (a) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611. (b) Ding, Q.; Wang, B.; Wu, J. *Tetrahedron* **2007**, *35*, 12166. (c) Asao, N.; Iso, K.; Yuda, S. S. *Org. Lett.* **2006**, *8*, 4149. (d) Sun, W.; Ding, Q.; Sun, X.; Fan, R.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 690. (e) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959. (f) Ye, Y.; Ding, Q.; Wu, J. *Tetrahedron* **2008**, *64*, 1378. (g) Iso, K.; Salprima, Y. S.; Menggenbateer; Asao, N. *Heterocycles* **2007**, *74*, 649. (h) Iso, K.; Yudha, S. S.; Asao, N. *Synthesis* **2008**, 820. (i) Ding, Q.; Yu, X.; Wu, J. *Tetrahedron Lett.* **2008**, *49*, 2752. (j) Su, S.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (k) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462. (l) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3822. (m) Asao, N.; Yuda, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 5526. (n) Nakamura, H.; Saito, H.; Nanjo, M. *Tetrahedron Lett.* **2008**, *49*, 2697. (o) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339.
(8) (a) Ohta, Y.; Kubota, Y.; Watabe, T.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 6299. (b) Sha, F.; Huang, X. *Angew. Chem. Int. Ed.* **2009**, *48*, 3458.
(9) Zhou, H.; Jin, H.; Ye, S.; He, X.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 4616.
(10) (a) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487. (b) Willy, B.; Müller, T. J. J. *Eur. J. Org. Chem.* **2008**, 4157.
(11) Willy, B.; Rominger, F.; Müller, T. J. J. *Synthesis* **2008**, 293.
(12) (a) Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2005**, 2581. (b) Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Eur. J. Org. Chem.* **2006**, 2991.
(13) (a) Yehia, N. A. M.; Polborn, K.; Müller, T. J. J. *Tetrahedron Lett.* **2002**, *43*, 6907. (b) Dediu, O. G.; Yehia, N. A. M.; Oeser, T.; Polborn, K.; Müller, T. J. J. *Eur. J. Org. Chem.* **2005**, 1834. (c) Schramm, O. G.; Oeser, T.; Müller, T. J. J. *J. Org. Chem.* **2006**, *71*, 3494.
(14) (a) Karpov, A. S.; Müller, T. J. J. *Org. Lett.* **2003**, *5*, 3451. (b) Karpov, A. S.; Müller, T. J. J. *Synthesis* **2003**, 2815. (c) Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6951.
(15) Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005**, *61*, 11311.
(16) Rotaru, A. V.; Druta, I. D.; Oeser, T.; Müller, T. J. J. *Helv. Chim. Acta* **2005**, *88*, 1798.
(17) Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2003**, *5*, 2441.
(18) Willy, B.; Müller, T. J. J. *Synlett* **2009**, 1255.
(19) Willy, B.; Frank, W.; Müller, T. J. J. *Org. Biomol. Chem.* **2010**, *8*, 90.
(20) (a) Karpov, A. S.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2004**, 1502. (b) Karpov, A. S.; Rominger, F.; Müller, T. J. J. *Org. Biomol. Chem.* **2005**, *3*, 4382.
(21) (a) Arcadi, A.; Rossi, E. *Synlett* **1997**, 667. (b) Arcadi, A.; Rossi, E. *Tetrahedron* **1998**, *54*, 15253. (c) Arcadi, A.; Attanasi, O. A.; Guidi, B.; Rossi, E.; Santeusanio, S. *Chem. Lett.* **1999**, 59. (d) Arcadi, A.; Attanasi, O. A.; Guidi, B.; Santeusanio, S.; Rossi, E. *Eur. J. Org. Chem.* **1999**, 3117. (e) Abbiati, G.; Beccalli, E.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, 2477.
(22) (a) Abbiati, G.; Arcadi, A.; Bellinazzi, A.; Beccalli, E.; Rossi, E.; Zanzola, S. *J. Org. Chem.* **2005**, *70*, 4088. (b) Abbiati, G.; Arcadi, A.; Beccalli, E.; Rossi, E. *Tetrahedron Lett.* **2003**, *44*, 5331.
(23) Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, 2852.
(24) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, **2006**.
(25) (a) Mori, A.; Mohamed Ahmed, M. S.; Sekiguki, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756. (b) Mohamed Ahmed, M. S. M.; Mori, A. *Org. Lett.* **2003**, *5*, 3057. (c) Ahmed, M. S. M.; Mori, A. *Tetrahedron* **2004**, *60*, 9977.
(26) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (b) Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Wu, M.-J. *Synlett* **2004**, 1497. (c) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139. (d) Mondal, S.; Nogami, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 9496.

(27) Godet, T.; Vaxelaire, C.; Michel, C.; Milet, A.; Belmont, P. *Chem. Eur. J.* **2007**, *13*, 5632.
(28) Gulías, M.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2003**, *5*, 1975.
(29) For some representative examples, see: (a) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403. (b) Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653. (c) Gil-Moltó, J.; Nájera, C. *Eur. J. Org. Chem.* **2005**, 4073. (d) Bakherad, M.; Keivanloo, A.; Bahramian, B.; Mihanparast, S. *Tetrahedron Lett.* **2009**, *50*, 6418.
(30) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.
(31) **Synthesis of 3-(4-Methoxyphenyl)isoquinoline (3d)**
In a sealed MW test tube, to a solution of 2-bromobenzaldehyde (**1a**, 185 mg, 0.116 mL, 1 mmol) in THF (1 mL), 4-ethynylanisole (159 mg, 0.156 mL, 1.2 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (7.02 mg, 0.01 mmol) were added. The solution was stirred at r.t. for 10 min, then NH_3 (2.5 M aq, 3 mL) and CuI (3.81 mg, 0.02 mmol) were added. The stirred reaction mixture was heated at 130 °C (max. power setting = 500 W) in a multimode microwave oven (Microsinth Milestone®) for 2 h. The reaction mixture was diluted with H_2O (70 mL) and extracted with EtOAc (3 × 70 mL). The organic layer dried with Na_2SO_4, was evaporated to dryness, and the crude material was purified by flash chromatography over a silica gel column (hexane–EtOAc = 96:4) yielding the isoquinoline **3d** (132 mg, 56%) as brown solid; mp 85–87 °C. IR (KBr): 1626, 1606, 1584, 1512, 1447, 1292, 1249, 1179, 1024, 834 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, CH_3), 7.04 (d, 2 H, arom, *J* = 8.8 Hz), 7.57 (ddd, 1 H, arom, *J* = 8.1, 7.0, 1.1 Hz), 7.67 (ddd, 1 H, arom, *J* = 8.4, 7.0, 1.5 Hz), 7.85 (d, 1 H, arom, *J* = 8.1 Hz), 7.95–7.99 (m, 2 H, arom), 8.08 (d, 2 H, arom, *J* = 8.8 Hz), 9.31 (s, 1 H, arom). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 55.6 (CH_3), 114.5, 115.5, 126.8, 126.9, 127.8, 128.4, 130.6, 152.5 (CH arom), 127.7, 132.6, 137.0, 151.4, 160.5 (C quat.). ESI-MS: *m/z* (%) = 236 (100) $[M + 1]^+$. Anal. Calcd for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.77; H, 5.60; N, 5.93.
(32) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.