Ruthenium Catalyzed Regioselective beta-C(sp³)-H Functionalization of N-Alkyl-N'-p-nitrophenyl Substituted Piperazines using Aldehydes as Alkylating Agents

V Muruges, Apurba Ranjan Sahoo, Mathieu Achard, Gangavaram V. M. Sharma, Christian Bruneau, Suriseti Suresh

► To cite this version:

V Muruges, Apurba Ranjan Sahoo, Mathieu Achard, Gangavaram V. M. Sharma, Christian Bruneau, et al.. Ruthenium Catalyzed Regioselective beta-C(sp³)-H Functionalization of N-Alkyl-N'-p-nitrophenyl Substituted Piperazines using Aldehydes as Alkylating Agents. *Advanced Synthesis and Catalysis*, 2021, 363 (2), pp.453-458. 10.1002/adsc.202001060 . hal-03100328

HAL Id: hal-03100328

<https://hal.science/hal-03100328>

Submitted on 12 Jan 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Ruthenium Catalyzed Regioselective β -C(sp³)-H Functionalization of *N*-Alkyl-*N'*-*p*-nitrophenyl Substituted Piperazines using Aldehydes as Alkylating Agents

V. Murugesh,^{a,b} Apurba Ranjan Sahoo,^c Mathieu Achard,^c Gangavaram V. M. Sharma,^a Christian Bruneau,^c and Suriseti Suresh^{*a,b}

^a Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad 500 007, India. E-mail: suriseti@iict.res.in; suresh.suriseti@yahoo.in.

^b Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India.

^c Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes) UMR 6226, F-35000 Rennes, France.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

Abstract. Herein, we disclose a ruthenium-catalyzed regioselective β -C(sp³)-H bond functionalization on the piperazine core using aldehydes as alkylating agents. The present transformation appears to go through the dehydrogenation of the piperazine to propagate to enamine *in situ*, followed by nucleophilic addition to the aldehyde and hydrogenation to result in the regioselective β -C(sp³)-H alkylation. A variety of aromatic, heteroaromatic, aliphatic aldehydes were employed for the C-3 alkylation of *N*-alkyl-*N'*-*p*-nitrophenyl substituted piperazines.

Keywords: Regioselective; C(sp³)-H functionalization; piperazine; ruthenium catalysis; alkylation

Identical reactivity of C(sp³)-H bonds in saturated heterocyclic molecules makes selective C(sp³)-H bond functionalization as an attractive challenge for the researchers. Literature witnessed the directing group guided or catalyst controlled site selective C(sp³)-H bond functionalizations.^[1] However, this requires installation of specific directing groups and specially designed catalysts/ligands. Site-selective C(sp³)-H functionalization based on natural reactivity of substrate attracts the chemists attention. Innate C(sp³)-H functionalization^[2] is demanding compared to the guided one^[1] because of its merits such as obviating the use of the directing group installation and its removal, designed ligands and catalysts. Although α -C(sp³)-H functionalization of saturated nitrogen heterocycles has been well-reported,^[3] the β -C(sp³)-H functionalization has received significantly less attention. In this context, the research groups of Bruneau and Seidel, independently, made seminal contributions to the development of β -C(sp³)-H functionalization of saturated nitrogen heterocycles without using directing groups.^[4,5] Regioselective C(sp³)-H bond functionalization of challenging saturated *N*-heterocyclic compounds^[6] like piperazine remains a critical issue and a welcoming challenge in

organic synthesis. This is due to the reason that piperazine is the 3rd most appeared 'privileged' *N*-heterocyclic core structure in the marketed drugs.^[7] Among the top 100 best selling drugs, piperazine containing drugs occupy a significant number. In particular, C-substituted piperazines have received considerable attention from the scientific community owing to their potential therapeutic values being useful for the treatment of infections, viral diseases, malaria and CNS related disorders (**Figure 1**).^[8]

Figure 1. Drugs and biologically active compounds containing C-substituted piperazine moiety.

The synthesis of C-substituted piperazines, from the parent piperazine core, mainly relies on the reduction of pyrazinium salts^[9] and C(sp³)-H bond functionalization reactions.^[10] Literature survey revealed that most of the methods for activating C(sp³)-H bonds on piperazine depend on α -C(sp³)-H functionalization^[11,6a] in the presence of stoichiometric amounts of strong bases (**Scheme 1a**), while very few methods were reported under photoredox catalysis conditions (**Scheme 1b**).^[10b,c] Catalytic approaches to construct regioselective C(sp³)-C bonds from piperazine's inert-C(sp³)-H bonds is a challenging transformation due to the

presence of two nitrogen atoms at 1,4-positions in its ring.

Our previous ruthenium-catalyzed protocol^[12] on the intramolecular C(sp³)-H functionalization for the synthesis of piperazine fused indoles (**Scheme 1c**) paved a way and inspired us to develop a regioselective intermolecular β -C(sp³)-H bond functionalization method on piperazines. We envisaged the regioselective functionalization of piperazine C(sp³)-H bonds by varying the substitution pattern on the nitrogen atoms of the saturated ring. The *N*-substitution pattern on the two nitrogen atoms plays a crucial role. Piperazine having an electron withdrawing group on the nitrogen N(4), which is adjacent to the targeted C(sp³)-H bond and the other nitrogen N(1) bearing an alkyl substituent, would serve as a model substrate to test the β -C(sp³)-H bond functionalization. Under ruthenium catalysis conditions, we anticipated the regioselective formation of C-C bond through the events of the dehydrogenation of piperazine, formation of iminium species to propagate enamine that could undergo nucleophilic addition to the aldehyde followed by hydrogenation to eventually result in the regioselective β -C(sp³)-H alkylation (**Scheme 1d** and *vide infra*).

Scheme 1. Literature reports on C(sp³)-H bond functionalization on piperazine derivatives and This work.

To prove our hypothesis, we designed a substrate such as **1a** having an electron-withdrawing *p*-nitrophenyl group on nitrogen (N4) which is adjacent to the targeted C(sp³)-H bond and an electron-rich methyl substituent on the other nitrogen (N1). 1-Methyl-4-(4-nitrophenyl)piperazine **1a** was treated with benzaldehyde (**2a**) in the presence of [Ru(*p*-cymene)Cl₂]/ camphorsulfonic acid (CSA) catalytic

system followed by the addition of formic acid as the external hydrogen source.^[4] Delightfully, the expected alkylated product **3a** was obtained in 62% yield (Table 1, entry 1). Encouraged by this finding, we conducted an optimization assay (Table 1) for this transformation in order to improve the yield of **3a**. We screened different Ru(II), Ir(III)-catalysts for this regioselective transformation. The Ru-catalyst **B** and Ir-catalyst **C**, bearing phosphino-benzene sulfonate ligands, gave only moderate yields of **3a** (Table 1, entries 2 and 3). Other ruthenium catalysts **D** or **E** bearing triphenylphosphine or bipyridine ligands were not efficient for this regioselective alkylation (Table 1, entries 4 and 5). The ruthenium(0) complex Ru₃(CO)₁₂ **F** did not provide the desired product **3a** (Table 1, entry 6). Additives such as HCOOH, trifluoroacetic acid (TFA) or methanesulfonic acid (MSA) did not give better results (Table 1, entries 7–9). We observed better yields of **3a** with 20 mol% of CSA (Table 1, entry 10). Further increase in the amount of CSA did not improve the yield of **3a** (Table 1, entry 11). No reaction took place in the absence of catalyst (Table 1, entry 12), which highlights the crucial role of the catalyst in the C(sp³)-H bond functionalization (see supporting information, for an extensive optimization study).

Table 1. Optimization study^a.

Catalysts:
A: [Ru(*p*-cymene)Cl₂]₂
B: Tris(triphenylphosphine)ruthenium(II) dichloride
C: Tris(2,2'-bipyridyl)ruthenium(II)Cl₂·6H₂O
F: Triruthenium dodecacarbonyl

Entry ^a	Catalyst	Additive (mol%)	%Yield of 3a ^b
1	A	CSA (10)	62
2	B	CSA (10)	46
3	C	CSA (10)	15
4	D	CSA (10)	27
5	E	CSA (10)	18
6	F	CSA (10)	—
7	A	HCOOH (10)	29
8	A	MSA (10)	22
9	A	TFA (10)	32
10	A	CSA (20)	73
11	A	CSA (30)	62
12	—	CSA (20)	—

^a) Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), catalyst (5 mol%), additive (x mol%), toluene (2 mL), at 150 °C for 18 h, then HCOOH (1 mmol), at 150 °C for 12 h; ^b) Yields are of isolated products.

Note that the optimized conditions (Table 1, entry 10) enabled gram scale synthesis of **3a** in 60% yield (**Scheme 2**). After selecting the optimized reaction conditions, we turned our attention to check the substrate scope of the ruthenium-catalyzed β -C(sp³)-H bond functionalization of piperazine (**Scheme 2**). Firstly, we examined the scope of the ruthenium-catalyzed C-alkylation of **1a** with various aldehydes. The regioselective alkylation tolerated substituted benzaldehydes containing different functional groups like halogens, electron-donating and electron-withdrawing groups. Halogen substituted benzaldehydes produced the corresponding C-alkylated piperazine derivatives **3b-g** in moderate to good yields, while the *ortho*-substituted ones gave lower yields. The benzaldehydes containing electron-donating groups such as *o*-OH, *o*-OMe, *p*-OMe, *p*-Me and *p*-NMe₂ furnished the corresponding C-alkylated piperazine derivatives **3h-l** in moderate to good yields. The benzaldehyde bearing a *p*-CF₃ electron-withdrawing group tolerated for this transformation as the reaction of **1a** and 4-(trifluoromethyl)benzaldehyde afforded the corresponding C-alkylated piperazine **3m** in 48% yield. The structure of **3m** was further confirmed with the aid of X-ray crystal structure analysis^[14] besides the standard spectroscopic characterization methods (see the Supporting Information, for X-ray data details).

The benzaldehydes comprising multiple substituents also worked well as 2,5-dibromobenzaldehyde, 2-bromo-5-fluorobenzaldehyde, and 6-bromopiperonal proved to be successful alkylating agents to deliver the corresponding C-alkylated products **3n-p** in 61%, 62% and 52% yields, respectively. Polyaromatic aldehydes such as 2-naphthaldehyde and biphenyl-4-carboxaldehyde gave their respective C-alkylated piperazines **3q** and **3r** in 66% and 58% yields, respectively. Aliphatic aldehydes including cyclohexanecarboxaldehyde, cyclopropanecarboxaldehyde, and 2,2-diphenylacetaldehyde delivered the corresponding C-alkylated products **3s-u** in reasonable yields. Heteroaromatic aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde were suitable reagents to alkylate **1a** to produce the corresponding C-alkylated products **3v** and **3w** in 61% and 52% yields, respectively. However, our efforts towards the regioselective alkylation with ketones were not successful. Later we checked the scope with different substituents on N(1) of piperazine. Piperazine derivatives comprising N(1)-ethyl, -propyl, -phenethyl, -benzyl substitution furnished their corresponding C-alkylated products **3x-aa** in low to moderate yields upon reaction with benzaldehyde under the ruthenium catalysis settings. Some unidentifiable byproducts were observed in the cases of the products with low to moderate yields.

Scheme 2. Substrate scope of the regioselective β -C(sp³)-H functionalization of piperazines.

Based on the substitution pattern of the piperazine substrate, there are two possibilities for the present regioselective C(sp³)-H functionalization: (i) β -C(sp³)-H functionalization to the N(1) atom and (ii) α -C(sp³)-H functionalization to the N(4) atom. To investigate the possibilities, we conducted control experiments. By using the optimized reaction conditions, we treated benzaldehyde with 1-(4-nitrophenyl)piperidine **4a** or 4-(4-nitrophenyl)morpholine **4b**, which lack the second

nitrogen atom in the saturated rings of **4a** or **4b** compared to that of the piperazine **1**. However, we did not observe the corresponding alkylation products **5a** (or) **5b**, which implies that the β -C(sp³)-H functionalization on piperazines **1** is operating from N(1). It may be noted that under ruthenium catalysis conditions *N*-methylpiperidine underwent β -C(sp³)-H functionalization by using benzaldehyde as alkylation agent.^[4c,d] These results may also suggest the crucial role of the methylene group^[4] on the N(1) nitrogen of the piperazine **1**, which may be acting as an innate directing group for the β -C(sp³)-H functionalization of **1** (Scheme 3).

Scheme 3. Control experiments to confirm β -C(sp³)-H functionalization.

A plausible mechanism was proposed for the present regioselective β -C(sp³)-H functionalization on piperazine based on the control experiments and literature reports (Scheme 4)^[4a-b,12,13]. The iminium cation intermediate **I** would form from the piperazine substrate **1** by the action of ruthenium catalyst *via* hydrogen atom transfer process.^[4a-b] Then an azo-methine intermediate **II** would result from the intermediate **I** *via* proton abstraction of the ruthenium hydride species.^[4a-b] In the presence of acid, an enamine intermediate **III** would form from intermediate **II**.^[4a-b,12,13] The enamine **III** would add to aldehyde **2** to give intermediate **IV**. Dehydration of the intermediate **IV** would provide intermediate **V**. In the presence of ruthenium species and acidic source, the imine functionality and unsaturation in the intermediate **V** might undergo reduction^[4a-b] to produce the C-alkylated piperazine derivative **3**. As shown the proposed mechanism might operate in two successive catalytic cycles. The presence of exocyclic C-H bond at N(1) allows the azo-methine formation at this nitrogen position only. On the other hand, the attracting *p*-nitrophenyl group at N(4) polarizes the enamine double bond to favour the regioselective formation of C-C bond at C(3).

The presence of the electron deficient -NO₂ moiety on the resulting products can be judiciously used for further post-functionalization. Accordingly, we synthesized 4-(2-benzyl-4-methylpiperazin-1-yl)aniline **6** by reducing the nitro group on **3a** (Scheme 5), which will increase its synthetic utility for further transformations including cross coupling reactions, arylations, alkylations, amidations, Schiff's base formation reactions *etc.*^[15]

Scheme 4. Plausible mechanism.

Scheme 5. Reduction of nitro group on **3a**.

In summary, we designed and developed a regioselective, intermolecular β -C(sp³)-H functionalization method to access C-substituted piperazines by using aldehydes as alkylating agents in the presence of ruthenium catalysis. A wide range of aldehydes including aromatic, aliphatic, heteroaromatic aldehydes have been employed as alkylating agents for the C-alkylation of piperazines to access the corresponding C-alkylated piperazine derivatives in moderate to good yields. Therefore, the presented strategy offers a useful protocol to alkylate the “privileged” piperazine moieties with high levels of predictable regioselectivity.

Experimental Section

Synthesis of **3a** to **3aa**

In a dry schlenk tube 5 mol% of [RuCl₂(*p*-cymene)]₂ (0.025 mmol, 0.015 g), 20 mol% of CSA (0.1 mmol, 0.023 g) and 0.6 mmol of piperazine **1** were taken, vacuum was applied (2-5 sec) to the reaction tube and degassed with N₂. Then added 0.5 mmol of aldehyde **2** under nitrogen atmosphere followed by the addition of 2 mL of degassed toluene. The reaction tube was placed on a preheated metal-heating block and stirred at 150 °C for 18 h. The reaction was cooled to room

temperature, then added 2 equiv of formic acid (1 mmol, 0.037 mL) and stirred at 150 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (2 x 20 mL), washed with water (2 x 20 mL) followed by brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and the solvent was removed under the reduced pressure to afford a crude residue. The crude was subjected to silica gel column chromatography by using EtOAc/hexane as eluent to obtain pure C-alkylated piperazine derivatives **3a-3aa**.

Acknowledgements

We thank the Indo-French Centre for the Promotion of Advanced Research (CEFIPRA/IFCPAR No. 5105-4) for financial support. SS thanks the Science & Engineering Research Board (SERB), Department of Science and Technology (DST), India for an Extramural Research grant (EMR/2017/002601). VM thanks UGC, New Delhi, for a fellowship. ARS thanks CEFIPRA for financial support. We thank Dr. N. Jagadeesh Babu, CSIR-IICT for single crystal X-ray structure analysis. We thank the Director, CSIR-IICT for the support (Communication No. IICT/Pubs./2020/085)

References

- [1] a) A. Millet, P. Larini, E. Clot, O. Baudoin, *Chem. Sci.* **2013**, *4*, 2241–2247; b) M. Schinkel, L. Wang, K. Bielefeld and L. Ackermann, *Org. Lett.* **2014**, *16*, 1876–1879; c) B. Mondal, B. Roy, U. Kazmaier, *J. Org. Chem.* **2016**, *81*, 11646–11655; d) D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley, M. J. Gaunt, *Science* **2016**, *354*, 851–857; e) L. Gonnard, A. Guérinot, J. Cossy, *Tetrahedron* **2019**, *75*, 145–163.
- [2] a) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99; b) Z. Song, G. Wang, W. Lia, S. Li, *Org. Chem. Front.* **2019**, *6*, 1613–1618.
- [3] For selected reviews on α -C(sp³)-H functionalization of saturated nitrogen heterocycles, see: a) M.-X. Cheng, S.-D. Yang, *Synlett* **2017**, 159–174; b) J. W. Beatty, C. R. J. Stephenson, *Acc. Chem. Res.* **2015**, *48*, 1474–1484; c) D. Seidel, *Acc. Chem. Res.* **2015**, *48*, 317–328; d) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; e) Y. Qin, J. Lv, S. Luo, *Tetrahedron Lett.* **2014**, *55*, 551–558; f) C.-V. T. Vo, J. W. Bode, *J. Org. Chem.* **2014**, *79*, 2809–2815; g) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142; h) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; i) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084; j) S.-I. Murahashi, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443–2465. h) S.-S. Li, X. Lv, D. Ren, C.-L. Shao, Q. Liuc, J. Xiao, *Chem. Sci.* **2018**, *9*, 8253–8259. i) S.-S. Li, L. Zhou, L. Wang, H. Zhao, L. Yu, J. Xiao, *Org. Lett.* **2018**, *20*, 138–141. j) S. Wang, Y.-B. Shen, L.-F. Li, B. Qiu, L. Yu, Q. Liu, J. Xiao, *Org. Lett.* **2019**, *21*, 8904–8908. k) K. Duan, X.-D. An, L.-F. Li, L.-L. Sun, B. Qiu, X.-J. Li, J. Xiao, *Org. Lett.* **2020**, *22*, 7, 2537–2541.
- [4] For selected reports, see: a) B. Sundararaju, Z. Tang, M. Achard, G. V. M. Sharma, L. Toupet, C. Bruneau, *Adv. Synth. Catal.* **2010**, *352*, 3141–3146; b) B. Sundararaju, M. Achard, G. V. M. Sharma, C. Bruneau, *J. Am. Chem. Soc.* **2011**, *133*, 10340–10343; c) Í. Özdemir, S. D. Dusunceli, N. Kaloğlu, M. Achard, C. Bruneau, *J. Organomet. Chem.* **2015**, *799–800*, 311–315. d) N. Kaloğlu, *Tetrahedron* **2019**, *75*, 2265–2272.
- [5] For selected reports, see: a) W. Chen, Y. Kang, R. G. Wilde, D. Seidel, *Angew. Chem. Int. Ed.* **2014**, *53*, 5179–5182; b) L. Ma, A. Paul, M. Breugst, D. Seidel, *Chem. Eur. J.* **2016**, *22*, 18179–18189; c) W. Chen, A. Paul, K. A. Abboud, D. Seidel, *Nat. Chem.* **2020**, *12*, 545–550.
- [6] a) Z. Ye, K. E. Gettys, M. Dai, *Beilstein J. Org. Chem.* **2016**, *12*, 702–715; b) K. E. Gettys, Z. Ye, M. Dai, *Synthesis* **2017**, *49*, 2589–2604; c) D. Antermite, J. A. Bull, *Synthesis* **2019**, *51*, 3171–3204 and references cited therein. d) L. Zhou, Y.-B. Shen, X.-D. An, X.-J. Li, S.-S. Li, Q. Liu, J. Xiao, *Org. Lett.* **2019**, *21*, 8543–8547. e) L. Zhou, X.-D. An, S. Yang, X.-J. Li, C.-L. Shao, Q. Liu, J. Xiao, *Org. Lett.* **2020**, *22*, 776–780.
- [7] a) M. Asif, *Int. J. Adv. Sci. Res.* **2015**, *1*, 05–11; b) M. Al-Ghorbani, A. B. Begum, Zabiulla, S. V. Mamatha, S. A. Khanum, *J. Chem. Pharm. Res.* **2015**, *7*, 281–301.
- [8] a) G. L. Plosker, S. Noble, *Drugs* **1999**, *58*, 1165–1203. b) G. L. Plosker, *Drugs* **2014**, *74*, 223–242; c) J.-Y. Chai, *Infect. Chemother.* **2013**, *45*, 32–43; d) G. KesavaReddy, R. J. Gralla, P. J. Hesketh, *Support. Cancer Ther.* **2006**, *3*, 140–142; e) M. Peter, M. D. Hartmann, *Am. Fam. Physician* **1999**, *59*, 159–161; f) C. Schultz, *Ophthalmol. Eye Dis.* **2012**, *4*, 65–70.
- [9] a) J.-P. Leclerc, K. Fagnou, *Angew. Chem. Int. Ed.* **2006**, *45*, 7781–7786; b) H. Andersson, T. S.-L. Banchelin, S. Das, M. Gustafsson, R. Olsson, F. Almquist, *Org. Lett.* **2010**, *12*, 284–286; c) W.-X. Huang, C.-B. Yu, L. Shi, Y.-G. Zhou, *Org. Lett.* **2014**, *16*, 3324–3327; d) W.-X. Huang, L.-J. Liu, G.-S. Feng, B. Wang, Y.-G. Zhou, *Org. Lett.* **2016**, *18*, 3082–3085.
- [10] a) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics* **1997**, *16*, 3615–3622; b) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117; c) J. B. McManus, N. P. R. Onuska, M. S. Jeffreys, N. C. Goodwin, D. A. Nicewicz, *Org. Lett.* **2020**, *22*, 679–683.
- [11] a) M. Berkheij, L. van der Sluis, C. Sewing, D. J. den Boer, J. W. Terpstra, H. Hiemstra, W. I. I. Bakker, A. van den Hoogenband, J. H. van Maarseveen, *Tetrahedron Lett.* **2005**, *46*, 2369–2371; b) G. Barker, P. O'Brien, K. R. Campos, *Org. Lett.* **2010**, *12*, 4176–4179; c) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937–1949; d) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142.

- [12] a) V. Muruges, C. Bruneau, M. Achard, A. R. Sahoo, G. V. M. Sharma, S. Suresh, *Chem. Commun.* **2017**, 53, 10448–10451.
- [13] a) C. Zhang, D. Seidel, *J. Am. Chem. Soc.* **2010**, 132, 1798–1799. c) I. Deb, D. Das, D. Seidel, *Org. Lett.* **2011**, 13, 812–815. d) D.-H. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, 2, 803–806.
- [14] Crystal data for **3m**: $2(\text{C}_{19}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_2)$, $M = 758.76$, Monoclinic, space group $P2_1/c$, $a = 21.062(3) \text{ \AA}$, $b = 15.641(2) \text{ \AA}$, $c = 11.2315(14) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 99.894(4)^\circ$, $\gamma = 90^\circ$, $V = 3645.1(8) \text{ \AA}^3$, $Z = 4$, $D_c = 1.383 \text{ g/cm}^3$, $F_{000} = 1584$, MoK α radiation, $\lambda = 0.71073 \text{ \AA}$, $T = 293(2) \text{ K}$, 21984 reflections collected, 6387 unique ($R_{\text{int}} = 0.0834$), Final $GooF = 1.003$, $RI = 0.0783$, $wR2 = 0.2003$, R indices based on 2603 reflections with $I > 2\sigma(I)$ (refinement on F^2), 490 parameters, $\mu = 0.112 \text{ mm}^{-1}$, Min. and Max. Resd. Dens. = $-0.296, 0.378 \text{ e/\AA}^3$. CCDC 1982965 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [15] a) T. R. M. Rauws, B. U. W. Maes, *Chem. Soc. Rev.* **2012**, 41, 2463–2497; b) Z.-Y. Tian, C.-P. Zhang, *Chem. Commun.* **2019**, 55, 11936–11939.

Ruthenium Catalyzed Regioselective β -C(sp³)-H Functionalization of *N*-Alkyl-*N'*-*p*-nitrophenyl Substituted Piperazines using Aldehydes as Alkylating Agents

Adv. Synth. Catal. **2020**, Volume, Page – Page

V. Murugesh,^{a,b} Apurba Ranjan Sahoo,^c Mathieu Achard,^c Gangavaram V. M. Sharma,^a Christian Bruneau,^c and Suriseti Suresh*,^{a,b}