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One-Pot Synthesis of Phthalazines and Pyridazino-aromatics: A Novel Strategy for Substituted Naphthalenes

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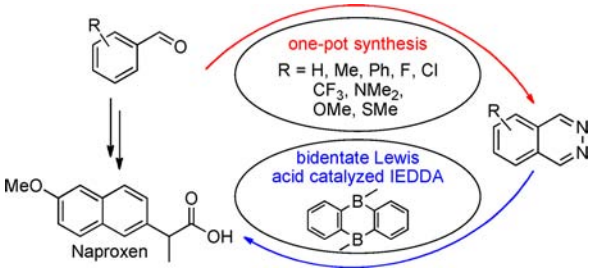
ABSTRACT



A new one-pot strategy for the synthesis of phthalazines and pyridazino-aromatics starting from aromatic aldehydes has been developed. A variety of substituents ranging from electron withdrawing to donating is tolerated furnishing the desired 1,2-diazine in good to excellent yields. The products have been applied to the bidentate Lewis acid catalyzed inverse electron-demand Diels–Alder (IEDDA) reaction opening a novel two-step entry into substituted naphthalenes, such as Naproxen.

Nitrogen containing heterocycles are of tremendous importance in medicinal as well as material sciences. Phthalazines and pyridazino annulated aromatics represent a special class of compounds. In these materials two nitrogen atoms are placed adjacent to each other resulting in distinct properties. In nature this functional entity has been scarcely found,[1] yet in the past decade diverse bioactivity and medical applications of phthalazines or pyridazino heteroaromatics emerged.[2] Also, phthalazine derivatives have been used in material sciences[3] or employed as ligands for a variety of transition metals.[4] Some of them are important catalysts,[5] most prominently in the asymmetric dihydroxylation[6] of alkenes.

(1) (a) Grote, R.; Chen, Y.; Zeeck, A.; Chen, Z.; Zähner, H.; Mischnick-Lübbecke, P.; König, W. A. *J. Antibiot.* **1988**, *41*, 595–601. (b) Cho, J. Y.; Kwon, H. C.; Williams, P. G.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 2471–2474. (c) Winter, J. M.; Jansma, A. L.; Handel, T. M.; Moore, B. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 767–770.

(2) (a) For recent studies on anti-inflammatory effects, see: Herberich, B.; Cao, G.-Q.; Chakrabarti, P. P.; Falsey, J. R.; Pettus, L.; Rzasa, R. M.; Reed, A. B.; Reichelt, A.; Sham, K.; Thaman, M.; Wurz, R. P.; Xu, S.; Zhang, D.; Hsieh, F.; Lee, M. R.; Syed, R.; Li, V.; Grosfeld, D.; Plant, M. H.; Henkle, B.; Sherman, L.; Middleton, S.; Wong, L. M.; Tasker, A. S. *J. Med. Chem.* **2008**, *51*, 6271–6279. (b) For antitumor activity, see: Miller-Moslin, K.; Peukert, S.; Jain, R. K.; McEwan, M. A.; Karki, R.; Llamas, L.; Yusuff, N.; He, F.; Li, Y.; Sun, Y.; Dai, M.; Perez, L.; Michael, W.; Sheng, T.; Lei, H.; Zhang, R.; Williams, J.; Bourret, A.; Ramamurthy, A.; Yuan, J.; Guo, R.; Matsumoto, M.; Vattay, A.; Maniara, W.; Amaral, A.; Dorsch, M.; Kelleher, J. F. *J. Med. Chem.* **2009**, *52*, 3954–3968. (c) For DNA-intercalation, see: Martínez, V.; Burgos, C.; Alvarez-Builla, J.; Fernández, G.; Domingo, A.; García-Nieto, R.; Gago, F.; Manzanares, I.; Cuevas, C.; Vaquero, J. J. *J. Med. Chem.* **2004**, *47*, 1136–1148. (d) For anticonvulsant activity, see: Sivakumar, R.; Kishore Gnanasam, S.; Ramachandran, S.; Thomas Leonard, J. *Eur. J. Med. Chem.* **2002**, *37*, 793–801. (e) For vasorelaxant, see: Watanabe, N.; Adachi, H.; Takase, Y.; Ozaki, H.; Matsukura, M.; Miyazaki, K.; Ishibashi, K.; Ishihara, H.; Kodama, K.; Nishino, M.; Kakiki, M.; Kabasawa, Y. *J. Med. Chem.* **2000**, *43*, 2523–2529.

(3) (a) Achelle, S.; Plé, N.; Turck, A. *RSC Adv.* **2011**, *1*, 364. (b) Liu, Y.; Zhang, F.; He, C.; Wu, D.; Zhuang, X.; Xue, M.; Feng, X. *Chem. Commun.* **2012**, *48*, 4166–4168.

(4) (a) Kettler, P. B.; Chang, Y.-D.; Chen, Q.; Zubieta, J.; Abrams, M.; J. Larsen, S. K. *Inorg. Chim. Acta* **1995**, *231*, 13–20. (b) Kuzelka, J.; Farrell, J. R.; Lippard, S. J. *Inorg. Chem.* **2003**, *42*, 8652–8662. (c) Bullock, G.; Cook, A.; Foster, A.; Rosenberg, L.; Thompson, L. K. *Inorg. Chim. Acta* **1985**, *103*, 207–215. (d) Yamaguchi, T.; Koike, T.; Akita, M. *Organometallics* **2010**, *29*, 6493–6502. (e) Shi, L.; Su, J.; Wu, Z. *Inorg. Chem.* **2011**, *50*, 5477–5484. (f) Paolucci, G.; Stelluto, S.; Sitran, S.; Ajò, D.; Benetollo, F.; Polo, A.; Bombieri, G. *Inorg. Chim. Acta* **1992**, *193*, 57–75. (g) Rashidi, M.; Nabavizadeh, S. M.; Zare, A.; Jamali, S.; Puddephatt, R. J. *Inorg. Chem.* **2010**, *49*, 8435–8443.

(5) (a) Barrios, A. M.; Lippard, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 9172–9177. (b) Xu, Y.; Fischer, A.; Duan, L.; Tong, L.; Gabrielsson, E.; Åkermark, B.; Sun, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8934–8937.

(6) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

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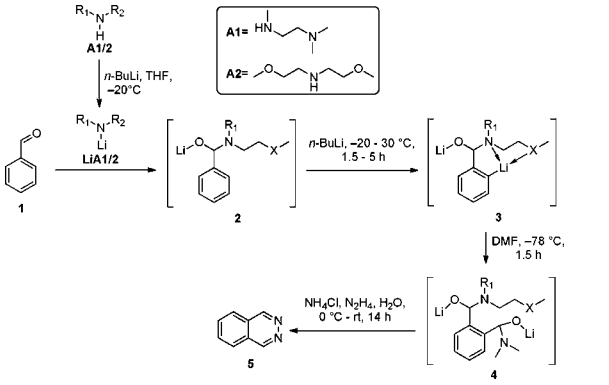
The synthesis of phthalazine derivatives commonly involves multistep procedures concluding with ring closing reactions, ring enlargement, or aromatization of 1,2-dihydro- or 1,2,4,5-tetrahydrophthalazines.[7] Also reported are inverse electron-demand Diels–Alder (IEDDA) reactions of 1,2,4,5-tetrazines with arynes[8] and arenes[8d] or pyridazino[4,5-*d*]pyridazine with enamines[9] as a method for the synthesis of phthalazine derivatives. The first synthesis of phthalazine in 1893 by Gabriel et al.[10] involved the ring closing reaction of *ortho*-carbonylbenzaldehyde or 1,2-bis-dichloromethylbenzene with hydrazine. This transformation, the ring closure of *ortho*-dicarbonyls with hydrazine, still comprises the standard route for the preparation of phthalazines.[11,12] Phthalazines with halogen substituents in the 1,4-position are usually synthesized via halogenation of 2,3-dihydrophthalazine-1,4-dione.[13] Both methods, however, are often preceded by many synthetic steps, depending on the degree of substitution in positions 5 to 8 of the resulting phthalazine. For example, Tsoungas et al. reported such a procedure of six steps starting from 5-methoxy-2-nitrobenzaldehyde via final reaction of the formed dialdehyde with hydrazine to give 6-methoxyphthalazine (**5i**) in a overall yield of less than 20%.[11b] Another ring closing reaction is the cyclization of aromatic aldazines, which is conducted in liquid $AlCl_3/AlBr_3$, comprising rather harsh conditions.[14]

Despite these efforts no approaches for a direct method for a wide range of substituted phthalazines in one pot from simple starting materials are reported to the best of our knowledge. As 1,2-diazines represent a valuable

Scheme 1. Strategy for a One-Pot Method To Access Phthalazines



starting material for the bidentate Lewis acid catalyzed IEDDA reaction developed in our lab,[15] we set out to close this gap in the synthesis portfolio of heterocycles. Herein, we present a general method by which not only 4- to 8-substituted phthalazines, but also pyridazino-heteroaromatics, are prepared in a one-pot procedure from simple aromatic aldehydes in good to excellent yields.

The key step of this new method is the transformation of an aromatic aldehyde into a directed *ortho*-metalation group (DMG). Directed *ortho*-lithiation is a very elegant method to form *ortho*-substituted aromatics and has been widely applied.[16] Although an aldehyde is per-se no directing group they can be reacted with lithium amides to form α-aminoalkoxides **2**, which in turn are moderate to good DMGs.[17] Based on this principle first applied by Comins et al.,[17a,b] we developed a new highly efficient protocol for this strategy (Scheme 1). Commonly, the auxiliary *N,N,N′*-trimethylethylenediamine (TMDA) **A1** is used as lithium amide Li**A1** for the formation of α-aminoalkoxides **2**. Herein, we report for the first time the application of bis(2-methoxyethyl)amine (BMEA) **A2** for this purpose constituting a much cheaper solution than **A1**. The bis(2-methoxyethyl)amino group itself is a chelating ligand intensively studied in the lithiation of *N*,*N*-bis(2-methoxyethyl)-2-methylprop-2-en-1-amine.[18] After the in

(7) (a) Patel, N. R. In *Chemistry of Heterocyclic Compounds: A Series of Monographs*; Castle, R. N., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA; Vol. 27, pp 323–760. (b) Brown, D. D. J. *Cinnolines and Phthalazines: Supplement II, Volume 64*; Chemistry of Heterocyclic Compounds: A Series Of Monographs; 2005.

(8) (a) Margetić, D.; Murata, Y.; Komatsu, K.; Marinić, Ž. *Helv. Chim. Acta* **2009**, *92*, 298–312. (b) Girardot, M.; Nomak, R.; Snyder, J. K. *J. Org. Chem.* **1998**, *63*, 10063–10068. (c) Baumann, L.; Folkerts, A.; Imming, P.; Klindert, T.; Massa, W.; Seitz, G.; Wocadlo, S. *Liebigs Ann.* **1995**, *1995*, 661–666. (d) Seitz, G.; Hoferichter, R.; Mohr, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 332–334.

(9) (a) Haider, N.; Loll, C. *J. Heterocycl. Chem.* **1994**, *31*, 357–360. (b) Haider, N. *Tetrahedron* **1991**, *47*, 3959–3968.

(10) (a) Gabriel, S.; Neumann, A. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 521–527. (b) Gabriel, S.; Pinkus, G. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2210–2216.

(11) For 1,4-unsubstituted phthalazines, see: (a) Meresse, P.; Bertounesque, E.; Imbert, T.; Monneret, C. *Tetrahedron* **1999**, *55*, 12805–12818. (b) Tsoungas, P. G.; Searcey, M. *Tetrahedron Lett.* **2001**, *42*, 6589–6592.

(12) For 1,4-substituted phthalazines, see: (a) Wharton, C. J.; Wrigglesworth, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 809–813. (b) A. Joule, J.; Karim Karim, A.; Armengol, M. *Heterocycles* **2001**, *55*, 2139. (c) Kotali, A.; Lafazanis, I.; Harris, P. *Synthesis* **2009**, *2009*, 836–840. (d) Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 3926–3929. (e) G. Tsoungas, P.; Cordopatis, P.; Gardikis, Y.; Potamitis, C.; Zervou, M. *Heterocycles* **2011**, *83*, 1291–1302.

(13) (a) Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844–849. (b) Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940–3941. (c) Sun, X.-Y.; Hu, C.; Deng, X.-Q.; Wei, C.-X.; Sun, Z.-G.; Quan, Z.-S. *Eur. J. Med. Chem.* **2010**, *45*, 4807–4812. (d) Carling, R. W.; Moore, K. W.; Street, L. J.; Wild, D.; Isted, C.; Leeson, P. D.; Thomas, S.; O'Connor, D.; McKernan, R. M.; Quirk, K.; Cook, S. M.; Atack, J. R.; Wafford, K. A.; Thompson, S. A.; Dawson, G. R.; Ferris, P.; Castro, J. L. *J. Med. Chem.* **2004**, *47*, 1807–1822.

(14) Robev, S. K. *Tetrahedron Lett.* **1981**, *22*, 345–348.

(15) (a) Kessler, S. N.; Neuburger, M.; Wegner, H. A. *Eur. J. Org. Chem.* **2011**, 3238–3245. (b) Kessler, S. N.; Wegner, H. A. *Org. Lett.* **2010**, *12*, 4062–4065. (c) Wegner, H.; Kessler, S. *Synlett* **2012**, 699–705. For selected pioneering examples of noncatalyzed IEDDA reactions of 1,2-diazines, see: (d) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 6027–6030. (e) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240–2245. (f) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415–1423. (g) Oishi, E.; Taido, N.; Iwamoto, K.; Miyashita, A.; Higashino, T. *Chem. Pharm. Bull.* **1990**, *38*, 3268–3272.

(16) (a) Mongin, F. *Tetrahedron* **2001**, *57*, 4059–4090. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

(17) (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213–4216. (b) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078–1083. (c) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104–109. (d) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69–73. (e) Comins, D. L. *Synlett* **1992**, 615–625.

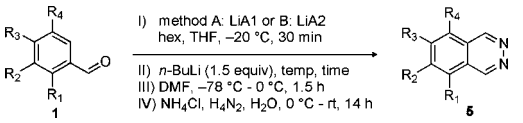
(18) (a) Fraenkel, G.; Qiu, F. *J. Am. Chem. Soc.* **1997**, *119*, 3571–3579. (b) Fraenkel, G.; Chow, A.; Fleischer, R.; Liu, H. *J. Am. Chem. Soc.* **2004**, *126*, 3983–3995.

situ formation of the DMG by either Li**A1** or Li**A2** the dianion **3** is formed via *ortho*-lithiation with *n*-BuLi. Consecutive reaction with dimethylformamide (DMF) gives the *ortho*-bis(aminoalkoxide) **4**. Final hydrolysis with an aqueous solution of ammonium chloride and hydrazine furnishes phthalazines **5** in good yield.

The development of the method involved the optimization of each aforementioned step, mainly the *ortho*-lithiation. Existing protocols for the *ortho*-lithiation of aminoalkoxides were commonly conducted with a large amount of lithiating agent (3 equiv of *n*-BuLi) and an inconvenient reaction temperature of −20 °C over an extended period of 3 h for chlorobenzaldehydes, 24 h for benzaldehyde, and up to 48 h for *p*-tolualdehyde.[17b] The applicability to a one-pot procedure demanded a considerable decrease of reaction time and amounts of *n*-BuLi and enhancement of the efficiency of each elementary transformation. Since *n*-BuLi in pure THF has a half-life time of only 1.78 h at 20 °C a change in the reaction media was crucial for the optimization.[19] Recently, it was shown that already 1 equiv of THF in a 1 M solution of *n*-BuLi in cyclohexane at 25 °C holds similar deoligomerization potential for the lithium organyl as pure THF, but only minor decomposition of the THF was observed after 24 h.[20] In our case 3.3 equiv of THF in an ∼0.5 M solution of *n*-BuLi in hexane gave the best results. In the THF/hexane solvent mixture it was possible to perform the directed *ortho*-metalation step at rt. Simultaneously, we were able to significantly lower the amount of lithiation agent to only 1.5 equiv of *n*-BuLi. Consequently, considerably shorter reaction times were achieved: 1.5−2.5 h at rt (25−30 °C) if the auxiliary **A1** and 2−5 h at 0 °C if **A2** was applied

Benzaldehyde was used as a test substrate for the optimization. The use of both the common auxiliary TMDA **A1** and BMEA **A2** allowed a comparison of performance in the *ortho*-metalation of benzaldehyde (see Table 1 in the Supporting Information, p S2). Thus, after 4 h of lithiation at 0 °C the one-pot reaction applying TMDA **A1** and BMEA **A2** yielded 73% and 56% of phthalazine **5a**, respectively. TMDA **A1** performs slightly better than BMEA **A2**, but in some cases, especially for the more acidic substrates, **A2** gives comparable or even better results. It is important to mention that the yield of phthalazine in the case of BMEA **A2** as the auxiliary augments to 72% after a lithiation time of 5 h at 0 °C. If the *ortho*-lithiation step was conducted at rt (25 °C) for 2 h, using TMDA **A1**, a yield of 74% was obtained. Using BMEA **A2**, the yield decreases substantially to only 35%. Even with an *ortho*-lithiation at 10 °C for 3 h the loss in yield was significant compared to the case involving a lithiation temperature of 0 °C. This results concerning BMEA **A2** as the *ortho* directing auxiliary points toward an accelerated decomposition of the α-aminoalkoxide **2a** at temperatures >0 °C. The optimized protocol on the basis of benzaldehyde **1a** was shown to be applicable to a broad range of substituted benzaldehydes producing benzo-substituted phthalazines with good to excellent yields of up to 91% (Table 1). Not only electron withdrawing fluoro, chloro, and trifluoromethyl substituents (Table 1, entries 3−7) but also electron donating substituents such as methoxy, methylthio (Table 1, entries 9−11, 14−16), and even dimethylamino groups (Table 1, entry 12) are well tolerated.

Table 1. Synthesis of Substituted Phthalazines



entry	ArCHO	1,2-diazine	yield (method)	
			A	B
1			74%	72%
2			84%	–
3			53%	67%
4			–	75%
5			79%	91%
6			75%	–
7			89%	–
8			80%	–
9			81%	–
10			79%	50%
11			51%	–
12			62%	–
13			66%	–
14			61%	–
15			44%	–
16			36%	–
17			68%	–

(19) Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514–1515.

(20) Slocum, D. W.; Carroll, A.; Dietzel, P.; Eilerman, S.; Culver, J. P.; McClure, B.; Brown, S.; Holman, R. W. *Tetrahedron Lett.* **2006**, *47*, 865–868.

Scheme 2. Synthesis of 1-Substituted Phthalazine

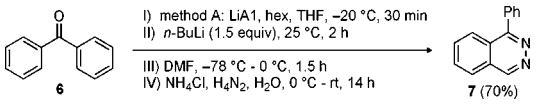
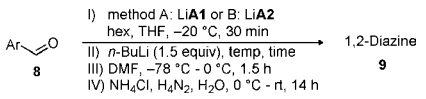


Table 2. Synthesis of Pyridazino-heteroaromatics



entry	ArCHO	1,2-diazine	method	time / h	Temp / °C	yield
1			A	2	0	48%
	8a	9a	B	2.5	–20	66%
2	8b		B	1	–20	81%
3	8c	9b	A	2	0	55%
			B	2.5	–20	53%
4	8d	9c	A	2	–20	63%
			B	2	–20	50%
5	8e	9d	A	2	0	52%
			B	2.5	–20	53%
6	8f	9e	B	1.3	–20	59%

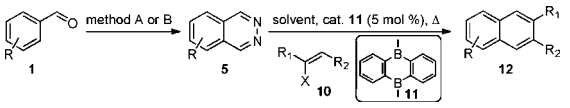
Also benzoketones omitting α-protons can be successfully employed in a one-pot reaction resulting in 1-substituted phthalazines, as demonstrated with benzophenone **6** resulting in 1-phenylphthalazine **7** in a 70% yield (Scheme 2).

The more acidic heteroaromatics require milder lithiation conditions (Table 2). Hence, lithiation at 0 °C employing BMEA **A2** as an auxiliary for the directed *ortho*-lithiation were satisfying. In these cases decreasing the temperature from 0 °C further to −20 °C and shortening the reaction times compared to the case of benzaldehyde **1a** gave even better results (Table 2), most pronounced in the case of thiophene-3-aldehyde **8b** (from 61% to 81%). At similar conditions the auxiliary TMDA performed slightly better than BMEA though; BMEA in turn presents a much more cost-effective solution (Table 2, entries 3−5).

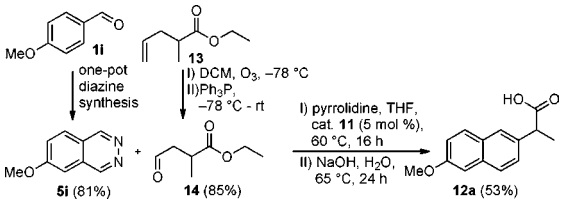
Recently, we presented the bidentate Lewis acid catalyzed inverse electron-demand Diels−Alder reaction using phthalazines **5** as electron deficient dienes with a variety of dienophiles **10**, which produces 2,3-substituted naphthalenes in a highly efficient way.[15] Joining the herein introduced one-pot synthesis of pyridazino-aromatics with our catalyzed IEDDA reaction concludes an extremely short

(21) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203–205.

Scheme 3. Two-Step Protocol for the Synthesis of Naphthalenes



Scheme 4. Preparation of Naproxen via the One-Pot Phthalazine Synthesis and Bidentate Lewis Acid Catalyzed IEDDA Reaction



and very convenient two-step synthesis of, for example, complex, highly substituted naphthalenes (Scheme 3). In order to put this powerful approach into context a prominent naphthalene candidate, (±)-Naproxen **12a**, has been chosen to demonstrate the utility of our methodology. (±)-Naproxen **12a**, one of the most common nonsteroidal anti-inflammatory drugs,[21] can be accessed in one-pot from the according diazine **5i** and aldehyde **14** with a yield of 53% after basic workup (Scheme 4).

Interestingly, the desired 2,6-substitution pattern (compared to the 1,7-isomer) is obtained in a selectivity greater 9:1 (by ^{1}H NMR). Such an outcome is in accordance with the frontier molecular orbital (FMO) theory, which rationalizes the result based on the analysis of the orbital coefficients of the participating highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).

On the basis of the auxiliary directed *ortho*-metalation of aromatic aldehydes we herein provide a new and highly efficient one-pot procedure for the preparation of a wide range of substituted and unsubstituted pyridazino aromatics. At the same time we present bis(2-methoxyethyl)-amine (BMEA) as a new and cost-effective auxiliary for this purpose. Furthermore, we developed a novel two-step strategy for the synthesis of highly substituted naphthalenes demonstrated in the synthesis of (±)-Naproxen.

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Supporting Information Available. Complete data for experimental details, and compound spectral characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.