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Regiospecific Synthesis of Substituted 2-Nitrobenzaldehydes from Benzaldehydes through Palladium-Catalyzed Chelation-Assisted C–H Nitration

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A regiospecific synthesis of substituted 2-nitrobenzaldehydes from substituted benzaldehydes has been developed that involves a three-step process with palladium-catalyzed chelation-assisted C–H nitration as the key step. In the process, *O*-methyl aldoxime serves as a removable directing group for the palladium-catalyzed *ortho*-nitration of substituted benzaldoximes and it can be removed in subsequent conversion of the resulting 2-nitrobenzaldoximes into 2-nitrobenzaldehydes.

Introduction

2-Nitrobenzaldehydes, an important class of nitroarenes,[1] are widely used as building blocks in organic chemistry, medicinal chemistry, dyes, and material sciences.[2] 2-Nitrobenzaldehydes are also important and useful precursors of a range of functional molecules such as amines, alcohols, benzoic acids, nitriles, and alkynes.[1,3] Although nitration processes involving electrophilic aromatic substitution have long been the predominant synthetic approach for the preparation of nitroarenes,[4] its application in the regiospecific synthesis of 2-nitrobenzaldehydes from related benzaldehydes is generally not feasible for three main reasons: (1) the electron-withdrawing nature of the formyl group leads to deactivation of the benzene ring, thereby retarding electrophilic aromatic substitution reaction by nitrating agents;[5] (2) the electrophilic nitration of benzaldehyde always gives *meta*-nitrobenzaldehyde as the predominant product along with a small amount of *ortho*- and *para*-nitrobenzaldehyde because the formyl group acts as a *meta*-directing group;[4,6] (3) when substituted benzaldehydes are used as substrates, the regioselectivity of nitration depends on the combined effects of all substituents and thus becomes complex and difficult to predict.[4,7] As a consequence, the regiospecific synthesis of 2-nitrobenzaldehydes usually relies on methods other than the electrophilic nitration of benzaldehydes.[8] These include the oxidation of *o*-nitrotoluene[8a,8b] or 2-nitrobenzyl alcohol,[8c–e] the *ipso*-nitration of 2-halobenzaldehyde with nitrite ion catalyzed by a copper salt,[8f] the reaction of 2-nitrobromobenzene with *N*,*N*-dimethylformamide (DMF) in the presence of a lithium reagent,[8g] and others.[8h,8i] In view of the ready availability of benzaldehydes, the development of a general and regiospecific synthesis of substituted 2-nitrobenzaldehydes from related benzaldehydes free from the effect of the orientation rules is highly desirable, yet challenging.

The last two decades have witnessed great progresses in the area of transition-metal-catalyzed chelation-assisted C–H functionalizations.[9] Such strategies enable the introduction of functionalities to the position *ortho* to the directing groups, thus providing powerful and useful tools for the regioselective construction of carbon–carbon and carbon–heteroatom bonds. In this context, we reported the first palladium-catalyzed *ortho*-specific nitration of aromatic C–H bonds by using N-heterocycles as directing groups, although the latter groups were difficult to remove.[10] Later, a similar concept was employed in the copper- and rhodium-catalyzed *ortho*-nitration of aromatic C–H bonds by Bi,[11a] Wang,[11b] and Li,[11c] respectively, but again using N-heterocycles as directing groups. Recently, removable and/or modifiable directing group-mediated C–H bond functionalizations have received special attention because they can offer more advantages over conventional directing groups in practical syntheses and in the rapid construction of molecular diversity.[12] Previously, we have successfully achieved a palladium-catalyzed regiospecific synthesis of 2-nitro aryl ketones from related ketones involving the use of *O*-methyl ketoxime as a removable directing group.[10b] In contrast to the high reliability and efficiency of *O*-methyl ketoxime in C–H bond functionalizations,[10b,13] *O*-methyl aldoxime, however, was less stable under the conditions of C–H bond functionalizations and has thus seldom been used as a directing group.[13a,13f,14] As part of our ongoing project on the development of general and regiospecific syntheses of functionalized nitroarenes,[10] we herein report the first regiospecific synthesis of substituted 2-nitrobenz-

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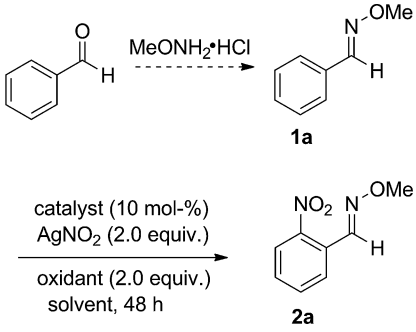
aldehydes from related benzaldehydes involving the use of *O*-methyl aldoxime as a removable directing group for the palladium-catalyzed C–H nitration.

Results and Discussion

Initially, *O*-methylbenzaldoxime (**1a**), which was readily prepared through condensation of benzaldehyde with methoxyammonium chloride, was selected as a model substrate to screen the general reaction conditions for the *ortho*-nitration of the C–H bond (Table 1). Several palladium catalysts were screened using $AgNO_2$ (2 equiv.) as a nitro source and $K_2S_2O_8$ (2 equiv.) as an oxidant in 1,2-dichloroethane (DCE) at 110 °C for 48 h. It was found that $Pd(OCOCF_3)_2$ and $Pd(OAc)_2$ were superior to other palladium sources, including $PdCl_2$ and $[Pd(PPh_3)_2Cl_2]$, affording the desired *o*-nitrobenzaldehyde **2a** in 85 and 75% GC yield, respectively (entries 1, 2, 5, and 6). Increasing or decreasing the reaction temperature did not favor the nitration (entry 4). The reaction gave inferior results when decreasing the catalyst loading (5 mol-%) or shortening the reaction time (entry 3). Control experiments showed that the reaction failed to give the desired product in the absence of a palladium catalyst (entry 7). Several solvents including DCE, MeCN, MeOH, 1,4-dioxane, tetrahydrofuran (THF), toluene, and DMF were surveyed for the reaction, among which DCE was found to be the most suitable solvent for the nitration (entries 2 and 8–13). The effects of oxidants were also investigated. It was found that Oxone could give a moderate yield of **2a** (66%; entry 14), whereas other oxidants including cerium(IV) ammonium nitrate (CAN) and $PhI(OAc)_2$ showed low efficiency (entries 15 and 16). Thus, the optimized reaction conditions for *ortho*-nitration of *O*-methylbenzaldoximes was established as $Pd(OCOCF_3)_2$ (10 mol-%) as catalyst, $AgNO_2$ (2 equiv.) as nitro source, and $K_2S_2O_8$ (2 equiv.) as the oxidant in DCE at 110 °C for 48 h.

Table 1. Optimization of reaction conditions for *ortho*-nitration of **1a**.[a]

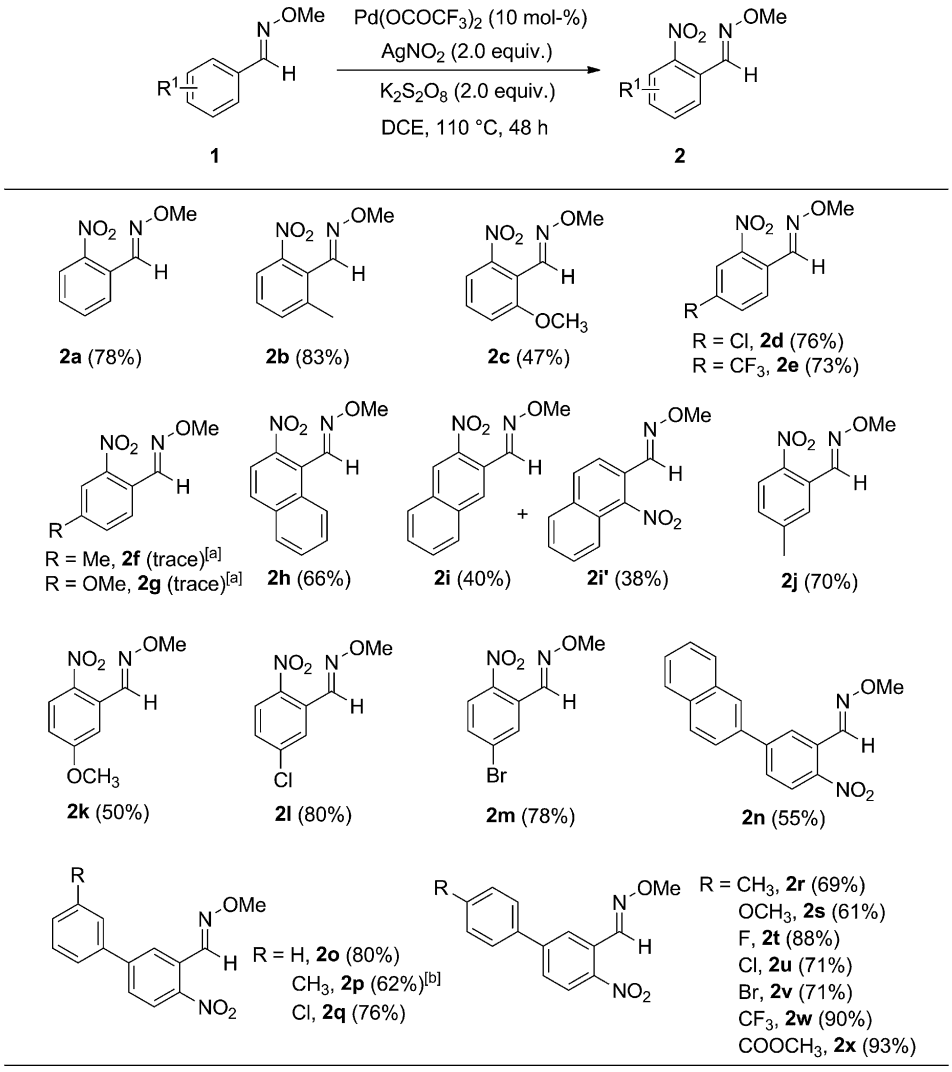


Entry	Catalyst	Oxidant	Temp. [°C]	Solvent[c]	Yield [%][b]
1	$Pd(OAc)_2$	$K_2S_2O_8$	110	DCE	75
2	**$Pd(OCOCF_3)_2$**	**$K_2S_2O_8$**	**110**	**DCE**	**85 (78[d])**
3	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	DCE	77[e]; 37[f]
4	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	120; 110	DCE	71; 69
5	$PdCl_2$	$K_2S_2O_8$	110	DCE	40
6	$Pd(PPh_3)_2Cl_2$	$K_2S_2O_8$	110	DCE	13
7	–	$K_2S_2O_8$	110	DCE	0
8	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	MeCN	30
9	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	MeOH	0
10	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	1,4-dioxane	trace
11	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	THF	trace
12	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	toluene	23
13	$Pd(OCOCF_3)_2$	$K_2S_2O_8$	110	DMF	trace
14	$Pd(OCOCF_3)_2$	Oxone	110	DCE	66
15	$Pd(OCOCF_3)_2$	CAN	110	DCE	30
16	$Pd(OCOCF_3)_2$	$PhI(OAc)_2$	110	DCE	trace

[a] Reaction conditions (unless otherwise noted): **1a** (0.3 mmol), catalyst (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol), solvent (3 mL), 48 h. [b] GC yields determined by using phenanthrene as internal standard. [c] DCE: 1,2-dichloroethane. [d] Isolated yield. [e] The reaction time was 36 h. [f] The catalyst loading of $Pd(OCOCF_3)_2$ was 5 mol-% based on **1a**.

A range of *O*-methylbenzaldoxime derivatives were then subjected to the optimized conditions to extend the scope of the present method. For some substrates, the reaction conditions were adjusted slightly to give the maximum yield of the desired product. The results are summarized in Scheme 1. A series of *O*-methylbenzaldoximes having various substituent-patterns including *ortho*-, *meta*-, and *para*-substituent patterns could be smoothly *ortho*-nitrated to furnish the desired products in moderate to good yields (**2a**–**x** except **2f** and **2g**, up to 93% yield; Scheme 1). For *para*-substituted *O*-methylbenzaldoximes, substrates substituted with electron-withdrawing groups could be smoothly *ortho*-nitrated (**2d**, **2e**, Scheme 1) whereas those substituted with electron-donating groups failed to be *ortho*-nitrated (**2f**, **2g**, Scheme 1). For *meta*-substituted *O*-methylbenzaldoximes, the present nitration method worked well for both electron-rich (**2j**, **2k**, Scheme 1) and electron-deficient arenes (**2l**, **2m**, Scheme 1). When 2-naphthaldehyde *O*-methyl oxime **1i** was used, two *ortho*-nitrated regioisomers **2i** and **2i′** were obtained in 40 and 38% yields, respectively. Surprisingly, a variety of *meta*-substituted benzaldehyde *O*-methyl oximes having two possible positions for nitration, exclusively gave one regioisomer in which the nitro group was introduced to the *para*-position relative to the already present substituent (**2j**–**x**, Scheme 1). We speculated that such regioselectivity could be ascribed to a steric effect upon the formation of the corresponding palladacycle intermediate, thus leading to cleavage of the less sterically hindered *ortho*-C–H bond.[10a,15] Apart from high regioselectivity, the present method exhibited excellent chemoselectivity; in all cases, only mononitrated products were obtained, and overnitrated products were not detected. It should be noted that a series of functional groups such as methyl, methoxy, trifluoromethyl, ester, and halo groups (F, Cl, and Br) could tolerate the present neutral conditions.

Sequential removal of the *O*-methyl oxime group was readily achieved by treatment of **2** with *p*TsOH (2 equiv.) and HCHO (10 equiv.) in THF/H_2O (10:1, v/v) at 100 °C for 8 h according to a modified procedure reported by Sakamoto and co-workers.[16] Several representative results are summarized in Scheme 2. A series of *ortho*-nitrated *O*-methylbenzaldoximes having different substituent patterns

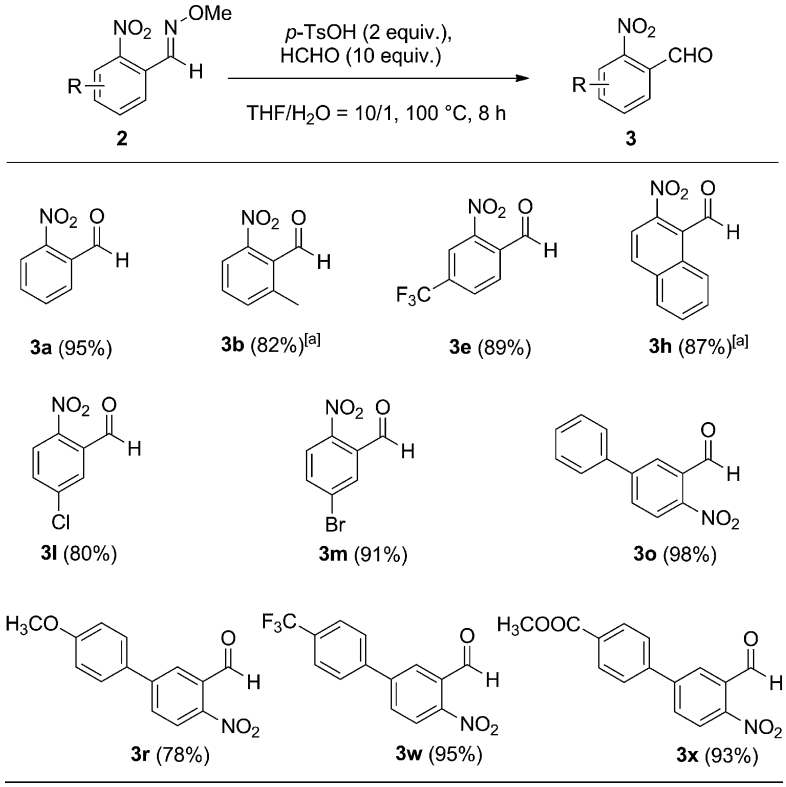


Scheme 1. The Pd-catalyzed *ortho*-nitration of *O*-methyl aldoximes **1**. *Reagents and conditions:* **2** (0.3 mmol), $Pd(OCOCF_3)_2$ (0.03 mmol), $AgNO_2$ (0.6 mmol), $K_2S_2O_8$ (0.6 mmol), DCE (3.0 mL), 110 °C, 48 h. Isolated yield given. [a] The starting material was recovered. [b] The reaction time was 60 h.

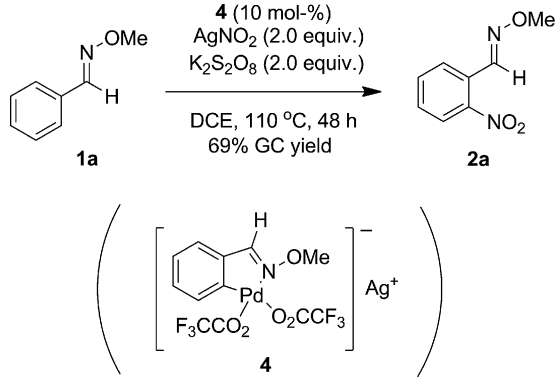
including *ortho*-, *meta*-, and *para*-substituted patterns could be smoothly converted into the corresponding *o*-nitrobenzaldehydes in moderate to excellent yields (78–98%; Scheme 2). For efficient removal of the *O*-methyl oxime group in **2b** and **2h**, the use of polyoxymethylene $(CH_2O)_n$ instead of HCHO solution was required. Note that various functional groups including methyl, methoxy, trifluoromethyl, chloro, bromo, and ester groups were tolerated over the course of the deprotection of the *O*-methyl oxime group. Thus, we have achieved a regiospecific conversion of substituted benzaldehydes into the related *o*-nitrobenzaldehydes in an overall three-step process involving Pd-catalyzed chelation-assisted *ipso*-nitration of C–H bond as the key step.

Several experiments were conducted to gain insight into the mechanism of the Pd-catalyzed C–H nitration. In 2013, Li[11c] and Yang[17] reported two nitration reactions using $NaNO_2$ as the nitro source. In our control experiments, $NaNO_2$ and KNO_2 were tested for the reaction instead of $AgNO_2$, but these reagents proved to be less effective (GC yield < 30%). Thus, we presume that the Ag salt may play an important role in our catalytic system. Palladacycle **4** was prepared according to a procedure reported by Cheng[14d] through stoichiometric reaction of **1a** with $Pd(OAc)_2$ and Ag_2O in trifluoroacetic acid (TFA). Using **4** as the catalyst, **1a** also gave the target product **2a** in 69% yield under conditions that were otherwise identical to the standard conditions developed above (Scheme 3), suggesting that $AgNO_2$ acted not only as a nitro source but also as a cocatalyst in the C–H nitration.[10,14c,14d]

To further probe the mechanism of C–H nitration, **1a**-d_1 and **1a**-d_5 were synthesized and subjected to the standard conditions for conducting the intramolecular and intermolecular competition experiment, respectively. The intramolecular k_H/k_D for substrate **1a**-d_1 was 2.3 ± 0.2, based on ^1H NMR spectroscopic analyses [Scheme 4, Eq. (1)]; the intermolecular k_H/k_D of **1a** to **1a**-d_5 was determined to be 4.0 ± 0.2 [Scheme 4, Eq. (2)]. This result suggests that *ortho*-C–H bond activation is the rate-determining step.



Scheme 2. Synthesis of *o*-nitrobezaldehydes **3** through removal of the *O*-methyl oximyl group in **2**. *Reagents and conditions:* **2** (0.2 mmol), 35 wt.-% HCHO solution (10 equiv.), THF/H_2O (10:1 v/v, 1 mL), 100 °C, 8 h, sealed tube. Isolated yield given. [a] HCHO solution was replaced by polyoxymethylene $(CH_2O)_n$.



Scheme 3. Studies on the catalytic species.

Finally, over the course of the C–H nitration, we could clearly observe the formation and gradual consumption of a brown gas in the sealed tube, which should be assigned to NO_2 gas.[18] The nitration of **1a** under the standard conditions was suppressed in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a radical scavenger,[19] demonstrating that the reaction may involve a radical process [Scheme 4, Eq. (3)].[20]

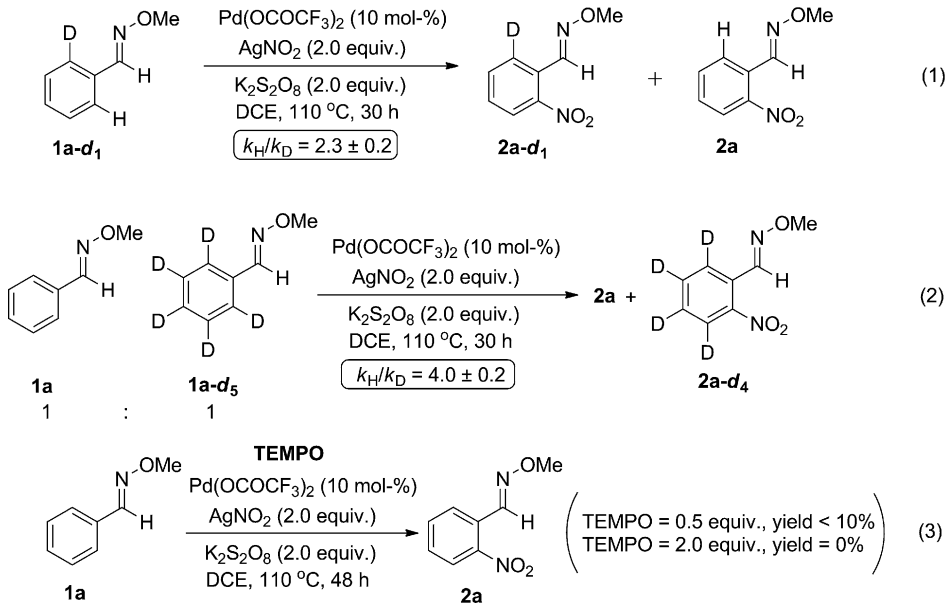
On the basis of the above experiments and on previous reports,[10,14c,14d,18–20] a proposed mechanism for the palladium-catalyzed *ortho*-nitration of *O*-methylbenzaldoximes is depicted in Scheme 5. The initial trigger starts from the formation of a five-membered palladacycle species **I**[14c,14d] through combination of **1**, $Pd(OCOCF_3)_2$, and $AgNO_2$. Subsequent addition of two NO_2 radicals[18–20] to **I** produces a Pd^{IV} species **II**.[10,14c] Reductive elimination from the Pd^{IV} center gives *ortho*-nitrated *O*-methylbenzaldoximes **2** and regenerates the Pd^{II} catalyst.[10,14c]

Conclusions

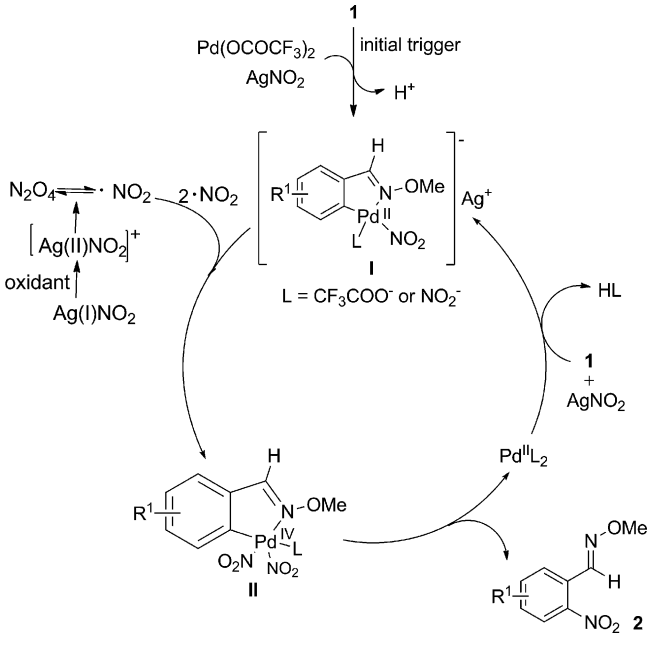
We have developed a general and efficient approach for the regiospecific synthesis of substituted *o*-nitrobenzaldehydes from the corresponding benzaldehydes in a three-step process involving the introduction of *O*-methyl aldoxime group, palladium-catalyzed C–H bond nitration, and subsequent removal of the directing group. The present protocol for the synthesis of substituted *o*-nitrobenzaldehydes can therefore overcome the regioselectivity and substrate deactivation issues associated with traditional electrophilic nitration of substituted benzaldehydes.

Experimental Section

General Information: Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purification. All solvents for reactions were dried and distilled prior to use according to standard methods. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a spectrometer at 25 °C in $CDCl_3$ at 500 and 125 MHz, respectively, with TMS as internal standard. Chemical shifts (δ) are expressed in ppm and coupling



Scheme 4. Mechanistic investigations using kinetic isotope effects and the radical scavenger TEMPO.



Scheme 5. Proposed mechanism.

constants J are given in Hz. The IR spectra were recorded with an FTIR spectrometer. GC–MS experiments were performed with EI source, high-resolution mass spectra (HRMS) were obtained with a TOF MS instrument with EI or ESI source.

Preparation of Aryl Aldehyde *O*-Methyl Oximes 1a–x: A mixture of aldehyde (5 mmol), $MeONH_2$·HCl (1.13 g, 13.5 mmol), anhydrous NaOAc (1.80 g, 22.0 mmol), and ethanol/H_2O (1:3 v/v, 60 mL) was placed in a 100 mL round-bottom flask. The mixture was stirred and heated to reflux at 70 °C for 2 h. Upon completion, the resulting mixture was extracted with ethyl acetate (3 × 45 mL), dried with $MgSO_4$, and filtered. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100–200 mesh; petroleum ether/EtOAc) to give the desired product **1**.

General Procedure for the Synthesis of *o*-Nitro Aryl Aldehyde *O*-Methyl Oximes 2: A mixture of aryl aldehyde *O*-methyl oxime **1** (0.30 mmol), $Pd(OCOCF_3)_2$ (10 mg, 0.03 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), and anhydrous DCE (3.0 mL) was sealed in a 25 mL Schlenk flask and the mixture was stirred and heated at 110 °C for 48 h. After cooling to room temperature, the mixture was filtered with Celite and the filtrate was evaporated in vacuo, the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) to give pure **2**.

(*E*)-2-Nitrobenzaldehyde *O*-Methyl Oxime (2a):[21] Yield 42.2 mg (78%); brown oil. IR (neat): $\tilde{\nu}$ = 1525 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 8.06 (d, J = 8.0 Hz, 1 H), 8.00 (d, J = 8.0 Hz, 1 H), 7.65 (t, J = 7.5 Hz, 1 H), 7.55 (dt, J = 8.5, 1.5 Hz, 1 H), 4.04 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.9, 144.9, 133.4, 130.1, 128.7, 127.3, 124.8, 62.5 ppm. MS (EI, 70 eV): m/z (%) = 180 (25) [M^+], 134 (18).

(*E*)-2-Methyl-6-nitrobenzaldehyde *O*-Methyl Oxime (2b): Yield 48.4 mg (83%); white solid; m.p. 49–50 °C. IR (KBr): $\tilde{\nu}$ = 1524 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 7.5 Hz, 1 H), 7.41 (t, J = 8.0 Hz, 1 H), 3.98 (s, 3 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7, 144.6, 140.0, 135.2, 129.2, 125.5, 122.1, 62.3, 20.8 ppm. MS (EI, 70 eV): m/z (%) = 194 (3) [M^+], 148 (5). HRMS (EI): m/z calcd. for $C_9H_{10}N_2O_3$ 194.0691; found 194.0699.

(*E*)-2-Methoxy-6-nitrobenzaldehyde *O*-Methyl Oxime (2c): Yield 29.6 mg (47%); white solid; m.p. 47–48 °C. IR (KBr): $\tilde{\nu}$ = 1534 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 149.8, 141.2, 130.5, 115.7, 114.7, 114.4, 62.2, 56.5 ppm. MS (EI, 70 eV): m/z (%) = 210 (33) [M^+], 164 (100). HRMS (EI): m/z calcd. for $C_9H_{10}N_2O_4$ 210.0641; found 210.0633.

(*E*)-4-Chloro-2-nitrobenzaldehyde *O*-Methyl Oxime (2d): Yield 48.9 mg (76%); white solid; m.p. 44–45 °C. IR (KBr): $\tilde{\nu}$ = 1521 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.57 (s, 1 H), 8.05 (d, J = 2.5 Hz, 1 H), 7.98 (d, J = 8.5 Hz, 1 H), 7.61 (dd, J = 8.5, 2.0 Hz, 1 H), 4.04 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ

= 148.0, 143.9, 136.1, 133.5, 129.7, 125.8, 124.9, 62.7 ppm. MS (EI, 70 eV): *m/z* (%) = 214 (38) [M+], 168 (21). HRMS (EI): *m/z* calcd. for $C_8H_7ClN_2O_3$ 214.0145; found 214.0150.

(*E*)-2-Nitro-4-(trifluoromethyl)benzaldehyde *O*-Methyl Oxime (2e): Yield 54.3 mg (73%); yellow oil. IR (neat): $\tilde{\nu}$ = 1502 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.63 (s, 1 H), 8.32 (s, 1 H), 8.19 (d, J = 8.5 Hz, 1 H), 7.88 (d, J = 8.5 Hz, 1 H), 4.07 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.5, 143.6, 132.3 (q, $J_{F,C}$ = 33.8 Hz), 130.6, 129.6 (q, $J_{F,C}$ = 3.1 Hz), 129.55, 122.6 (q, $J_{F,C}$ = 250.0 Hz), 122.2 (q, $J_{F,C}$ = 4.2 Hz), 62.9 ppm. MS (EI, 70 eV): *m/z* (%) = 248 (50) [M+], 202 (18). HRMS (EI): *m/z* calcd. for $C_9H_7F_3N_2O_3$ 248.0409; found 248.0414.

(*E*)-2-Nitro-1-naphthaldehyde *O*-Methyl Oxime (2h): Yield 45.6 mg (66%); yellow solid; m.p. 74–75 °C. IR (KBr): $\tilde{\nu}$ = 1519 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.49–8.47 (m, 1 H), 8.08–7.99 (m, 2 H), 7.96–7.94 (m, 1 H), 7.72–7.70 (m, 2 H), 4.08 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.4, 144.5, 135.3, 131.3, 130.7, 129.3, 128.6, 128.4, 127.7, 125.1, 120.1, 62.5 ppm. MS (EI, 70 eV): *m/z* (%) = 230 (45) [M+], 184 (12). HRMS (EI) for $C_{12}H_{10}N_2O_3$: calcd. 230.0691, found 230.0684.

(*E*)-3-Nitro-2-naphthaldehyde *O*-Methyl Oxime (2i): Yield 27.6 mg (40%); yellow solid; m.p. 120–121 °C. IR (KBr): $\tilde{\nu}$ = 1542 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 8.65 (s, 1 H), 8.37 (s, 1 H), 7.99 (t, J = 7.0 Hz, 2 H), 7.73–7.65 (m, 2 H), 4.08 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.8, 145.3, 134.8, 132.2, 130.1, 129.4, 129.3, 128.7, 128.5, 125.9, 123.4, 62.4 ppm. MS (EI, 70 eV): *m/z* (%) = 230 (83) [M+], 184 (12). HRMS (EI): *m/z* calcd. for $C_{12}H_{10}N_2O_3$ 230.0691; found 230.0686.

(*E*)-1-Nitro-2-naphthaldehyde *O*-Methyl Oxime (2i′): Yield 26.2 mg (38%); yellow solid; m.p. 86–87 °C. IR (KBr): $\tilde{\nu}$ = 1518 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.07 (dd, J = 8.5, 1.0 Hz, 1 H), 7.97 (dd, J = 8.0, 1.0 Hz, 1 H), 7.93 (dd, J = 7.5, 1.5 Hz, 1 H), 7.79 (d, J = 7.0 Hz, 1 H), 7.63 (t, J = 8.0 Hz, 1 H), 7.55 (t, J = 8.0 Hz, 1 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.3, 147.1, 135.1, 133.5, 130.4, 130.0, 127.3, 126.9, 124.8, 124.1, 122.0, 62.3 ppm. MS (EI, 70 eV): *m/z* (%) = 230 (10) [M+], 184 (60). HRMS (EI): *m/z* for $C_{12}H_{10}N_2O_3$ 230.0691; found 230.0682.

(*E*)-5-Methyl-2-nitrobenzaldehyde *O*-Methyl Oxime (2j): Yield 40.8 mg (70%); yellow solid; m.p. 51–52 °C. IR (KBr): $\tilde{\nu}$ = 1515 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.65 (s, 1 H), 8.00 (d, J = 8.5 Hz, 1 H), 7.76 (s, 1 H), 7.33 (d, J = 7.0 Hz, 1 H), 4.04 (s, 3 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.5, 144.9, 130.8, 129.1, 127.3, 125.0, 62.4, 21.4 ppm. MS (EI, 70 e V): *m/z* (%) = 194 (51) [M+], 148 (27). HRMS (EI): *m/z* calcd. for $C_9H_{10}N_2O_3$ 194.0691; found 194.0686.

(*E*)-5-Methoxy-2-nitrobenzaldehyde *O*-Methyl Oxime (2k): Yield 1.5 mg (50%); yellow solid; m.p. 69–70 °C. IR (KBr): $\tilde{\nu}$ = 1527 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.56 (s, 1 H), 7.92 (d, J = 9.0 Hz, 1 H), 7.53 (d, J = 2.5 Hz, 1 H), 7.17 (dd, J = 8.5, 2.5 Hz, 1 H), 4.01 (s, 3 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8, 148.6, 144.8, 129.8, 120.3, 119.7, 109.0, 62.3, 56.0 ppm. MS (EI, 70 eV): *m/z* (%) = 210 (29) [M+], 164 (16). HRMS (EI): *m/z* calcd. for $C_9H_{10}N_2O_4$ 210.0641; found 210.0637.

(*E*)-5-Chloro-2-nitrobenzaldehyde *O*-Methyl Oxime (2l): Yield 51.5 mg (80%); white solid; m.p. 87–88 °C. IR (KBr): $\tilde{\nu}$ = 1516 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.61 (s, 1 H), 8.04–8.00 (m, 2 H), 7.50 (dd, J = 9.0, 2.5 Hz, 1 H), 4.06 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 145.9, 143.9, 140.1, 130.0, 129.1, 128.4, 126.4, 62.8 ppm. MS (EI, 70 eV): *m/z* (%) = 214 (24) [M+], 168 (15). HRMS (EI): *m/z* calcd. for $C_8H_7ClN_2O_3$ 214.0145; found 214.0137.

(*E*)-5-Bromo-2-nitrobenzaldehyde *O*-Methyl Oxime (2m): Yield 60.6 mg (78%); white solid; m.p. 109–110 °C. IR (KBr): $\tilde{\nu}$ = 1515 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.59 (s, 1 H), 8.16 (d, J = 2.0 Hz, 1 H), 7.94 (d, J = 8.5 Hz, 1 H), 7.66 (dd, J = 8.5, 2.0 Hz, 1 H), 4.05 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.4, 143.8, 133.1, 131.4, 129.0, 128.5, 126.3, 62.8 ppm. MS (EI, 70 eV): *m/z* (%) = 258 (23) [M+], 212 (17). HRMS (EI): *m/z* calcd. for $C_8H_7BrN_2O_3$ 257.9640; found 257.9646.

(*E*)-5-(Naphthalen-2-yl)-2-nitrobenzaldehyde *O*-Methyl Oxime (2n): Yield 50.5 mg (55%); yellow solid; m.p. 103–104 °C. IR (KBr): $\tilde{\nu}$ = 1512 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.75 (s, 1 H), 8.30 (d, J = 2.0 Hz, 1 H), 8.20 (d, J = 8.5 Hz, 1 H), 8.13 (d, J = 1.0 Hz, 1 H), 7.99–7.90 (m, 3 H), 7.85 (dd, J = 8.5, 2.0 Hz, 1 H), 7.77 (dd, J = 8.5, 2.0 Hz, 1 H), 7.58–7.56 (m, 2 H), 4.09 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.52, 146.48, 145.4, 135.6, 133.5, 133.3, 129.0, 128.7, 128.5, 128.0, 127.8, 127.4, 127.0, 126.9, 126.8, 125.7, 124.9, 62.6 ppm. MS (EI, 70 eV): *m/z* (%) = 306 (38) [M+], 160 (21). HRMS (EI): *m/z* calcd. for $C_{18}H_{14}N_2O_3$ 306.1004; found 306.1014.

(*E*)-4-Nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2o): Yield 61.5 mg (80%). IR (neat): $\tilde{\nu}$ = 1517 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.17 (dd, J = 7.5, 2.0 Hz, 1 H), 7.73 (dd, J = 8.5, 2.0 Hz, 1 H), 7.68–7.66 (m, 2 H), 7.53–7.46 (m, 3 H), 4.06 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.6, 146.5, 145.3, 138.4, 129.2, 129.0, 128.5, 127.9, 127.4, 127.2, 125.6, 62.5 ppm. MS (EI, 70 eV): *m/z* (%) = 256 (21) [M+], 208 (38). HRMS (EI): *m/z* calcd. for $C_{14}H_{12}N_2O_3$ 256.0848; found 256.0839.

(*E*)-3′-Methyl-4-nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2p): Yield 50.3 mg (62%); yellow oil. IR (neat): $\tilde{\nu}$ = 1519 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 8.16–8.14 (m, 2 H), 7.72 (dd, J = 8.5, 2.0 Hz, 1 H), 7.46–7.29 (m, 4 H), 4.07 (s, 3 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.7, 146.4, 145.4, 138.9, 138.3, 129.8, 129.0, 128.5, 128.1, 127.9, 127.2, 125.5, 124.5, 62.5, 21.5 ppm. MS (EI, 70 eV): *m/z* (%) = 270 (32) [M+], 224 (26). HRMS (EI): *m/z* calcd. for $C_{15}H_{14}N_2O_3$ 270.1004; found 270.1012.

(*E*)-3′-Chloro-4-nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2q): Yield 66.3 mg (76%); yellow solid; m.p. 90–91 °C. IR (KBr): $\tilde{\nu}$ = 1513 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 8.17–8.15 (m, 2 H), 7.70 (dd, J = 8.5, 2.0 Hz, 1 H), 7.64–7.63 (m, 1 H), 7.54–7.52 (m, 1 H), 7.45–7.44 (m, 2 H), 4.07 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.8, 144.99, 144.95, 140.1, 135.1, 130.4, 129.0, 128.5, 128.0, 127.5, 127.2, 125.7, 125.6, 62.6 ppm. MS (EI, 70 eV): *m/z* (%) = 290 (26) [M+], 244 (19). HRMS (EI): *m/z* calcd. for $C_{14}H_{11}ClN_2O_3$ 290.0458; found 290.0450.

(*E*)-4′-Methyl-4-nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2r): Yield 55.9 mg (69%); yellow solid; m.p. 77–78 °C. IR (KBr): $\tilde{\nu}$ = 1511 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 8.16–8.14 (m, 2 H), 7.72 (dd, J = 8.5, 2.0 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 4.06 (s, 3 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.5, 146.2, 145.4, 139.2, 135.4, 129.9, 128.2, 127.9, 127.2, 126.9, 125.6, 62.5, 21.2 ppm. MS (EI, 70 eV): *m/z* (%) = 270 (100) [M+], 224 (42). HRMS (EI): *m/z* calcd. for $C_{15}H_{14}N_2O_3$ 270.1004; found 270.1009.

(*E*)-4′-Methoxy-4-nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2s): Yield 52.4 mg (61%). IR (neat): $\tilde{\nu}$ = 1514 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.15 (d, J = 8.5 Hz, 1 H), 8.13 (d, J = 8.5 Hz, 1 H),7.69 (dd, J = 9.0, 2.5 Hz, 1 H), 7.62

(d, J = 9.0 Hz, 2 H), 7.04 (d, J = 8.5 Hz, 2 H), 4.06 (s, 3 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.6, 146.2, 145.9, 145.5, 130.7, 128.6, 128.0, 127.8, 126.5, 125.7, 114.6, 62.6, 55.5 ppm. MS (EI, 70 eV): m/z (%) = 286 (100) [M^+], 240 (12). HRMS (EI): m/z calcd. for $C_{15}H_{14}N_2O_4$ 286.0954; found 286.0947.

(*E*)-4′-Fluoro-4-nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2t): Yield 72.4 mg (88%); yellow solid; m.p. 79–80 °C. IR (KBr): $\tilde{\nu}$ = 1513 (NO_2) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 8.15 (d, J = 8.5 Hz, 1 H), 8.13 (d, J = 2.0 Hz, 1 H), 7.68 (dd, J = 8.5, 2.0 Hz, 1 H), 7.65–7.62 (m, 2 H), 7.20 (t, J = 8.5 Hz, 2 H), 4.06 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3 (d, $J_{F,C}$ = 247.5 Hz), 146.4, 145.5, 145.2, 134.5 (d, $J_{F,C}$ = 3.8 Hz), 129.2 (d, $J_{F,C}$ = 7.5 Hz), 128.3, 128.0, 127.0, 125.7, 116.2 (d, $J_{F,C}$ = 21.3 Hz), 62.6 ppm. MS (EI, 70 eV): m/z (%) = 274 (34) [M^+], 228 (24). HRMS (EI): m/z calcd. for $C_{14}H_{11}FN_2O_3$ 274.0754; found 274.0760.

(*E*)-4′-Chloro-4-nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2u): Yield 61.9 mg (71%); yellow solid; m.p. 113–114 °C. IR (KBr): $\tilde{\nu}$ = 1512 (NO_2) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 8.16–8.14 (m, 2 H), 7.70 (dd, J = 8.5, 2.0 Hz, 1 H), 7.59 (d, J = 8.5 Hz, 2 H), 7.48 (d, J = 8.5 Hz, 2 H), 4.06 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.6, 145.2, 145.1, 136.7, 135.4, 129.4, 128.6, 128.3, 128.0, 127.0, 125.7, 62.6 ppm. MS (EI, 70 eV): m/z (%) = 290 (50) [M^+], 244 (34). HRMS (EI): m/z calcd. for $C_{14}H_{11}ClN_2O_3$ 290.0456; found 290.0451.

(*E*)-4′-Bromo-4-nitro-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2v): Yield 71.4 mg (71%); yellow solid; m.p. 123–124 °C. IR (KBr): $\tilde{\nu}$ = 1511 (NO_2) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 8.16 (d, J = 8.5 Hz, 1 H), 8.14 (d, J = 2.5 Hz, 1 H), 7.69 (dd, J = 8.5, 2.0 Hz, 1 H), 7.66–7.63 (m, 2 H), 7.54–7.51 (m, 2 H), 4.06 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.7, 145.3, 145.1, 137.2, 132.3, 128.9, 128.2, 128.1, 127.0, 125.7, 123.6, 62.6 ppm. MS (EI, 70 eV): m/z (%) = 334 (26) [M^+], 288 (15). HRMS (EI): m/z calcd. for $C_{14}H_{11}BrN_2O_3$ 333.9953; found 333.9959.

(*E*)-4-Nitro-4′-(trifluoromethyl)-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2w): Yield 87.5 mg (90%); yellow solid; m.p. 107–109 °C. IR (KBr): $\tilde{\nu}$ = 1513 (NO_2) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 8.21–8.18 (m, 2 H), 7.78–7.74 (m, 5 H), 4.07 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.1, 144.9, 144.8, 141.9, 131.0 (q, $J_{F,C}$ = 32.5 Hz), 128.6, 128.1, 127.8, 127.4, 126.1 (q, $J_{F,C}$ = 2.5 Hz), 125.7, 123.9 (q, $J_{F,C}$ = 270.0 Hz), 62.6 ppm. MS (EI, 70 eV): m/z (%) = 324 (74) [M^+], 278 (59). HRMS (EI): m/z calcd. for $C_{15}H_{11}F_3N_2O_3$ 324.0722; found 324.0718.

(*E*)-4-Nitro-4′-(Methoxycarbonyl)-[1,1′-biphenyl]-3-carbaldehyde *O*-Methyl Oxime (2x): Yield 87.7 mg (93%); white solid; m.p. 139–141 °C. IR (KBr): $\tilde{\nu}$ = 1733 (C=O), 1519 (NO_2) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 8.21–8.16 (m, 4 H), 7.76 (dd, J = 8.5, 2.0 Hz, 1 H), 7.73 (d, J = 8.5 Hz, 2 H), 4.06 (s, 3 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 147.0, 145.3, 144.9, 142.6, 130.5, 130.4, 128.6, 128.0, 127.41, 127.38, 125.6, 62.6, 52.3 ppm. MS (EI, 70 eV): m/z (%) = 314 (14) [M^+]. HRMS (EI): m/z calcd. for $C_{16}H_{14}N_2O_5$ 314.0903; found 314.0911.

General Procedure for the Synthesis of 2-Nitrated Aryl Aldehydes 3 from 2 through Removal of the *O*-Methyl Oxime Group: *o*-Nitro aryl aldehyde *O*-methyl oxime **2** (0.2 mmol), *p*TsOH (2 equiv.), and 35 wt.-% formaldehyde solution (10 equiv.) were dissolved in a THF/H_2O mixture (10:1 v/v, 1 mL) in a sealed tube, and the mixture was stirred at 100 °C for 8 h. Upon completion, the reaction mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and filtered. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (100–200 mesh; petroleum ether/EtOAc) to give pure **3**.

2-Nitrobenzaldehyde (3a):[22] Yield 28.7 mg (95%); yellow solid; m.p. 38–39 °C (ref.[21] 44 °C). IR (KBr): $\tilde{\nu}$ = 1528 (NO_2), 1698 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.44 (s, 1 H), 8.14 (dd, J = 8.0, 1.0 Hz, 1 H), 7.97 (dd, J = 7.5, 1.5 Hz, 1 H), 7.83–7.76 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.1, 149.6, 134.1, 133.7, 131.4, 129.6, 124.5 ppm. MS (EI, 70 eV): m/z (%) = 151 (18) [M^+], 121 (88).

2-Methyl-6-nitrobenzaldehyde (3b):[23] Yield 27.1 mg (82%); yellow solid; m.p. 51–52 °C. IR (KBr): $\tilde{\nu}$ = 1521 (NO_2), 1703 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.32 (s, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.59–7.52 (m, 2 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.4, 148.8, 139.3, 137.0, 132.0, 131.3, 122.0, 19.6 ppm. MS (EI, 70 eV): m/z (%) = 165 (1) [M^+], 135 (100).

2-Nitro-4-(trifluoromethyl)benzaldehyde (3e):[24] Yield 39.0 mg (89%); yellow oil; IR (neat): $\tilde{\nu}$ = 1543 (NO_2), 1705 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.49 (s, 1 H), 8.43 (s, 1 H), 8.11 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.9, 149.4, 135.6 (q, $J_{F,C}$ = 34.2 Hz), 134.0, 130.9 (q, $J_{F,C}$ = 2.5 Hz), 130.8, 122.3 (q, $J_{F,C}$ = 271.3 Hz), 122.0 (q, $J_{F,C}$ = 3.8 Hz) ppm. MS (EI, 70 eV): m/z (%) = 219 (18) [M^+], 189 (88).

2-Nitro-1-naphthaldehyde (3h):[25] Yield 35.0 mg (87%); yellow solid; m.p. 119–120 (ref.[25] 119 °C) °C. IR (KBr): $\tilde{\nu}$ = 1521 (NO_2), 1733 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.67 (s, 1 H), 8.31 (d, J = 8.4 Hz, 1 H), 8.17 (d, J = 9.0 Hz, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.01–7.99 (m, 1 H), 7.78–7.71 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.3, 145.8, 135.9, 132.6, 132.3, 130.0, 129.5, 128.8, 128.6, 126.7, 119.2 ppm. MS (EI, 70 eV): m/z (%) = 201 (8) [M^+], 171 (33).

5-Chloro-2-nitrobenzaldehyde (3l):[26] Yield 29.7 mg (80%); yellow solid; m.p. 77–78 °C (ref.[26] 77–79 °C). IR (KBr): $\tilde{\nu}$ = 1510 (NO_2), 1696 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.43 (s, 1 H), 8.13 (d, J = 8.5 Hz, 1 H), 7.91 (d, J = 2.0 Hz, 1 H), 7.72 (dd, J = 8.5, 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.8, 147.6, 141.3, 133.4, 132.8, 129.7, 126.2 ppm. MS (EI, 70 eV): m/z (%) = 185 (12) [M^+], 155 (74).

5-Bromo-2-nitrobenzaldehyde (3m):[27] Yield 41.9 mg (91%); brown solid; m.p. 72–73 °C (ref.[27] 70.2–71.3 °C). IR (KBr): $\tilde{\nu}$ = 1522 (NO_2), 1692 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.40 (s, 1 H), 8.05 (d, J = 2.0 Hz, 1 H), 8.03 (d, J = 8.5 Hz, 1 H), 7.89 (dd, J = 8.5, 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.7, 148.1, 136.5, 132.6, 129.5, 126.1 ppm. MS (EI, 70 eV): m/z (%) = 229 (10) [M^+], 199 (76).

4-Nitro-[1,1′-biphenyl]-3-carbaldehyde (3o):[28] Yield 44.5 mg (98%); brown solid; m.p. 73–74 °C (ref.[28] 71.0–73.4 °C). IR (KBr): $\tilde{\nu}$ = 1525 (NO_2), 1813 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.52 (s, 1 H), 8.23 (d, J = 8.5 Hz, 1 H), 8.14 (d, J = 1.5 Hz, 1 H), 7.95 (dd, J = 8.0, 2.0 Hz, 1 H), 7.68–7.66 (m, 2 H), 7.55–7.48 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.4, 148.1, 147.3, 137.6, 132.1, 131.5, 129.5, 129.3, 127.9, 127.4, 125.3 ppm. MS (EI, 70 eV): m/z (%) = 227 (53) [M^+], 197 (77).

4′-Methoxy-4-nitro-[1,1′-biphenyl]-3-carbaldehyde (3r): Yield 40.1 mg (78%); yellow solid; m.p. 104–105 °C. IR (KBr): $\tilde{\nu}$ = 1514 (NO_2), 1692 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.52 (s, 1 H), 8.20 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 2.0 Hz, 1 H), 7.89 (dd, J = 8.5, 2.0 Hz, 1 H), 7.62 (dd, J = 6.5, 2.0 Hz, 2 H), 7.04 (dd, J = 6.5, 1.5 Hz, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 188.6, 160.9, 147.4, 146.9, 132.2, 130.7, 129.8, 128.6, 127.1, 125.4, 114.8, 55.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 257 (53) [M^+], 227 (77). HRMS (EI): *m*/*z* calcd. for $C_{14}H_{11}NO_4$ 257.0688; found 257.0682.

4-Nitro-4′-(trifluoromethyl)-[1,1′-biphenyl]-3-carbaldehyde (3w): Yield 56.1 mg (95%); yellow solid; m.p. 83–84 °C. IR (KBr): $\tilde{\nu}$ = 1518 (NO_2), 1696 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.53 (s, 1 H), 8.27 (d, *J* = 8.5 Hz, 1 H), 8.17 (d, *J* = 2.0 Hz, 1 H), 7.98 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.0, 148.8, 145.7, 141.1, 132.1, 131.9, 131.5 (q, $J_{F,C}$ = 32.5 Hz), 128.3, 127.8, 126.3 (q, $J_{F,C}$ = 3.8 Hz), 125.5, 124.9, 123.9 (q, $J_{F,C}$ = 271.3 Hz) ppm. MS (EI, 70 eV): *m*/*z* (%) = 295 (53) [M^+], 265 (77). HRMS (EI): *m*/*z* calcd. for $C_{14}H_8F_3NO_3$ 295.0456; found 295.0463.

4-Nitro-4′-(Methoxycarbonyl)-[1,1′-biphenyl]-3-carbaldehyde (3x): Yield 53.1 mg (93%); yellow solid; m.p. 165–166 °C. IR (KBr): $\tilde{\nu}$ = 1719 (C=O), 1697 (C=O), 1515 (NO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.53 (s, 1 H), 8.26 (d, *J* = 8.5 Hz, 1 H), 8.19 (d, *J* = 6.5 Hz, 2 H), 8.18 (s, 1 H), 7.98 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 3.98 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.1, 166.5, 148.7, 146.2, 141.8, 132.2, 131.9, 131.1, 130.6, 128.3, 127.5, 125.5, 52.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 285 (10) [M^+]. HRMS (EI): *m*/*z* calcd. for $C_{15}H_{11}NO_5$ 285.0637; found 285.0645.

Mechanistic Studies

Nitration of Benzaldehyde *O*-Methyl Oxime 1a Catalyzed by Complex 4: Complex **4** was prepared according to a reported procedure.[14d] Compound **1a** (40.5 mg, 0.3 mmol), **4** (17.2 mg, 0.03 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), phenanthrene (21.4 mg, 0.12 mmol, internal standard), and anhydrous DCE (3.0 mL) were sequentially added to a 25-mL Schlenk flask. The flask was then sealed and the mixture was stirred at 110 °C for 48 h. Upon completion, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. A sample was taken for GC analysis, which showed a 69% yield of **2a**.

Intramolecular and Intermolecular Competition Experiments: Compound **1a**-d_1 (>99% deuterium-enrichment) and **1a**-d_5 (>99% deuterium-enrichment) were prepared by condensation of the corresponding deuterated benzaldehydes with $MeONH_2$·HCl as described in the above procedure. Procedure used for the intramolecular competition experiment on **1a**-d_1: To a 25-mL Schlenk flask were sequentially added **1a**-d_1 (40.8 mg, 0.3 mmol), $Pd(OCOCF_3)_2$ (10.0 mg, 0.03 mmol), $AgNO_2$ (92.4 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), and anhydrous DCE (3.0 mL). The flask was sealed and the mixture was heated to 110 °C for 30 h. The resulting mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (100–200 mesh; petroleum ether/EtOAc, 4:1 v/v). A mixture of **1a**-d_1 and **1a** in a molar ratio of 7:3 (based on ^1H NMR spectral analysis) was isolated. Based on the integrations related to different hydrogen resonances, the kinetic isotope effect was calculated to be k_H/k_D = 2.3 ± 0.2.

Procedure used for the intermolecular competition experiment on **1a** and **1a**-d_5: The procedure was the same as described for the intramolecular competition experiment except that the starting materials were **1a** (0.15 mmol) and **1a**-d_5 (0.15 mmol). The intermolecular kinetic isotope effect was calculated to be k_H/k_D = 4.0 ± 0.2 based on ^1H NMR spectral analyses.

Effect of Radical Scavenger TEMPO on the Nitration: Compound **1a** (40.5 mg, 0.3 mmol), $Pd(OCOCF_3)_2$ (10.0 mg, 0.03 mmol), $AgNO_2$ (92.3 mg, 0.6 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), TEMPO (0.15 mmol or 0.6 mmol), and anhydrous DCE (3.0 mL) were sequentially added to a 25-mL Schlenk flask. The flask was then sealed and the mixture was stirred at 110 °C for 48 h. Upon completion, the resulting mixture was analyzed by GC (trace of **2a**, TEMPO 0.5 equiv.; 0% of **2a**, TEMPO 2 equiv.).

Supporting Information (see footnote on the first page of this article): Charts for mechanistic studies as well as copies of ^1H and ^{13}C NMR spectra of the products.

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[1] a) N. Ono, in: *The Nitro Group in Organic Synthesis* Wiley-VCH, New York, **2001**; b) H. Feuer, A. T. Nielson, in: *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, New York, **1990**.

[2] a) H. Y. Kim, J.-Y. Li, K. Oh, *Angew. Chem. Int. Ed.* **2013**, *52*, 3736–3740; b) P. Selig, A. Turočkin, W. Raven, *Adv. Synth. Catal.* **2013**, *355*, 297–302; c) S. Xu, X. Zhuang, X. Pan, Z. Zhang, L. Duan, Y. Liu, L. Zhang, X. Ren, K. Ding, *J. Med. Chem.* **2013**, *56*, 4631–4640; d) H. R. Dholariya, K. S. Patel, J. C. Patel, A. K. Patel, K. D. Patel, *Med. Chem. Res.* **2013**, *22*, 5848–5860; e) U. Schulz, A. Grossmann, M. Witetschek, C. Lemmerhirt, M. Plozin, B. Haertel, H. Wanka, O. Morgenstern, *Bioorg. Med. Chem.* **2013**, *21*, 5518–5531; f) D. D. S. Bastos, A. C. Silva, A. L. M. Albert, W. M. R. Barros, G. B. C. A. Slana, J. N. Cardoso, R. S. C. Lopes, C. C. Lopes, *Tetrahedron Lett.* **2013**, *54*, 3144–3146; g) N. C. Desai, H. V. Vaghani, P. N. Shihora, *J. Fluorine Chem.* **2013**, *153*, 39–47; h) K. Parameswaran, P. Sivaguru, A. Lalitha, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3873–3878; i) J. Sun, M.-H. Li, S.-S. Qian, F.-J. Guo, X.-F. Dang, X.-M. Wang, Y.-R. Xue, H.-L. Zhu, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2876–2879; j) H. Zollinger, in: *Color Chemistry*, Wiley-VCH, New York, **1987**, p. 161; k) S. Ray, M. Brown, A. Bhaumik, A. Dutta, C. Mukhopadhyay, *Green Chem.* **2013**, *15*, 1910–1924; l) Y.-H. Zheng, H.-Y. Lu, M. Li, C.-F. Chen, *Eur. J. Org. Chem.* **2013**, 3059–3066; m) L. Li, A. Lv, X.-X. Deng, F.-S. Du, Z.-C. Li, *Chem. Commun.* **2013**, *49*, 8549–8551.

[3] a) E. Vasilikogiannaki, C. Gryparis, V. Kotzabasaki, I. N. Lykakis, M. Stratakis, *Adv. Synth. Catal.* **2013**, *355*, 907–911; b) J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618–3621; c) L. M. Doman, Q. Cao, J. C. A. Flanagan, J. J. Crawford, M. J. Cook, M. J. Muldoon, *Chem. Commun.* **2013**, *49*, 6030–6032; d) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 4017–4021; *Angew. Chem.* **2009**, *121*, 4077.

[4] a) G. A. Olah, R. Malhotra, S. C. Narang, in: *Nitration: Methods and Mechanisms*, VCH, New York, **1989**; b) K. Schofield, in: *Aromatic Nitration*, Cambridge University Press, Cambridge, UK, **1980**.

[5] a) H. Suzuki, S. Yonezawa, N. Nonoyama, T. Mori, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2385–2389; b) P. Ruggli, E. Brunner, *Helv. Chim. Acta* **1925**, *8*, 155–168.

[6] a) A. A. Kulkarni, V. S. Kalyani, R. A. Joshi, R. R. Joshi, *Org. Process Res. Dev.* **2009**, *13*, 999–1002; b) G. Aridoss, K. K. Laali, *J. Org. Chem.* **2011**, *76*, 8088–8094; c) S. A. Shackelford, M. B. Anderson, L. C. Christie, T. Goetzen, M. C. Guzman, M. A. Hananel, W. D. Kornreich, H. Li, V. P. Pathak, A. K. Rabinovich, R. J. Rajapakse, L. K. Truesdale, S. M. Tsank, H. N. Vazir, *J. Org. Chem.* **2003**, *68*, 267–275; d) B. Gigante,

Â. O. Przaeres, M. J. Marcelo-Curto, *J. Org. Chem.* **1995**, *60*, 3445–3447; e) R. R. Bak, A. J. Smallridge, *Tetrahedron Lett.* **2001**, *42*, 6767–6769.

[7] J. Y. Cassayre, P. Renold, T. Potterna, M. A. El Qacemi, PCT Int. Appl., 2013026931, 28 Feb. **2013**.

[8] a) T. Lu, Y. Mao, K. Yao, J. Xu, M. Lu, *Catal. Commun.* **2012**, *27*, 124–128; b) B. Ma, Z. Zhang, W. Song, X. Xue, Y. Yu, Z. Zhao, Y. Ding, *J. Mol. Catal. A* **2013**, *368–369*, 152–158; c) K. Layek, H. Maheswaran, R. Arundhathi, M. L. Kantam, S. K. Bhargava, *Adv. Synth. Catal.* **2011**, *353*, 606–616; d) A. S. Burange, R. V. Jayaram, R. Shukla, A. K. Tyagi, *Catal. Commun.* **2013**, *40*, 27–31; e) N. Sawatari, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2003**, *44*, 2053–2056; f) B. Holm, Ger. Offen., 3519864, 19 Dec. **1985**; g) D. Scherling, U. Pleiß, *J. Labelled Compd. Radiopharm.* **1988**, *25*, 1393–1400; h) F. Kienzle, *Helv. Chim. Acta* **1980**, *63*, 2364–2369; i) D. Enders, T. V. Nguyen, *Tetrahedron Lett.* **2012**, *53*, 2091–2095.

[9] For selected reviews on transition-metal-catalyzed chelation-assisted C–H activations, see: a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; c) O. Daugulis, H.-Q. Do, D. Shabashow, *Acc. Chem. Res.* **2009**, *42*, 1074–1086; d) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; *Angew. Chem.* **2009**, *121*, 5196; e) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949–957; f) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041–4047; g) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72.

[10] a) Y.-K. Liu, S.-J. Lou, D.-Q. Xu, Z.-Y. Xu, *Chem. Eur. J.* **2010**, *16*, 13590–13593; b) W. Zhang, S. Lou, Y. Liu, Z. Xu, *J. Org. Chem.* **2013**, *78*, 5932–5948.

[11] a) L. Zhang, Z. Liu, H. Li, G. Fang, B.-D. Barry, T. A. Belay, X. Bi, Q. Liu, *Org. Lett.* **2011**, *13*, 6536–6539; b) H. Zhang, L. Zhao, D.-X. Wang, M.-X. Wang, *Org. Lett.* **2013**, *15*, 3836–3839; c) F. Xie, Z. Qi, X. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 11862–11866.

[12] For review articles on using removable or modifiable directing groups for C–H activations, see: a) C. Wang, Y. Huang, *Synlett* **2012**, *23*, 145–149; b) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494; *Angew. Chem.* **2011**, *123*, 2498; c) W. Zhang, J. Zhang, Y. Liu, *Chin. J. Org. Chem.* **2014**, *34*, 36–53.

[13] For using *O*-methyl ketoxime as directing group for C–H functionalization, see recent examples: a) S. Sharma, M. Kim, J. Park, M. Kim, J. H. Kwak, Y. H. Jung, J. S. Oh, Y. Lee, I. S. Kim, *Eur. J. Org. Chem.* **2013**, 6656–6665; b) K.-H. Ng, Z. Zhou, W.-Y. Yu, *Chem. Commun.* **2013**, *49*, 7031–7033; c) B. Zhou, W. Hou, Y. Yang, Y. Li, *Chem. Eur. J.* **2013**, *19*, 4701–4706; d) M. Kim, J. Park, S. Sharma, A. Kim, E. Park, J. H. Kwak, Y. H. Jung, I. S. Kim, *Chem. Commun.* **2013**, *49*, 925–927; e) J. Kim, J. Kim, S. Chang, *J. Org. Chem.* **2013**, *78*, 11102–11109; f) T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10630–10633; g) H. Cai, D. Li, Z. Liu, G. Wang, *Huaxue Xuebao* **2013**, *71*, 717–721.

[14] Only limited examples are available on using *O*-methyl aldoxime as directing group for C–H functionalization, see: a) Z. Xu, B. Xing, P. Sun, *Eur. J. Org. Chem.* **2012**, 3069–3073; b) V. S. Thrunavukkarasu, C.-H. Cheng, *Chem. Eur. J.* **2011**, *17*, 14723–14726; c) E. Dubost, C. Fossey, R. S. Thomas, F. Fabis, *J. Org. Chem.* **2011**, *76*, 6414–6420; d) V. S. Thirunavukkarasu, K. Parthasarathy, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2008**, *47*, 9462–9465; *Angew. Chem.* **2008**, *120*, 9604.

[15] a) D.-H. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 17676–17677; b) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141–1144.

[16] T. Sakamoto, Y. Kikugawa, *Synthesis* **1993**, 563–564.

[17] Y.-M. Li, X.-H. Wei, X.-A. Li, S.-D. Yang, *Chem. Commun.* **2013**, *49*, 11701–11703.

[18] a) S. Maity, S. Manna, S. Rana, T. Naveen, A. Mallick, D. Maiti, *J. Am. Chem. Soc.* **2013**, *135*, 3355–3358; b) M. Stefanelli, M. Mastroianni, S. Nardis, S. Licoccia, F. R. Fronczek, K. M. Smith, W. Zhu, Z. Ou, K. M. Kadish, R. Paolesse, *Inorg. Chem.* **2007**, *46*, 10791–10799; c) B. Birkmann, B. T. Owens, S. Bandyopadhyay, G. Wu, P. C. Ford, *J. Inorg. Biochem.* **2009**, *103*, 237–242.

[19] For examples of the utilization of TEMPO as a radical scavenger, see: a) P. A. Sibbald, F. E. Michael, *Org. Lett.* **2009**, *11*, 1147–1149; b) A. C. Albéniz, P. Espinet, R. López-Fernández, A. Sen, *J. Am. Chem. Soc.* **2002**, *124*, 11278–11279.

[20] For silver-mediated radical reactions, see: a) F. Minisci, A. Citterio, *Acc. Chem. Res.* **1983**, *16*, 27–32; b) A. Kumar, P. Neta, *J. Am. Chem. Soc.* **1980**, *102*, 7284–7289; c) X. Liu, Z. Wang, X. Cheng, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 14330–14333.

[21] C. P. Salerno, M. Resat, D. Magde, J. Kraut, *J. Am. Chem. Soc.* **1997**, *119*, 3403–3404.

[22] A. Chacko, B. Mathew, *J. Appl. Polym. Sci.* **2003**, *90*, 3708–3717.

[23] M. L. McIntoch, R. C. Johston, O. Pattawong, B. O. Ashburn, M. R. Naffziger, P. H.-H. Cheong, R. G. Carter, *J. Org. Chem.* **2011**, *77*, 1101–1112.

[24] M. C. McLeod, G. Singh, J. N. Plampin III, D. Rane, J. L. Wang, V. W. Day, J. Aube, *Nat. Chem.* **2014**, *6*, 133–140.

[25] R. D. Topsom, J. Vaughan, *J. Chem. Soc.* **1957**, 2842–2843.

[26] J.-P. Wulf, K. Sienkiewicz, M. Makosza, E. Schmitz, *Liebigs Ann. Chem.* **1991**, *13*, 537–538.

[27] H. Venkatesan, F. M. Hocutt, T. K. Jones, M. H. Rabinowitz, *J. Org. Chem.* **2010**, *75*, 3488–3491.

[28] W.-Y. Li, X.-Q. Xiong, D.-M. Zhao, Y.-F. Shi, Z.-H. Yang, C. Yu, P.-W. Fan, M.-S. Cheng, J.-K. Shen, *Molecules* **2012**, *17*, 5497–5507.

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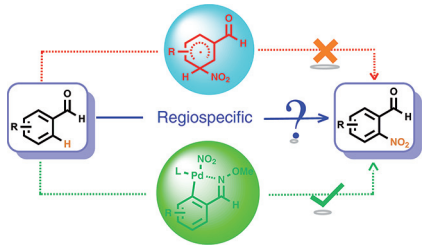
Regiospecific Nitration

An efficient and general method for the regiospecific synthesis of substituted 2-nitrobenzaldehydes from related benzaldehydes has been developed. The approach involves palladium-catalyzed chelation-assisted C–H nitration as the key step, and enables regiospecific nitration of C–H bonds free from the effect of orientation rules.



Keywords: Palladium / C–H activation / Nitro compounds / Nitration / Regioselectivity / Protecting groups

