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S,O-ligand-promoted palladium-catalyzed C–H functionalization of anisole and aniline derivatives

Sukowski, V.

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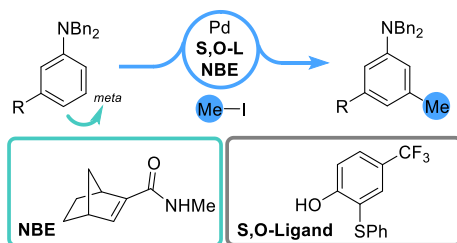
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Chapter 5

S,O-Ligand Promoted *meta*-C–H Methylation of Aromatic Amine Derivatives via Palladium/Norbornene Catalysis

5



5.1 Introduction

The addition of methyl groups to molecules plays a key role in the pharmaceutical industry.^[1] The installation of a methyl group in a lead pharmaceutical compound can have an immense impact on its pharmacological properties while maintaining similar physical properties like the lipophilicity. This phenomenon, often referred to as the "magic methyl effect," results from several factors, including favorable desolvation energies, changes in metabolic stability, and induced conformational alterations. In particular, conformational changes play a pivotal role in driving the magic methyl effect, with observed potency enhancements ranging from 100 to 1000-fold.^[1]

An illustrative case of the magic methyl effect was documented in the work of GlaxoSmithKline researchers. Here, the introduction of a methyl group in the *ortho*-position of a biaryl motif resulted in a remarkable increase in binding affinity (K_i) towards the p38 α MAP3 kinase, exceeding a 200-fold increase. This remarkable improvement in binding affinity can be attributed to the improved alignment of the compound's dihedral angle within the binding site of the protein. Specifically, the dihedral angle shifted from 50° (without the methyl group) to 65° (with the methyl group), resulting in an improved fit of 85° in the protein structure (Figure 1).^[1,2]

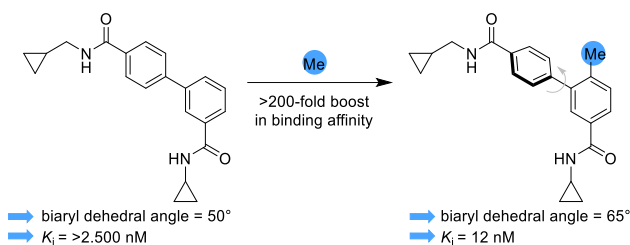
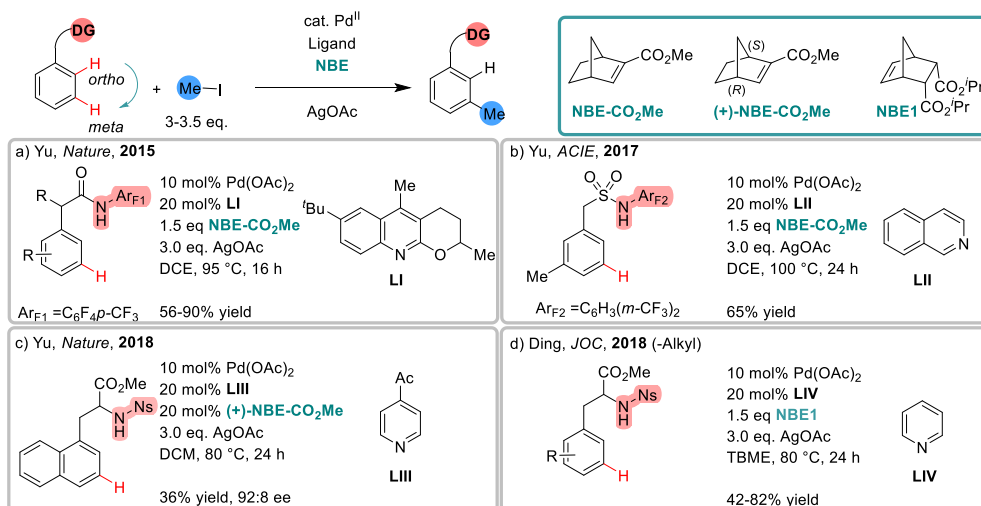


Figure 1. Example of "magic methyl" effect via conformational change.^[1,2]

Therefore, the development of new and efficient methylation methodologies is highly relevant due to the potential impact on the pharmacological properties of lead compounds. Traditional methylation reactions have frequently relied on Friedel-Crafts-type reactions, which take place under harsh reaction conditions with the methylation taking place at the most electron-rich site of the arene.^[3] In the context of C–H activation, methylation reactions have been realized using directing groups (DGs), leading to *ortho*-selectivity.^[1,4] On the other hand, the *meta*-position has been accessed by the application of DG-assisted *ortho*-C–H activation coupled with a norbornene (NBE) mediator. Directing groups such as amides,^[5] benzylsulfonamides,^[6] and nosyl,^[7,8] have been employed in this approach. A comprehensive overview of these methodologies, including reaction conditions, is presented in Scheme 1.



Scheme 1. Overview of Pd-catalyzed *meta*-C–H methylation reaction via *ortho*-DG/ NBE mediator.

In the context of non-directed C–H activation catalyzed by Pd/NBE systems, only arylation reactions have been achieved so far. Moreover, the realization of non-directed palladium-catalyzed C–H methylation reactions has not been accomplished to date. Given the effectiveness of our Pd/S,O-ligand/NBE catalytic system for arylation reactions involving aryl ether and amine derivatives (Chapters 3 and 4), we envisioned that we could develop the first non-directed C–H methylation reaction.

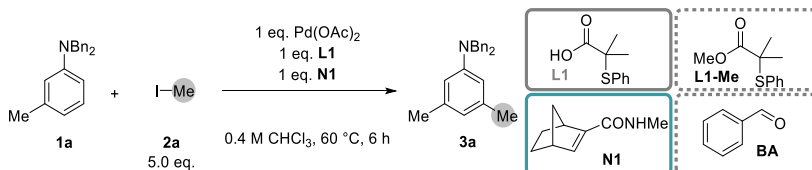
This chapter presents the optimization of the *meta*-C–H methylation reaction in non-directed aniline derivatives employing Pd/S,O-ligand/NBE cooperative catalysis. Key to the success of this methodology is the use of a phenolic S,O-ligand, which is much less prone to methylation than the related S,O-ligand, and therefore remains active during the reaction. Although the substrate scope is not yet finished, the few substrates that have been tested show promising results. Given the ubiquity of aromatic amines in pharmaceuticals, we anticipate that this methodology will have a tremendous impact on drug discovery through late-stage methylation of lead compounds.

5.2 Results and discussion

We initiated our studies by conducting the reaction of *N,N*-dibenzyl-3-methylaniline (**1a**), 5.0 eq. of methyl iodide (**2a**) in CHCl₃ using stoichiometric amounts of Pd(OAc)₂, S,O-ligand **L1**, and NBE **N1** (Table 1), as these reagents performed best in the *meta*-C–H arylation of anilines (Chapter 4). The reaction was conducted at 60 °C for 6 hours, both with and without the addition of 1.5 eq. of AgOAc. A yield of 100% was obtained in the presence of AgOAc, while a yield of 68% was achieved without its inclusion. Notably, the formation of the

methylated S,O-ligand was observed with yields of 40% and 10%. while no decomposition of the aniline occurred, as indicated by the absence of benzaldehyde (**BA**) (Table 1). These results indicate that the methylation of the ligand takes place after the C–H methylation reaction. As the reaction does not proceed to completion in the absence of AgOAc, we speculated that this result is due to the *in situ* formation of Pd⁰ species, which cannot be re-oxidized in the absence of silver salts.

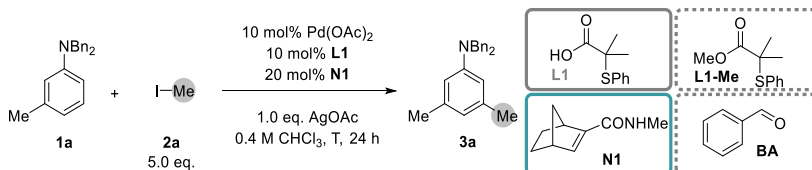
Table 1. *meta*-C–H methylation of aniline **1a** using stoichiometric amounts of catalyst.



#	Additive	¹ H-NMR yield [%] 3a	¹ H-NMR [%] L1-Me	¹ H-NMR [%] BA
1	1.0 eq. AgOAc	100	40	-
2	-	68	10	-

Based on the promising results of the stoichiometric reaction, its catalytic version with 10 mol% of Pd(OAc)₂/L1, 20 mol% of NBE **N1**, and 1.0 eq. of AgOAc was explored. Unfortunately, the catalytic reaction provided only 22–24% NMR yield over a temperature range of 40–90 °C. Once again, the methylation of the S,O-ligand was detected in the crude reaction mixture (Table 2).

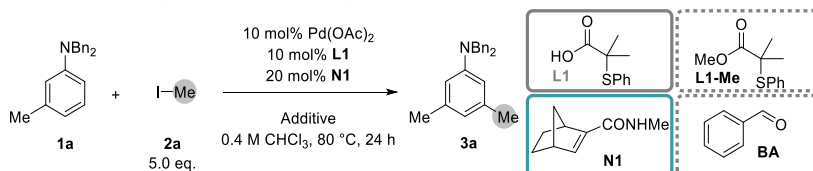
Table 2. Temperature screening for *meta*-C–H methylation of aniline **1a**.



#	Temperature [°C]	¹ H-NMR yield [%] 3a	¹ H-NMR [%] L1-Me	¹ H-NMR [%] BA
1	40	22	7	-
2	60	24	7	-
3	80	23	9	traces
4	90	23	9	traces

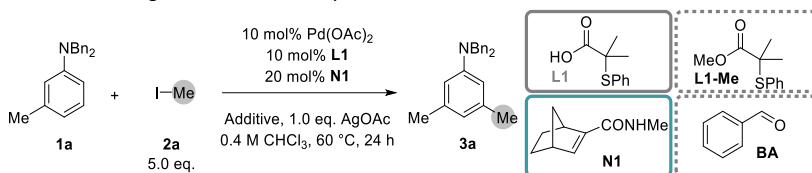
A screening of different silver salts was then carried out. Ag₂CO₃ exhibited comparable yield, while AgTFA gave trace amounts of product and AgF resulted in a slightly lower yield of 19%, indicating that silver is likely to be required for catalyst regeneration (Table 3). Again, the methylation of the S,O-ligand was detected.

Table 3. Silver salt screening for *meta*-C–H methylation of aniline **1a**.



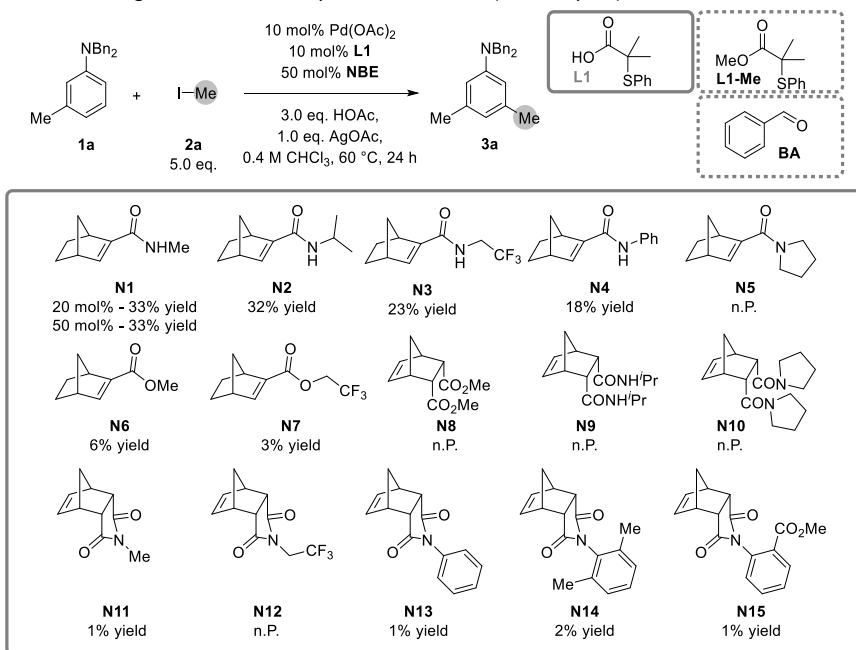
#	Additive	¹ H-NMR	¹ H-NMR	¹ H-NMR
		yield [%]	[%]	[%]
		3a	L1-Me	BA
1	1.0 eq. AgOAc	23	9	traces
2	0.5 eq. Ag ₂ CO ₃	26	10	traces
3	1.0 eq. AgTFA	3	10	traces
4	1.0 eq. AgF	19	10	traces
5	-	16	9	traces

From the previous results (Tables 1-3), we speculated that the regeneration of the catalyst and the methylation of the ligand have similar reaction rates. Since the methylated S,O-ligand cannot form an active catalyst,^[9,10] as observed in our group, we decided to add different amounts of AcOH to avoid its formation during the reaction (Table 4). The best result was obtained with 3 eq. of AcOH, with a yield of 33%. In addition, the addition of 3 eq. of HFIP was investigated, which gave the methylated product in only 13% (Table 4, entry 8).

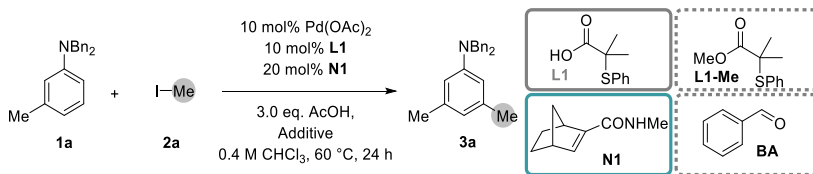
Table 4. Additive screening for *meta*-C–H methylation of aniline **1a**.

#	Additive	¹ H-NMR yield [%] 3a	¹ H-NMR [%] L1-Me	¹ H-NMR [%] BA
1	-	24	7	-
2	0.5 eq. AcOH	29	8	traces
3	1.0 eq. AcOH	29	7	traces
4	2.0 eq. AcOH	31	7	traces
5	3.0 eq. AcOH	33	7	traces
6	5.0 eq. AcOH	27	7	traces
7	10.0 eq. AcOH	18	6	traces
8	3.0 eq. HFIP	13	5	traces

Next, we decided to investigate the effect of different NBEs on the reactivity (Table 5). First, the reaction using 50 mol% of **N1** instead of 20 mol% showed no change in reactivity. While the reaction using 50 mol% of **N2** instead of 20 mol% showed a similar yield to the NBE **N1**, amide NBEs with -Ph **N4** and -CH₂CF₃ **N3** substituents gave a slightly lower yield of about 20%. No product formation was observed with the amide NBE without the N–H bond **N5**, indicating the need to form hydrogen bonds. This is also confirmed by the fact that all the other NBEs we tested with either an ester group at the C2 position (**N6** and **N7**) or 5,6-disubstituted NBEs (**N8-N15**) did not give yields higher than 6%. Based on the conclusions obtained in Chapter 4, we propose that the *meta*-C–H activation step may be the rate-determining step.

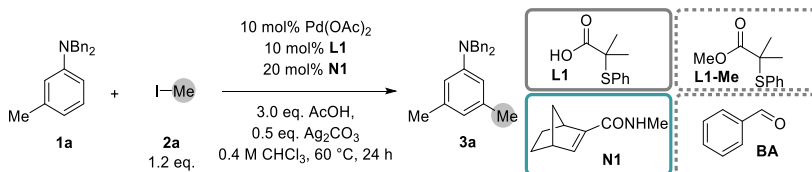
Table 5. NBE screening for *meta*-C–H methylation of aniline **1a** (¹H-NMR yield).

As our exploration of various NBEs failed to increase the reactivity, we turned our attention to preventing the methylation of the S,O-ligand (Table 6). By reducing the amount of methyl iodide from 5 eq. to 2 eq., we managed to achieve an improved yield of 41% (Table 6, entry 3). To have less basic conditions, we tested different quantities of Ag₂CO₃. While employing 1 eq. of Ag₂CO₃ showed no discernible increase in reactivity, a yield of 50% was attained using 0.5 eq. of Ag₂CO₃. Reducing the Ag₂CO₃ loading to 0.25 eq. resulted in a diminished yield of 33% due to insufficient catalyst regeneration (Table 6, entries 4-7). Further reduction of methyl iodide to 1.2 eq. using 0.5 eq. of Ag₂CO₃ resulted in a product yield of 55% (Table 6, entry 8).

Table 6. Screening varying the amounts of silver salt and Me-I for the *meta*-C–H methylation of aniline **1a**.

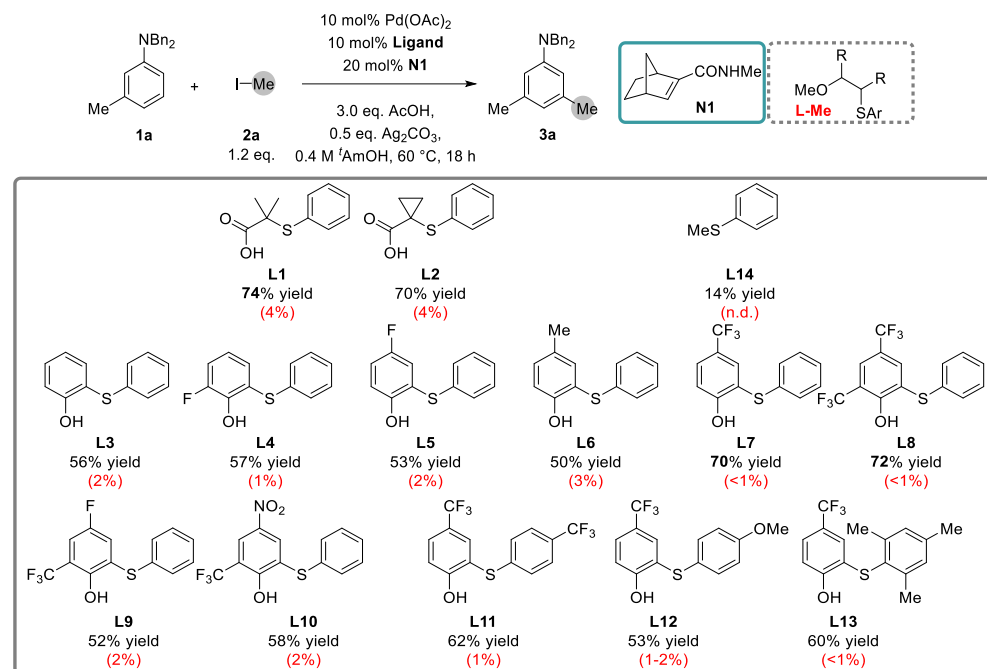
#	Me-I	Additive	¹ H-NMR	¹ H-NMR	¹ H-NMR
			yield [%] 3a	[%] L1-Me	[%] BA
1	5.0 eq.	1.0 eq. AgOAc	33	7	traces
2	5.0 eq.	2.0 eq. AgOAc	25	9	3
3	2.0 eq.	1.0 eq. AgOAc	41	9	3
4	2.0 eq.	1.0 eq. Ag ₂ CO ₃	42	8	3
5	2.0 eq.	0.75 eq. Ag ₂ CO ₃	43	9	4
6	2.0 eq.	0.5 eq. Ag ₂ CO ₃	50	7	traces
7	2.0 eq.	0.25 eq. Ag ₂ CO ₃	33	4	traces
8	1.2 eq.	0.5 eq. Ag₂CO₃	55	7	4

Different solvents were tested and it was found that chlorinated solvents such as DCM and DCE and ethers such as THF and TBME gave slightly lower yields of 17-27% (Table 7, entries 2-5). DMSO yielded only trace amounts of the product, and only 15% yield was obtained with MeCN (Table 7, entries 6-7). While acetone provided similar yield to CHCl₃, better results were obtained with EtOAc and ^tAmOH (62% and 74%, respectively). Different concentrations of ^tAmOH had minimal effect on the reaction (Table 7, entries 10-12). Notably, a lower amount of the methylated S,O-ligand was observed with non-chlorinated solvents.

Table 7. Solvent screening for *meta*-C–H methylation of aniline **1a**.

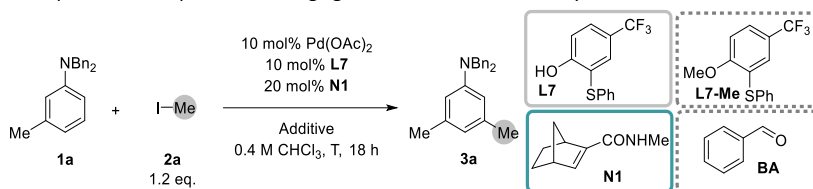
#	Solvent	Concentration	¹ H-NMR	¹ H-NMR	¹ H-NMR
			yield [%] 3a	[%] L1-Me	[%] BA
1	CHCl ₃	0.4	55	7	4
2	DCM	0.4	17	6	12
3	DCE	0.4	27	9	7
4	THF	0.4	27	3	3
5	TBME	0.4	18	3	5
6	DMSO	0.4	traces	-	7
7	MeCN	0.4	15	1	-
8	Acetone	0.4	50	3	5
9	EtOAc	0.4	62	3	6
10	^t AmOH	0.4	74	4	-
11	^t AmOH	0.2	70	5	traces
12	^t AmOH	0.6	73	5	traces

Subsequently, we re-evaluated different S,O-ligands using ^tAmOH as a solvent (Table 8). The established S,O-ligand **L1** yielded 74% product with 4% formation of the methylated ligand. A parallel result was achieved with **L2**, featuring a cyclopropane core. Several phenol-based S,O-ligands, introduced in Chapter 4, were also explored. The 2-(phenylthio)phenolic ligands **L3-L6**, either unsubstituted or substituted with -F or -Me, afforded the product in moderate yields of 50-57%, together with a reduced amount of methylated ligand (1-3%). Ligands **L7** and **L8**, with one or two -CF₃ groups, gave 70% and 72% yields, respectively, with a minimal amount of methylated ligand. Lower yields were obtained with the disubstituted ligands **L9-L10**. Ligands **L11-L13** with a *para*-CF₃ substituent on the phenolic ring and diverse substituents on the thiophenolic ring yielded less than **L7**. Further, the reaction with the thioether ligand **L14**, provided the product in 14% yield, highlighting the importance of the carboxylic acid or phenol moiety in the ligand.

Table 8. Ligand screening for *meta*-C–H methylation of aniline **1a** (¹H-NMR yield).

[a] The amount of methylated S,O-ligand is indicated in the red number in brackets.

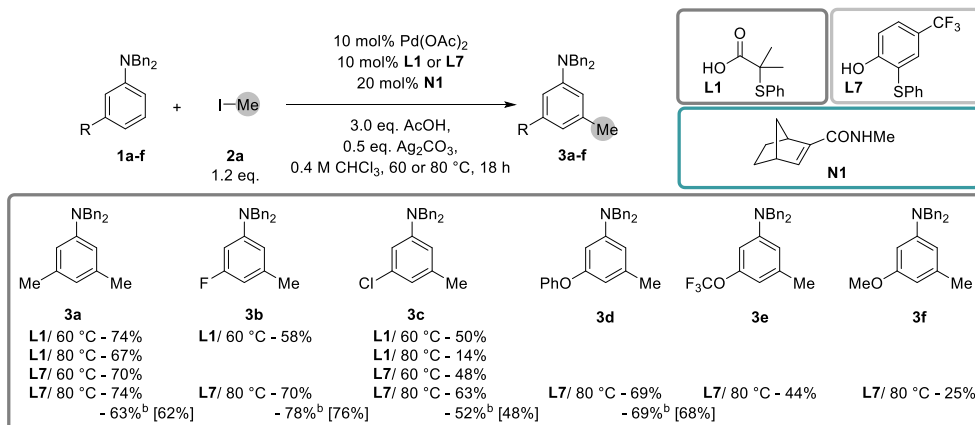
Although ligand **L1** provided the best result (74% yield), the lower formation of methylated ligand with **L7** and **L8**, prompted us to use **L7** in further studies (Table 9). Elevating the temperature to 80 °C matched the 74% yield achieved with ligand **L1**, while maintaining minimal ligand methylation. A further increase in temperature to 100 °C reduced the yield to 45%. The use of higher amounts of Ag₂CO₃ or AgOAc did not improve reactivity and substrate degradation was observed (Table 9, entries 4-6). Lastly, we assessed again the necessity of AcOH in the reaction. Notably, omitting AcOH led to a significantly lower yield of 30% and 5% methylation of the ligand, indicating that the presence of AcOH prevents the methylation of the ligand.

Table 9. Final optimization experiments using ligand **L7** for *meta*-C–H methylation of aniline **1a**.

#	Temperature [°C]	Silver	AcOH	¹ H-NMR	¹ H-NMR	¹ H-NMR
				yield [%] 3a	[%] L7-Me	[%] BA
1	60	0.5 eq. Ag ₂ CO ₃	3.0 eq. AcOH	70	<1	-
2	80	0.5 eq. Ag₂CO₃	3.0 eq. AcOH	74	<1	-
3	100	0.5 eq. Ag ₂ CO ₃	3.0 eq. AcOH	45	<1	-
4	80	0.75 eq. Ag ₂ CO ₃	3.0 eq. AcOH	72	<1	5 (+4 ^a)
5	80	1.5 eq. Ag ₂ CO ₃	3.0 eq. AcOH	22	<2	10 (+33 ^a)
6	80	1.5 eq. AgOAc	3.0 eq. AcOH	43	<1	5 (+4 ^a)
7	80	0.5 eq. Ag ₂ CO ₃	-	30	5	2

[a] Additional imine peak was observed.

With the optimized reaction conditions in hand, we decided to evaluate the substrate scope (Table 10). We evaluated both ligands **L1** and **L7** at temperatures of 60 or 80 °C. Using our model substrate *N,N*-dibenzyl-3-methylaniline (**1a**), comparable yields were achieved with both ligands and temperatures. However, for anilines with *meta*-F (**3b**) or -Cl (**3c**) substituents, notably higher yields were attained at 80 °C with ligand **L7** (70% and 63%, respectively) compared to ligand **L1** at 60 °C (58% and 50%, respectively). Remarkably, when the *meta*-Cl-substituted substrate **3c** was evaluated using **L1** at 80 °C, the yield dropped dramatically to 15%, probably due to the rapid methylation of the ligand **L1** at higher temperatures. These results highlight the advantage of using ligand **L7**, as it offers the possibility of using higher temperatures with less reactive substrates. We continued the scope using ligand **L7** at 80 °C. Aniline substrates with a *meta*-OPh **3d**, -OCF₃ **3e** and -OMe **3f** group provided 69%, 44% and 25% yield, respectively. We attributed this trend to the effect of the substituent on the pK_a of the hydrogen in the *meta*-position, with substrate **3f** having the less acidic *meta*-C–H bond. This initial evaluation demonstrates the great potential of the Pd/S,O-ligand/NBE catalyst for late-stage *meta*-methylation of bioactive molecules containing aniline moieties.

Table 10. Substrate scope of the *meta*-methylation of aniline derivatives.^a

[a] The reactions were performed on a 0.1 mmol scale. [b] The reactions were performed on a 0.25 mmol scale, for isolation. Yield was determined by ¹H NMR analysis of the crude mixtures using CH₂Br₂ as an internal standard. The crude reaction was purified by flash column chromatography providing mixtures of the aniline starting material and the methylated product. The mass fraction of the product was used to determine the isolated yield, which is given in square brackets.

5.3 Conclusion

In conclusion, we have efficiently optimized the first *meta*-selective C–H-methylation of aromatic amines by Pd/ S,O-ligand/ NBE catalysis. The main challenge during the optimization of the reaction conditions was the methylation of the S,O-ligand, which was overcome by the use of a novel phenol-type S,O-ligand, coupled with meticulous additive and solvent screening. The initial evaluation of the substrate scope shows promising results, highlighting the potential applicability of this protocol in late-stage methylation of pharmaceuticals. Further studies to expand the substrate scope are underway in our laboratory.

5.4 Acknowledgements

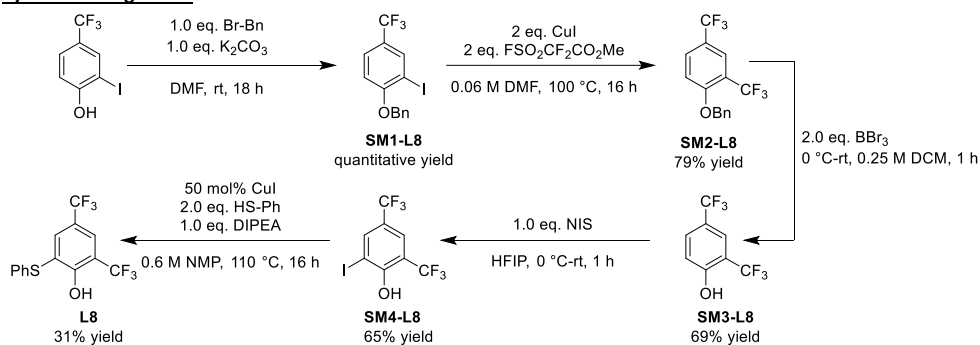
I gratefully acknowledge Teun Erven and Patrick Peters for their work on the optimization of the *meta*-methylation, Soma Rudi and Pier Wessel for the synthesis of the ligand **L8**. Finally, I would like to acknowledge Manuela for her helping hand in this project.

5.5 Experimental section

General information

Chromatography: Flash column chromatography was performed using Macherey-Nagel Silica 60 (particle size 0.04–0.063 mm) under compressed air flow or a Buchi C-850 automatic column machine with FlashPure silica cartridges, TLC: Merck TLC plates (0.25 mm) precoated with silica gel 60 F₂₅₄. Visualization of the TLC was performed by UV and KMnO₄ staining. Anhydrous DCM, Et₂O and THF were obtained from pre-dried materials via an MBRAUN SPS-800 machine and stored under nitrogen atmosphere. High-resolution mass spectra (HRMS) were recorded on an AccuTOF GC v 4g, JMST100GCV mass spectrometer (JEOL, Japan) and HR-ToF Bruker Daltonik GmbH (Bremen, Germany) Impact II, an ESI-ToF MS capable of resolution of at least 40,000 FWHM. The FD/FI probe was equipped with an FD Emitter, Carbotec, FD = 10 μm. Current rate = 51.2 mA/min over 1.2 min using field desorption (FD) as an ionization method. Bruker DRX-300 and 400 MHz instruments were used to record NMR spectra. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CDCl₃: δ 7.26 for ¹H, δ 77.16 for ¹³C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet triplet, bs = broad singlet, m = multiplet), coupling constants (Hz), and integration. ATR technique was used in IR spectroscopy on a Bruker Alpha-P. Melting points (M.P.) were measured in Buchi M-565 melting point apparatus. All reagents and solvents were used as received. Pd(OAc)₂ was purchased from Strem. The procedure for the synthesis of aniline substrates **3a-3f**, **L3-L7** and **L9-L13** are described in the Experimental section of Chapter 4. **L1-L2** were available in our laboratory and were synthesized following the literature.^[9] Ligand **L14** is commercially available.

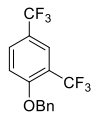
Synthesis of ligand L8



Scheme 11. Synthesis of ligand L8.

1-(Benzyloxy)-2-iodo-4-(trifluoromethyl)benzene (SM1-L8)

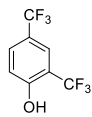
To a Schlenk flask under nitrogen atmosphere 2-iodo-4-(trifluoromethyl)benzene (2.0 g, 6.94 mmol, 1.0 eq.), K₂CO₃ (0.96 g, 6.94 mmol, 1.0 eq.) and dry DMF (20 mL, 0.35 M) were added. Then, benzyl bromide (0.825 mL, 6.94 mmol, 1.0 eq.) was added slowly and the reaction mixture stirred at rt for 16 h. The mixture was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to yield **SM1-L8** as a colorless oil (quantitative yield, 2.6 g). ¹H NMR (300 MHz, CDCl₃) δ 8.02 (d, *J* = 12.6 Hz, 1H), 7.58–7.44 (m, 3H), 7.46–7.25 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 1H), 5.18 (s, 2H).

1-(Benzyloxy)-2,4-bis(trifluoromethyl)benzene (SM2-L8)

A procedure described in the literature was adapted for the synthesis of **SM2-L8**.^[11]

To a Schlenk flask under nitrogen atmosphere CuI (1.01 g, 5.3 mmol, 2.0 eq.), dry DMF (44 mL, 0.06 M), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.02 g, 5.3 mmol, 2.0 eq.) and 1-(Benzyloxy)-2-iodo-4-(trifluoromethyl)benzene (**SM1-L8**) were added. The mixture was stirred at 100 °C for 16 h.

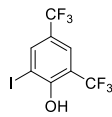
SM2-L8 Then, the mixture was cooled to room temperature and quenched with sat. NH₄Cl solution. The mixture was extracted with DCM (× 5). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Pentane) to yield **SM2-L8** as a colorless oil (79% yield, 0.67 g). ¹H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H), 7.74 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.49 – 7.32 (m, 5H), 7.13 (d, *J* = 8.7 Hz, 1H), 5.27 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 159.00, 135.50, 130.71 (q, *J*_{C-F} = 3.8 Hz), 128.92, 128.45, 124.99 (dt, *J*_{C-F} = 5.5, 3.8, 2.2 Hz), 123.84 (q, *J*_{C-F} = 271.4 Hz), 123.09 (q, *J*_{C-F} = 272.7 Hz), 122.85 (q, *J*_{C-F} = 33.7 Hz), 119.82 (q, *J*_{C-F} = 31.9 Hz), 126.95, 113.48, 70.77. ¹⁹F NMR (377 MHz, CDCl₃) δ -62.02, -62.97.

2,4-Bis(trifluoromethyl)phenol (SM3-L8)

A procedure described in the literature was adapted for the synthesis of **SM3-L8**.^[12]

To a Schlenk flask under nitrogen atmosphere 1-(benzyloxy)-2,4-bis(trifluoromethyl)benzene (**SM2-L8**) (2.66 g, 8.32 mmol, 1.0 eq.) and dry DCM (33 mL, 0.25 M) were added. Then, a solution of BBr₃ in DCM (16.64 mL, 16.64 mmol, 2.0 eq., 1 M) was added slowly and the reaction mixture stirred at rt for

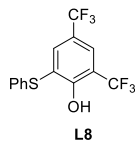
SM3-L8 1 h. The mixture was quenched with water and extracted with DCM (× 3). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography Pentane / DCM (7:3 v/v) to yield **SM3-L8** as a colorless oil (69% yield, 1.39 g). ¹H NMR (500 MHz, CDCl₃) δ 8.69 (s, 1H), 7.81 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 157.60, 130.26 (q, *J*_{C-F} = 3.5 Hz), 124.83 – 124.52 (m), 126.69 – 119.72 (m), 123.78 (q, *J*_{C-F} = 271.2 Hz), 122.10 (q, *J*_{C-F} = 33.7 Hz), 117.41 (q, *J*_{C-F} = 31.7 Hz), 117.38. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.66, -61.95. HRMS (ESI): *m/z* calculated for C₈H₃F₆O [M-H]⁻ = 229.0088; found = 229.0085.

2-Iodo-4,6-bis(trifluoromethyl)phenol (SM4-L8)

A procedure described in the literature was adapted for the synthesis of **SM4-L8**.^[13]

In a round bottom flask containing a suitable stirring bar a solution of the 2,4-bis(trifluoromethyl)phenol (1.3 g, 5.65 mmol, 1.0 eq.) in HFIP (22 mL, 0.25 M) was prepared and cooled to 0 °C. *N*-Iodosuccinimide (1.27 g, 5.65 mmol, 1.0 eq.) was slowly added. The ice bath was removed, and the reaction stirred for 1 h at room temperature. The reaction was evaporated under

SM4-L8 reduced pressure. Then Et₂O was added to the crude mixture causing a white precipitate to form (Succinimide), which was filtered off. The Et₂O layer was washed with sat. Na₂S₂O₃ solution and dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to yield **SM4-L8** as a colorless oil (65% yield, 1.4 g). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 2.1 Hz, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 6.16 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 155.39, 139.17 (q, *J*_{C-F} = 3.7 Hz), 125.56 (p, *J*_{C-F} = 4.2 Hz), 124.68 (q, *J*_{C-F} = 34.3 Hz), 122.60 (q, *J*_{C-F} = 272.2 Hz), 122.30 (q, *J*_{C-F} = 273.4 Hz), 117.29 (q, *J*_{C-F} = 32.7 Hz), 87.84. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.06, -63.35.

2-(Phenylthio)-4,6-bis(trifluoromethyl)phenol (L8)

A procedure described in the literature was adapted for the synthesis of **L8**.^[14]

A microwave tube equipped with CuI (29.4 mg, 0.15 mmol, 0.5 eq.) was flushed with nitrogen for 10 min. Through a septum the 2-Iodo-4,6-bis(trifluoromethyl)phenol (110 mg, 0.3 mmol, 1 eq.) and *N*-methyl-2-pyrrolidone (NMP) (0.5 mL, 0.6 M) were added. The thiol substrate (63 μL, 0.6 mmol, 2.0 eq.) was added dropwise. The flask was placed in a pre-heated oil bath at 110 °C

and after 5 min *N,N*-diisopropylethylamine (DIPEA) (54 μL, 0.3 mmol, 1.0 eq.) was added, and the reaction stirred overnight at 110 °C. The reaction was cooled to room temperature and quenched with 10% aq. NaOH. The resulting

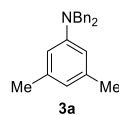
reaction was washed with hexane ($\times 3$). The water layer was acidified to pH=1 with aq. HCl (2 M), extracted with EtOAc ($\times 3$) and washed with sat. NH_4Cl ($\times 3$). The combined organic layers were dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Pentane / DCM gradient) to yield **L8** as a colorless oil (31% yield, 32 mg). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.03 (s, 1H), 7.92 (s, 1H), 7.45 (s, 1H), 7.38 – 7.32 (m, 3H), 7.32 – 7.27 (m, 1H), 7.22 – 7.16 (m, 2H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 157.34, 136.96, 133.00, 127.71, 121.19, 117.75. (Due to the low sample concentration the carbons coupled to fluorine atoms were not clearly visible). $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -61.95, -63.24. **HRMS** (ESI): m/z calculated for $\text{C}_{14}\text{H}_7\text{F}_6\text{OS}$ [M-H] $^-$ = 337.0122; found = 337.0121.

General C–H methylation synthetic procedure

General Procedure for the optimization of the *meta*-C–H methylation of aniline derivatives: The reaction for the optimization are conducted on 0.1 mmol scale. A pressure tube containing a suitable stirring bar, was charged with all solid components, after liquid components are added. First the ligand is added in a 0.1 M solution in the used solvent of the reaction, then the electrophile, after other additives like AcOH. Final the remaining solvent is used to rinse all reagents to the bottom of the pressure tube. **[Note: The order of the addition of the ligand solution, Me-I and AcOH is crucial for the success of the reaction]**. The tube was placed into a pre-heated oil bath and stirred for the indicated time. After cooling to room temperature, the reaction was filtered through Celite[®] and rinsed with EtOAc. The solvent was evaporated under reduced pressure. To the crude mixture CH_2Br_2 (7.08 μL , 0.1 mmol) was added as internal standard, the mixture was dissolved in CDCl_3 and $^1\text{H NMR}$ was measured.

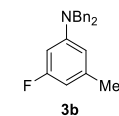
General Procedure **A**: In a pressure tube containing a suitable stirring bar, **N2** (7.6 mg, 0.05 mmol, 20 mol%), $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.025 mmol, 10 mol%), Ag_2CO_3 (34.5 mg, 0.25 mmol, 0.5 eq.), aniline derivative (0.25 mmol, 1.0 eq.), a stock solution of S,O-ligand **L1** in $^i\text{PrOH}$ (250 μL , 0.1 M, 0.025 mmol, 10 mol%), methyl iodide (18.6 μL , 0.3 mmol, 1.2 eq.), AcOH (42.9 μL , 0.75 mmol, 3 eq.) and $^i\text{PrOH}$ (0.375 mL, 0.4 M) were added. **[Note: The order of the addition of the ligand solution, Me-I and AcOH is crucial for the success of the reaction]**. The tube was placed into a pre-heated oil bath at 60 $^\circ\text{C}$ and stirred for 24 h. After cooling to room temperature, the reaction was filtered through Celite[®] and rinsed with EtOAc. The solvent was evaporated under reduced pressure. To the crude mixture CH_2Br_2 (17.7 μL , 0.25 mmol) was added as internal standard, the mixture was dissolved in CDCl_3 and $^1\text{H NMR}$ was measured. Subsequently, the product was purified by flash column chromatography.

N,N-dibenzyl-3,5-dimethylaniline (**3a**)



General procedure **A** was followed using *N,N*-dibenzyl-3-methylaniline (71.8 mg, 0.25 mmol, 1.0 eq.) as substrate, providing the arylated product in 63% $^1\text{H NMR}$ yield. Purification by column chromatography on silica gel using Pentane / DCM (99:1 v/v) as an eluent provided the title compound together with the aniline starting material **1a** (mass fraction of product: 46.5 mg, 62% yield, total amount of isolated fraction 70.6 mg). R_f = 0.44 (Cy / DCM = 1:1). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40 – 7.30 (m, 4H), 7.30 – 7.23 (m, 6H), 6.47 – 6.37 (m, 3H), 4.63 (4, 1H), 2.23 (s, 6H). The $^1\text{H-NMR}$ signal of the isolated material corresponds to the signals reported in the literature.^[15]

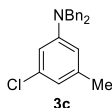
N,N-dibenzyl-3-fluoro-5-methylaniline (**3b**)



General procedure **A** was followed using *N,N*-dibenzyl-3-fluoroaniline (72.8 mg, 0.25 mmol, 1.0 eq.) as substrate, providing the arylated product in 78% $^1\text{H NMR}$ yield. Purification by column chromatography on silica gel using Pentane / DCM (99:1 v/v) as an eluent provided the title compounds with the aniline starting material **1b** (mass fraction of product: 58 mg, 76% yield, total amount of isolated fraction 73.2 mg). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40 (t, J = 7.4 Hz, 4H), 7.36 – 7.25 (m, 6H), 6.41 (s, 1H), 6.32 (s, 1H), 6.30 (s, 1H), 4.68 (s, 4H), 2.29 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 164.24 (d, $J_{\text{C-F}}$ = 241.2 Hz), 150.89 (d, $J_{\text{C-F}}$ = 11.4 Hz), 140.78 (d, $J_{\text{C-F}}$ = 10.1 Hz), 128.84, 127.15, 126.72, 108.64 (d, $J_{\text{C-F}}$ = 1.6

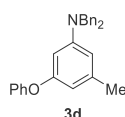
Hz), 104.37 (d, J_{C-F} = 21.5 Hz), 96.92 (d, J_{C-F} = 26.3 Hz), 54.17, 22.07. **^{19}F NMR** (282 MHz, CDCl_3) δ -113.54 – -113.68 (m). **HRMS** (ESI): m/z calculated for $\text{C}_{21}\text{H}_{21}\text{FN}$ [$\text{M}+\text{H}$] $^+$ = 306.1658; found = 306.1648.

N,N-dibenzyl-3-chloro-5-methylaniline (**3c**)



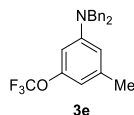
General procedure **A** was followed using *N,N*-dibenzyl-3-chloroaniline (76.8 mg, 0.25 mmol, 1.0 eq.) as substrate, providing the arylated product in 52% ^1H NMR yield. Purification by column chromatography on silica gel using Pentane / DCM (99:1 v/v) as an eluent provided the title compound with the aniline starting material **1c** (mass fraction of product: 38.6 mg, 48% yield, total amount of isolated fraction 69.3 mg). **^1H NMR** (400 MHz, CDCl_3) δ 7.47 – 7.21 (m, 10H), 6.61 (s, 1H), 6.58 (s, 1H), 6.49 (s, 1H), 4.66 (s, 4H), 2.26 (s, 3H). **^{13}C NMR** (101 MHz, CDCl_3) δ 150.43, 140.50, 138.07, 135.02, 128.85, 127.17, 126.73, 117.76, 111.32, 109.64, 53.97, 21.86. **HRMS** (ESI): m/z calculated for $\text{C}_{21}\text{H}_{21}\text{ClN}$ [$\text{M}+\text{H}$] $^+$ = 322.1363; found = 322.1368.

N,N-dibenzyl-3-methyl-5-phenoxyaniline (**3d**)



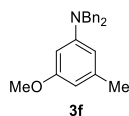
General procedure **A** was followed using *N,N*-dibenzyl-3-phenoxyaniline (91.3 mg, 0.25 mmol, 1.0 eq.) as substrate, providing the arylated product in 69% ^1H NMR yield. Purification by column chromatography on silica gel using Pentane / DCM (1:0-4:1 v/v) as an eluent provided the title compound with the aniline starting material **1d** (mass fraction of product: 64.7 mg, 68% yield, total amount of isolated fraction 92.8 mg). **^1H NMR** (300 MHz, CDCl_3) δ 7.47 – 7.25 (m, 13H), 7.07 – 6.98 (m, 2H), 6.43 (s, 1H), 6.35 (t, J = 2.3 Hz, 1H), 6.25 (s, 1H), 4.67 (s, 4H), 2.27 (s, 3H). **^{13}C NMR** (75 MHz, CDCl_3) δ 158.30, 157.28, 150.74, 140.39, 138.48, 129.60, 128.74, 127.00, 126.81, 122.86, 118.89, 108.39, 108.04, 100.93, 54.23, 22.11. **HRMS** (FI): m/z calculated for $\text{C}_{27}\text{H}_{25}\text{NO}$ [M] $^+$ = 379.1936; found = 379.1941.

N,N-dibenzyl-3-methyl-5-(trifluoromethoxy)aniline (**3e**)



General Procedure **A** was followed on a 0.1 mmol scale using *N,N*-dibenzyl-3-(trifluoromethoxy)aniline (35.7 mg, 0.1 mmol, 1.0 eq.) as substrate, providing the arylated product in 44% ^1H NMR yield. Representative NMR signals from the crude NMR: **^1H NMR** (400 MHz, CDCl_3) δ 6.50 (s, 1H), 6.46 – 6.37 (m, 2H), 4.65 (s, 4H), 2.27 (s, 3H).

N,N-dibenzyl-3-methoxy-5-methylaniline (**3f**)



General Procedure **A** was followed on a 0.1 mmol scale using *N,N*-dibenzyl-3-methoxyaniline (30.3 mg, 0.1 mmol, 1.0 eq.) as substrate providing the arylated product in 25% ^1H NMR yield. Representative NMR signals from the crude NMR: **^1H NMR** (400 MHz, CDCl_3) δ 6.25 (s, 1H), 6.15 (s, 2H), 4.63 (s, 4H), 3.70 (s, 3H), 2.07 (s, 3H).

5.6 References and notes

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