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Fast Pd- and Pd/Cu-Catalyzed Direct C−H Arylation of Cyclic Nitrones. Application to the Synthesis of Enantiopure Quaternary α-Amino Esters

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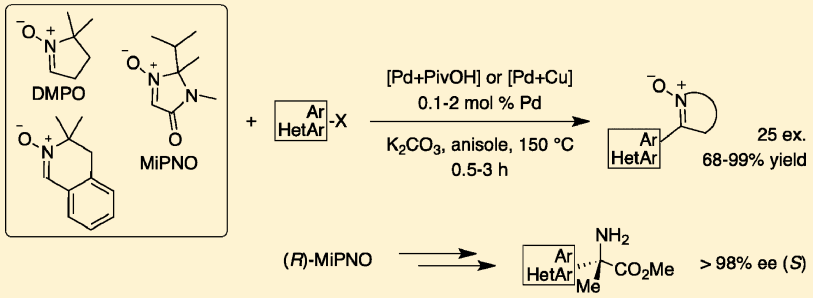
Supporting Information



ABSTRACT: Cocatalysis by pivalic acid or copper bromide allows a very fast, clean, and high-yielding palladium-catalyzed coupling of a large array of aryl, thienyl, and pyridyl halides with cyclic nitrones, including DMPO. The study of the reaction conditions, scope, and mechanism is presented. Applied to the chiral nitrone MiPNO, this transformation provides a straightforward access to enantiopure α-methyl α-arylglycine esters.

INTRODUCTION

In the past decade, a rapidly increasing number of methods for the direct arylation of arenes and heteroarenes has been developed.[1] In this regard, nitrogen-containing heteroaromatic compounds have been the subject of extensive research,[1,2] whereas scarce examples of direct arylation involving *non*-aromatic nitrogen heterocycles are found. The arylation of 4,4-dimethyloxazoline was investigated by Bergman and Ellman with Rh catalysts,[3] and Ackermann reported very recently a Pd-catalyzed version.[4] Finally, the Daugulis Cu-catalyzed direct arylation[1f] was applied to the synthesis of 5-arylbenzotriazepines.[5]

Our continued interest in the preparation and reactivity of nitrones[6] led us to the design of the chiral cyclic nitrone **1** (MiPNO; Figure 1) as a versatile precursor of α-amino acids.[7]

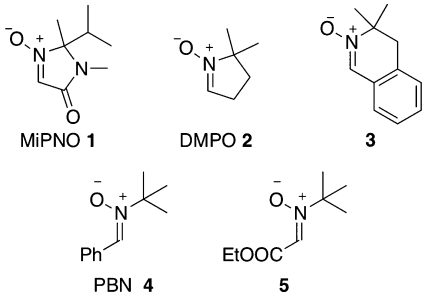


Figure 1. Nitrones referred to in this study.

MiPNO is conveniently stable to heat, and we assumed that it could be a worthy substrate for the study of direct coupling reactions with aromatic halides. We hypothesized that cyclic nitrones should behave like pyridine *N*-oxide, which is an excellent substrate for Pd-catalyzed direct arylation.[8,9] Indeed, aromatic amine *N*-oxides share common reactivity features with nitrones: for instance, they undergo addition of Grignard reagents at the ortho position[10] and cycloaddition reactions with dipolarophiles.[11] The same idea was independently explored by Zhao and Wang, who very recently reported on the Pd-catalyzed direct arylation of imidazolone *N*-oxides with aryl bromides.[12] Our own investigations led us to the development of two catalytic systems: indeed, the use of cocatalysts allows a very fast and efficient Pd-catalyzed direct C−H arylation of cyclic nitrones **1**−**3** (Figure 1) with a large array of aryl and heteroaryl halides. We present herein our study of the reaction conditions, scope, and mechanism. The obtained products still present a reactive nitrone function which renders them valuable intermediates.[13] As a first example, we show that direct arylation of the chiral nitrone MiPNO, followed by a totally diastereoselective Grignard addition, provides a straightforward access to enantiopure α-methyl α-arylglycine esters.

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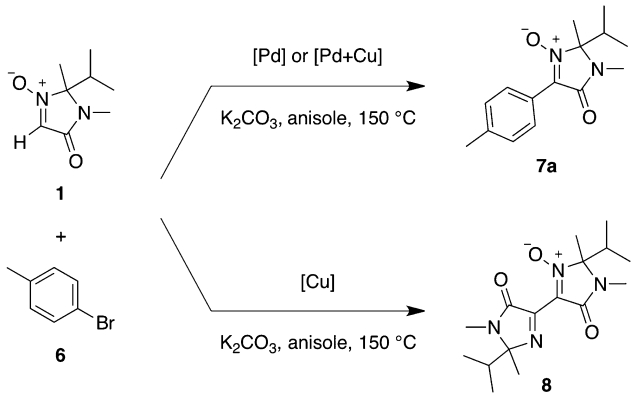
RESULTS AND DISCUSSION

Pd- and Pd/Cu-Catalyzed Direct Arylation of Nitrones.

We first studied the reaction of nitrone **1** with 4-bromotoluene **6** in the presence of a Pd catalyst (Scheme 1); representative

Scheme 1. Palladium-Catalyzed Direct Arylation of Nitrone 1 vs Copper-Catalyzed Self-Condensation



results are gathered in Table 1. We started with experiments conducted in closed vessels under microwave irradiation. Using conditions based on Fagnou's work (toluene, $Pd(OAc)_2$ 2 mol %, SPhos 2 mol %, K_2CO_3, 150 °C, 1.5 h; entry 1), we found that nitrone **1** and 4-bromotoluene **6** reacted remarkably cleanly to give adduct **7a** in 40−50% conversions. Moreover, the addition of pivalic acid[14] (PivOH, 20 mol %, entry 2) dramatically improved the result: complete conversion (92% isolated yield in **7a**) was achieved in 1.5 h. At this point we decided to proceed with conventional heating at atmospheric pressure; we chose anisole as the solvent, so that temperatures up to 150 °C could be reached. The reaction proved slower under these conditions (compare entries 3 vs 2). However, if the Pd^{II} precursor and the ligand are premixed in anisole beforehand (entry 5), or if a Pd^0 precursor is used (entry 7), a high activity is regained. One equivalent of phosphine per Pd is required (compare entries 3, 4, and 6). The positive effect of the PivOH additive was confirmed (compare entries 8 and 7).

We next investigated the nature of the phosphine ligand (entries 9−14). In comparison to SPhos, XPhos and tri-*tert*-butylphosphine ligands gave similar results; however, in the latter case the experimental protocol could be misleading (compare entries 12 vs 11). Finally, the simple, inexpensive triphenylphosphine proved to be the ligand of choice for this reaction: complete conversion of MiPNO **1** into ketonitrone **7a** (95% isolated yield) is achieved in 1 h using triphenylphosphine in combination with $Pd_2(dba)_3$ (entries 13 and 14) or $PdCl_2(PPh_3)_2$ (entry 15). The absence of the PivOH additive was detrimental (compare entries 16 vs 13) and could not be entirely compensated by the use of $Pd(OAc)_2$ as the Pd source (entries 17 and 18).

In addition, recent work indicates that Cu could be a cocatalyst[8d,e,15] or a catalyst.[16] Indeed, if PivOH was replaced by CuBr·DMS and 1,10-phenanthroline (5 mol % each), the model reaction of **1** and **6** proceeded even more quickly than the PivOH-catalyzed version (compare entries 19 and 20 vs entry 13). PivOH and Cu showed no synergetic effect (compare entries 21 and 20). On the other hand, without the cooperation of Pd (entry 22), Cu causes extensive self-condensation of nitrone **1** to furnish **8** (Scheme 1). This makes the Cu cocatalyst less robust than the Pd-PivOH system, since self-condensation of the nitrone could compete with the coupling. Therefore, we selected conditions A: 2 mol % Pd, 2 mol % PPh_3 (from $Pd_2(dba)_3$ + PPh_3),[17] and 20 mol % PivOH to investigate the scope of the direct arylation of nitrones. Although the reaction can be performed efficiently at 100 °C (entry 23), it remains very clean at 150 °C and we found no drawback in developing our examples at this temperature so that most of the reactions are complete in 1 h. Several literature reports hint that higher temperatures allow reduced catalyst loading.[18] Actually, with only 0.1 mol % Pd, the model reaction is complete within 3 h at 150 °C (entry 25). In contrast, with 0.2 mol % Pd at 100 °C, the product was still contaminated with starting **1** (8%) after 2 days (entry 24).

The substrate scope is outlined in Figure 2. To our delight, the reaction could in particular be extended to DMPO **2**,[19] notwithstanding the potentially labile H atoms in positions α to the double bond.[8c] Using conditions A, nitrones **1**−**3**[20] reacted cleanly with various aryl and pyridyl bromides to give ketonitrones **7a**−**m**, **9a**−**d**, and **10a**−**c**, respectively.[21] Complete conversion was generally achieved in 0.5−2 h; the isolated yields reflect only purification issues. In a sole instance the formation of byproduct was noticeable: the coupling of 5-bromo-2,4-dimethoxybenzaldehyde (68% yield in **7h**) was accompanied by some hydrodebromination.

Whereas compounds **1**−**3**, representative of three classes of cyclic nitrones, turned out to be excellent substrates for this Pd-catalyzed direct arylation, all attempts to extend the reaction to acyclic nitrones (*Z* configuration)[22] such as **4** and **5** failed: PBN **4** was recovered intact and glyoxylic nitrone **5** underwent degradation. The Pd-PivOH conditions also failed with some nitrogen-containing aryl bromides.[23] Whereas 3-bromopyridine[8e] and 4-bromopyridine could be easily coupled with nitrone **1** under conditions A (leading to compounds **7k,l**, respectively), 2-bromopyridine,[9a] 2,5-dibromopyridine, and bromoanilines remained unchanged. In such case, Cu cocatalysis comes as an efficient solution: the coupling of MiPNO **1** with nitrogen-containing aryl bromides using a Pd/Cu cocatalysis (2 mol % Pd, 2 mol % PPh_3, 5 mol % CuBr·DMS, 5 mol % 1,10-phenanthroline, no PivOH; conditions B in Figure 2) provided the expected adducts **7n**−**p** in excellent yields. The action of Cu salts as counter-poisons has been marginally mentioned in the case of pyridine *N*-oxide.[8d,e]

The case of dibromides deserves attention. Reaction of *o*- and *m*-dibromobenzenes (conditions A) and 2,6-dibromopyridine and 2,5-dibromothiophene (conditions B) with 2 equiv of enantiopure (*S*)-**1** led in high yields to the bis-nitrone products **7i,j** and **7q,r**, respectively, uncontaminated by monocoupling or hydrodebromination products.[24] This illustrates further the efficiency and cleanness of each coupling step. The possibility of grafting several cyclic nitrones on one aromatic structure offers an easy access not only to new families of conjugated polynitrones with unexplored properties but also, since reduction of nitrones to imines[12] is easy, to new enantiopure C_2-symmetric diimine ligands.

In addition, we investigated the reactivity of other aryl halides[12] in the present coupling. Methyl 4-chlorobenzoate was unreactive under conditions A (<15% nitrone **1** conversion after 72 h) or B (conversion of nitrone **1** was complete in 1 h but self-condensation of the nitrone competed with the arylation: a 1/1 ratio of **7f** and **8** was obtained). Changing triphenylphosphine for XPhos[25] under conditions A brought about success: methyl 4-chlorobenzoate was totally converted

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Table 1. Direct Arylation of Nitrone 1 with 4-Bromotoluene 6[a]

entry	Pd source	ligand	additive[b]	additional information	time	conversion (%)[c]
1	$Pd(OAc)_2$	SPhos		toluene (solvt),[d] μw[e]	1.5 h	40−50
2	$Pd(OAc)_2$	SPhos	PivOH	toluene (solvt),[d] μw[e]	1.5 h	100 (92)[f]
3	$Pd(OAc)_2$	SPhos	PivOH		1.5 h	50
					16 h	100 (85)[f]
4	$Pd(OAc)_2$	SPhos	PivOH	4 mol % SPhos	1.5 h	50
					24 h	100
5	$Pd(OAc)_2$	SPhos	PivOH	preformed complex[g]	1 h	94
6	$Pd(OAc)_2$		PivOH		16 h	0
7	$Pd_2(dba)_3$	SPhos	PivOH		15 min	50
					1 h	85
					17 h	100
8	$Pd_2(dba)_3$	SPhos			1 h	27
					18 h	90
9	$Pd_2(dba)_3$	XPhos	PivOH		30 min	50
					2 h	85
10	$Pd_2(dba)_3$	XPhos	PivOH	preformed complex[g]	15 min	70
					1 h	85
					2 h	100
11	$Pd_2(dba)_3$	P^tBu_3,HBF_4	PivOH		18 h	15
12	$Pd_2(dba)_3$	P^tBu_3,HBF_4	PivOH	preformed complex[g]	5 min	7
					15 min	30
					1 h	72
					2 h	100
13	$Pd_2(dba)_3$	PPh_3	PivOH		7 min	50
					1 h	100 (95)[f]
14	$Pd_2(dba)_3$	PPh_3	PivOH	4 mol % PPh_3	7 min	50
					1 h	100
15	$PdCl_2(PPh_3)_2$		PivOH		5 min	39
					7 min	50
					10 min	60
					1 h	100
16	$Pd_2(dba)_3$	PPh_3			1 h	40
					18 h	95
17	$Pd(OAc)_2$	PPh_3			25 min	19
					50 min	38
					1.5 h	62
					18 h	100
18	$Pd(OAc)_2$	PPh_3		preformed complex[g]	20 min	25
					50 min	56
					1.5 h	79
19	$Pd_2(dba)_3$	PPh_3	CuBr·DMS		30 min	50
					18 h	100
20	$Pd_2(dba)_3$	PPh_3	CuBr·DMS Phen		4 min	50
					20 min	100
21	$Pd_2(dba)_3$	PPh_3	CuBr·DMS Phen PivOH		4 min	50
					18 min	100
22			CuBr·DMS Phen		1 h	product: **8** (95)[h]
23	$Pd_2(dba)_3$	PPh_3	PivOH	100 °C	2 h	100
24	$PdCl_2(PPh_3)_2$		PivOH	0.2 mol % Pd, 100 °C	4 h	40
					48 h	92
					120 h	93
25	$PdCl_2(PPh_3)_2$		PivOH	0.1 mol % Pd	30 min	50
					3 h	100 (90)[f]

[a]Conditions unless otherwise stated: MiPNO **1** (1 mmol), 4-bromotoluene (1.1 equiv), K_2CO_3 (1.5 equiv), Pd (2 mol %), phosphine ligand (2 mol %), anisole (0.5 M), 150 °C (preheated oil bath). The Pd source, the ligand, and all other reagents were charged into the vessel, the solvent was added, and the vessel was plunged in the hot bath. [b]Conditions: PivOH (20 mol %), CuBr·DMS (5 mol %), 1,10-phenanthroline (Phen, 5 mol %). [c]Conversion evaluated by ^1H NMR analysis of reaction aliquots. [d]solvt: reaction solvent, if not anisole. [e]μw: reaction performed under microwave irradiation. [f]Isolated yield (%) in **7a**. [g]Preformed complex: Pd source, ligand, and K_2CO_3 were mixed at room temperature in anisole prior to addition of substrates. [h]Isolated yield (%) in **8**.

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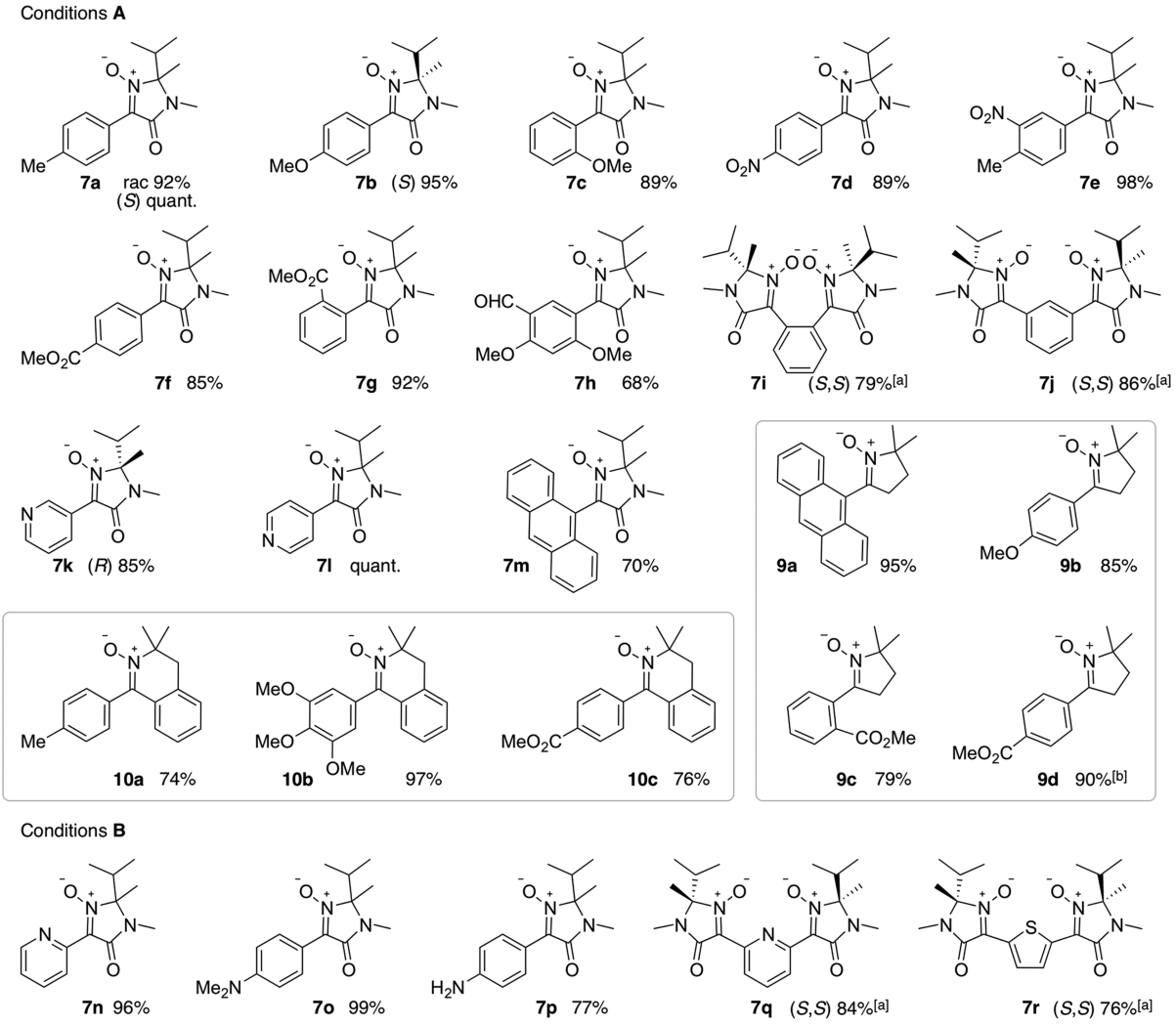

Figure 2. Ketonitrones **7**, **9**, and **10** prepared by Pd-catalyzed direct arylation of nitrones **1**−**3** with aryl bromides. General conditions: ArBr (1.1 equiv), K_2CO_3 (1.5 equiv), anisole (0.5 M), 150 °C, 0.5−2 h. Conditions A: Pd (2 mol %), PPh_3 (2 mol %), PivOH (20 mol %). Conditions B: Pd (2 mol %), PPh_3 (2 mol %), CuBr·DMS (5 mol %), 1,10-phenanthroline (5 mol %). Legend: (a) 2 equiv of nitrone (*S*)-**1**; (b) run performed with 5 mol % Pd/PPh_3.

in less than 30 min (91% isolated yield), and the less reactive 4-chlorotoluene required only 2 h (94% isolated yield). As for aryl iodides, the arylation reaction was sluggish under conditions A (methyl 4-iodobenzoate: 49% nitrone **1** conversion after 2 h) and the degradation of the catalyst was visible. Conditions B were the solution, however, providing arylation products **7a**,**b**,**f** in excellent yields (92%, 95%, and 85%, respectively) within 2 h.

Mechanistic Considerations. In terms of mechanism, many features of the present reaction are analogous to those met in Fagnou's azine *N*-oxide direct arylation, such as importance of carboxylate base, weak influence of the nature of the aryl bromide, and kinetic isotopic effect (KIE).[26] With regard to the latter, we compared in separate experiments[27] the relative rate of reaction of nitrone **1** and deuterated analogue *d*-**1** (aryl bromide **6**, $PdCl_2(TPP)_2$ (0.2 mol %), 150 °C) and found a k_H/k_D ratio of 3. Thus, the C−H bond cleavage occurs during the turnover-limiting step.

The possibility of an addition−elimination process, where the C−C bond is formed prior to the rupture of the C−H bond (usually referred to as "Heck-like" in discussions on C−H activation),[28] could be considered (Figure 3, intermediate I). In this hypothesis, to account for the primary KIE, the elimination step should be turnover-determining. Then, since intermediate I would accumulate, decomposition byproduct could be present. We have studied earlier[7b] the addition of aryl Grignard reagents to nitrone **1** and noted that the corresponding hydroxylamine adducts were prone to dehydration in basic media, to produce the corresponding imines. Neither hydroxylamine nor imine byproducts were ever detected in the crude products of the present coupling. Moreover, this hypothesis does not explain the absence of reaction of acyclic *Z* nitrones. Hence, the possibility of a Heck-like mechanism was discarded.

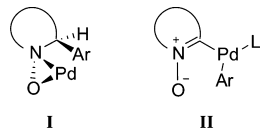

Figure 3. Postulated intermediates in the case of a Heck-like mechanism (I) and a deprotonation/metalation mechanism (II).

A common hypothesis for the C−H arylation of (hetero)-aromatic substrates is a deprotonation/metalation mechanism, leading to intermediate II (Figure 3).[29] The deuteration

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experiments gathered in Table 2 suggest that such a deprotonation is relatively easy.[30] Qualitatively, nitrone **1** is more acidic than nitrone **2** and pyridine *N*-oxide PNO, which are both inert in the presence of K_2CO_3. The decomposition of **2** in the presence of KOH illustrates the general sensitivity of cyclic nitrones;[31] in contrast, the linear *Z* nitrone **4** is inert toward KOH and ^{t}BuOK. On the other hand, heating **1** with ^{t}BuOK in d_8-toluene (140 °C, 30 min, microwave irradiation) produced the self-condensation product **8**, whereas nitrone **1** remained unchanged under the coupling conditions (K_2CO_3, anisole, 150 °C) when Pd was omitted.

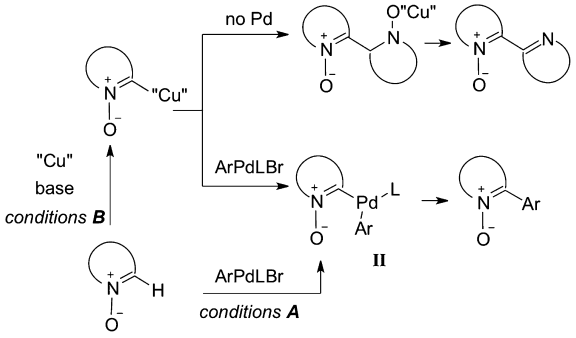
Table 2. Deuterium Exchange with d_6-Acetone[a]

	base		
compd	K_2CO_3	KOH	^{t}BuOK
1	deuteration (98%)		
2	no reaction	decomposition[b]	
4		no reaction	no reaction
PNO	no reaction	deuteration (91%)	

[a]The compound was heated in d_6-acetone (140 °C, 30 min, microwave irradiation) with >1 equiv of base. [b]Compound **2** decomposed also at 20 °C with substoichiometric KOH.

When Cu is used as the sole catalyst (Table 1, entry 22), product **8** is obtained. This proves that Cu-assisted deprotonation of **1** can take place, the organocopper species reacting with excess **1** (Scheme 2). In the Pd-catalyzed direct arylation, CuBr accelerates the coupling: under these conditions B, the deprotonation of the nitrone probably occurs in the coordination sphere of Cu (Scheme 2), and a transmetalation from Cu to Pd would provide intermediate II. Conversely under conditions A, the fact that no self-condensation product was observed in the absence of Pd indicates that the nitrone is presumably coordinated to Pd in the deprotonation step.

Scheme 2. Possible Pathways for the Direct Arylation of Nitrones



The hypothesis of a concerted metalation−deprotonation (CMD) mechanism,[26,29,32] proposed for the Pd-catalyzed direct arylation of (hetero)arenes including azine *N*-oxides, was next considered. Gorelsky[33] and others[30a] performed extended DFT calculations over a large variety of substrates and met good agreement with experimental data. In order to find out how nitrones are positioned among other C−H arylation substrates, we reproduced Gorelsky's calculations[26] on three simplified models of nitrones, **1′**, **2′**, and **4′** (Figure 4). It appeared that the calculated free energies of activation ($\Delta G^{\ddagger}_{298\ K}$, kcal mol^{-1}) for **1′** (19.4) and **2′** (22.2) were among the lowest reported. This modeling also provides an explanation for the non-reactivity of linear, *Z* nitrones: in the case of **1′**, **2′**, and PNO, the metalated intermediates II (Figure 4) are stabilized by a strong Pd−O interaction (N−C−Pd angles 94−96°, O−Pd distances 2.3−2.4 Å), making the transformation reasonably endothermic ($\Delta G_{298\ K}$ = 11.8−16.5 kcal mol^{-1}). In contrast, the calculated deprotonation of the *Z* model **4′** is highly endothermic: $\Delta G_{298\ K}$ = +29.1 kcal mol^{-1}, which is higher than the highest transition state of the series.

Thus, a metalation−deprotonation model is reasonable. It can be considered concerted insofar as it takes place in the coordination sphere of Pd. The exact nature of the species (inner- or outer-sphere approach of the carboxylate,[26] precise nature of the Pd ligands[34]) was not sought further in the present study.

Application to the Synthesis of Enantiopure α-Methyl α-Arylglycine Esters. MiPNO **1** is a chiral glycine equivalent,[7] and the present direct arylation of nitrones can be easily applied to the preparation of enantiopure quaternary α-arylglycines which have been developed in particular for their restricted conformational flexibility.[35] To demonstrate this, we submitted adducts **7a,b,k** prepared from enantiopure samples of (*S*)- and (*R*)-**1** to excess MeMgCl in THF (Scheme 3). The corresponding hydroxylamines **11a,b,k** were obtained in quantitative yields. The diastereoselectivity of the addition was excellent: only one diastereomer was detected by ^{1}H NMR analysis of the crude reaction mixtures. The relative configuration of **11a** was confirmed by X-ray analysis:[36] as expected, the methyl group was transferred anti to the bulky isopropyl group.[37] Reduction of the N−O bond was performed using zinc in acetic acid, under sonication. Hydrolysis of the imidazolidinone ring required harsh conditions: a *p*-anisyl group was deprotected. The obtained amino acids were esterified for purification, providing the methyl esters of α-methyl-α-arylglycines **12a,b,k** in 43−66% overall yields from **7a,b,k** (four steps) with an excellent enantiomeric purity (>98%, ^{1}H NMR analysis).[38]

CONCLUSION

Thus, we have disclosed two sets of conditions for the direct arylation of cyclic nitrones. The acceleration effect of the cocatalysts allows the reaction to be very fast and suitable for substrates such as DMPO **2**. We are currently investigating the broadening of this new direct C−H arylation reaction to other cyclic nitrones. A wide range of aryl and heteroaryl halides reacted smoothly under our conditions, giving access to highly functionalized compounds. Beyond the possible applications of this reaction to the synthesis of non-natural amino acids or new ligands,[39] the present work contributes to indicate that Pd-catalyzed arylation of heterocyclic C(sp^2)−H bonds is not intrinsically limited to aromatic systems.

EXPERIMENTAL SECTION

General Methods. All experiments were carried out under a nitrogen atmosphere in oven-dried glassware equipped with a magnetic stir bar. Standard inert-atmosphere techniques were used in handling all air- and moisture-sensitive reagents. Anisole was washed with 10% aqueous NaOH and water, dried over magnesium sulfate, distilled, stored, and handled under a N_2 atmosphere. HPLC grade THF, Et_2O, toluene, and CH_2Cl_2 were dried and purified in a solvent purification system. Palladium sources were stored in a desiccator and were weighed out in air. All other reagents and solvents were purchased from commercial sources and used as received. Product purifications by dry column vacuum chromatography[40] were

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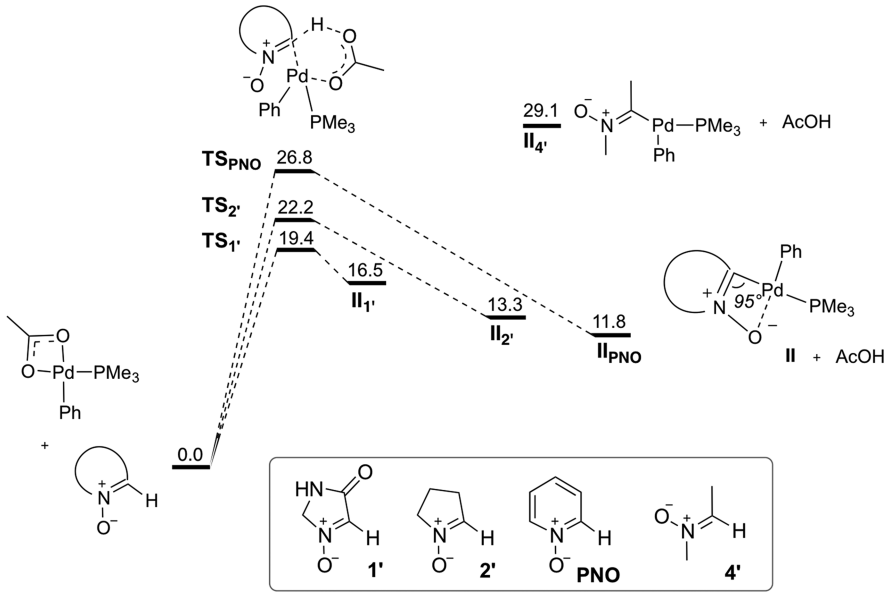
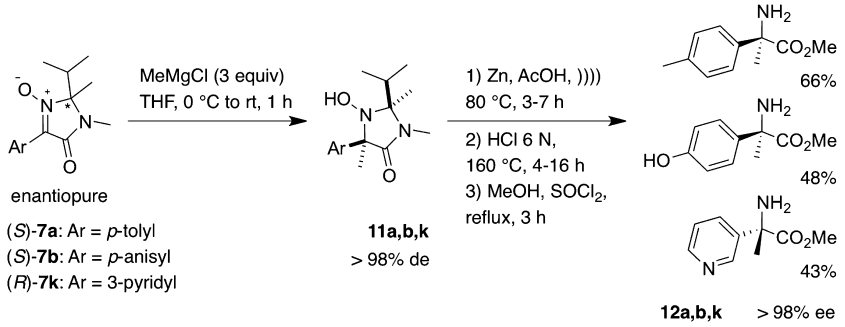


Figure 4. Free Gibbs energy profile (kcal mol^{-1}) calculated for carboxylate-assisted CMD processes (DFT, B3LYP, basis set DZVP for Pd and TZVP for others).

Scheme 3. Preparation of α-Methyl α-Arylglycine Esters 12



performed using Macherey Nagel silica gel 60 (0.015−0.04 mm) and gradient elution: cyclohexane/ethyl acetate (10/0 to 0/10), then ethyl acetate/ethanol (10/0 to 9/1).

Melting points (mp) are given uncorrected. For optical rotations [α], the corresponding concentration is given in g per 100 cm^{-3}. Infrared spectra (IR) were recorded using ATR (attenuated total reflection); wavenumbers are reported in reciprocal centimeters (cm^{-1}). The chemical shifts (δ) of the NMR spectra are given in ppm using TMS as internal reference. Multiplicities are declared as follows: s (singlet), d (doublet), hept (heptuplet), m (multiplet), q (quadruplet); br (broad). Coupling constants (*J*) are given in hertz.

Nitrones. Racemic and enantiopure MiPNO **1** (2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1*H*-imidazole 3-oxide) was prepared according to ref 7; DMPO **2** (2,2-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide) is commercially available.

3,3-Dimethyl-3,4-dihydroisoquinoline 2-Oxide ***3****.*[20] The title compound was synthesized from 2-methyl-1-phenylpropan-2-amine,[41] with slight modifications from the literature protocols.[20] A 250 mL flask was charged with 2-methyl-1-phenylpropan-2-amine (8.4 g, 50 mmol) and dichloromethane (50 mL). To the solution was added Et_3N (12 mL, 86 mmol) and *p*-toluenesulfonyl chloride (11.5 g, 60 mmol). The solution was stirred overnight at room temperature. The reaction mixture was quenched with a saturated aqueous Na_2CO_3 solution (50 mL). The organic layer was washed with a saturated aqueous Na_2CO_3 solution (50 mL) and then with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 4-methyl-*N*-(2-methyl-1-phenylpropan-2-yl)benzenesulfonamide (13.5 g, 90%). In a 250 mL flask were introduced the crude sulfonamide (13.5 g, 45 mmol), dimethoxymethane (100 mL), and $BF_3{\cdot}OEt_2$ (25 mL). The solution was stirred overnight. The reaction mixture was quenched with water (100 mL) and diluted with dichloromethane (50 mL), and the two phases were separated. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was recrystallized from ethanol to afford 3,3-dimethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (4.7 g, 33%). In a 250 mL three-necked flask equipped with an ammonia condenser was added the *N*-tosylamine (4.7 g, 15 mmol). The flask and condenser were cooled to −50 °C, and ammonia (50 mL) was condensed to give a suspension of the *N*-tosylamine in ammonia. Lithium (740 mg, 105 mmol) was then added to the suspension to give a dark blue solution. The cold bath was removed so that the flask temperature rose to −33 °C (reflux of ammonia), the condenser being maintained at −50 °C. The solid *N*-tosylamine was consumed. When the solution turned yellow with solid still present, fresh lithium was added until total consumption of the *N*-tosylamine. The condenser was removed, and ammonia was evaporated by flushing the flask with nitrogen. Dichloromethane (30 mL) and ice (30 g) were added. The mixture was stirred for 20 min. The aqueous phase was extracted with diethyl ether (2 × 70 mL) and dichloromethane (50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (2.5 g, quantitative). In a 250 mL flask, the crude amine (2.5 g, 15 mmol) was dissolved in methanol (50 mL) and water (50 mL). An aqueous solution of Na_2WO_4 (500 mg, 1.5 mmol in 5 mL of water) was added. Hydrogen

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peroxide (4.2 mL of a 30 wt % solution in water, 45 mmol) was added dropwise. The reaction was followed by TLC. After completion, MnO_2 (200 mg) was added cautiously to the reaction mixture. The suspension was then filtered over Celite, and methanol was removed under reduced pressure. The aqueous layer was extracted with dichloromethane (2 × 40 mL). The crude product was purified over silica gel to yield nitrone **3** (1.2 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.29−7.24 (m, 2H), 7.21−7.14 (m, 1H), 7.12−7.07 (m, 1H), 3.07 (s, 2H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 132.7, 129.9, 129.1, 128.4, 127.6, 127.4, 124.7, 66.9, 41.8, 24.7.

Direct Arylation of Nitrones. *General Procedure A.* A 10 mL Schlenk flask under an N_2 atmosphere was charged with nitrone, aryl bromide (1.1 equiv), $Pd_2(dba)_3$ (1 mol %; i.e. 2 mol % Pd), triphenylphosphine (2 mol %),[17] pivalic acid (0.2 equiv), and K_2CO_3 (1.5 equiv). The flask was evacuated and purged with N_2, and anisole was added to give a 0.5 M solution. The Schlenk flask was plunged into a 150 °C preheated oil bath, and the reaction was monitored by ^{1}H NMR spectroscopy of small aliquots. After completion of the reaction, the crude solution was purified over silica gel to give the arylnitrone.

General Procedure B. A 10 mL Schlenk flask under an N_2 atmosphere was charged with nitrone, aryl bromide (1.1 equiv), $Pd_2(dba)_3$ (1 mol %; i.e. 2 mol % Pd), triphenylphosphine (2 mol %),[17] CuBr·DMS (5 mol %), 1,10-phenanthroline (5 mol %), and K_2CO_3 (1.5 equiv). The flask was evacuated and purged with N_2, and anisole was added to give a 0.5 M solution. The Schlenk flask was plunged into a 150 °C heated oil bath, and the reaction was monitored by ^{1}H NMR spectroscopy of small aliquots. After completion of the reaction, the crude solution was purified over silica gel to give the arylnitrone.

*2-Isopropyl-1,2-dimethyl-5-oxo-4-(p-tolyl)-2,5-dihydro-1H-imidazole 3-Oxide (**7a**).* The title compound was prepared according to general procedure A starting from MiPNO (170 mg, 1.0 mmol) and 4-bromotoluene (188 mg, 1.1 mmol): 1 h; colorless crystals (242 mg, 92%). Mp: 75−76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 8.3, 2H), 7.28 (d, J = 8.3, 2H), 3.08 (s, 3H), 2.48−2.35 (m, 4H), 1.72 (s, 3H), 1.02 (d, J = 7.1, 3H), 0.96 (d, J = 6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 141.3, 130.6, 129.0, 127.5, 123.2, 90.8, 35.0, 26.5, 21.7, 21.5, 16.3, 15.6. IR: 3370, 3079, 2971, 2879, 1690, 1556, 1356, 826. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.58; H, 7.58; N 10.83.

(+)-**7a** (1.30 g, quantitative) was obtained from (*S*)-MiPNO (850 mg, 5.0 mmol) as a yellow solid. $[\alpha]_D^{25}$ = +91.6° (c 1.87, $CHCl_3$).

*2-Isopropyl-4-(4-methoxyphenyl)-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7b**).* The title compound was prepared according to general procedure A starting from MiPNO (170 mg, 1.0 mmol) and 4-bromoanisole (248 mg, 1.1 mmol): 1.5 h; yellow oil (267 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, J = 9.2, 2H), 6.98 (d, J = 9.2, 2H), 3.86 (s, 3H), 3.08 (s, 3H), 2.42 (qq, J = 7.2, 6.8, 1H), 1.71 (s, 3H), 1.02 (d, J = 7.2, 3H), 0.96 (d, J = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 161.3, 130.2, 129.4, 118.8, 113.6, 90.5, 55.3, 34.9, 26.5, 21.4, 16.3, 15.6. IR: 3085, 2968, 2838, 1695, 1604, 1557, 1506, 1356, 1252, 1180, 1028, 837.

(+)-**7b** (1.31 g, 95%) was obtained from (*S*)-MiPNO (850 mg, 5.0 mmol) as a yellow solid. Mp: 122−123 °C. $[\alpha]_D^{25}$ = +93.5° (c 1.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.14; H, 7.40; N, 9.97.

*2-Isopropyl-4-(2-methoxyphenyl)-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7c**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and 2-bromoanisole (208 mg, 1.1 mmol): 18 h; white solid (245 mg, 89%). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.40 (m, 2H), 7.04 (td, J = 7.5, 0.9, 1H), 7.01−6.96 (m, 1H), 3.85 (s, 3H), 3.08 (s, 3H), 2.40 (qq, J = 7.1, 6.8, 1H), 1.74 (s, 3H), 1.07 (d, J = 7.1, 3H), 1.04 (d, J = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 158.3, 132.9, 131.9, 130.8, 120.6, 113.9, 111.8, 92.0, 55.9, 34.7, 26.6, 21.5, 16.2, 15.4. IR: 3066, 2965, 2841, 1690, 1564, 1361, 1282, 753. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 64.95; H, 7.36; N, 10.15.

*2-Isopropyl-1,2-dimethyl-4-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7d**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and 4-bromonitrobenzene (223 mg, 1.1 mmol): 1 h; colorless crystals (245 mg, 89%). Mp: 155−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (d, J = 9.3, 2H), 8.30 (d, J = 9.3, 2H), 3.12 (s, 3H), 2.43 (qq, J = 7.1, 6.8, 1H), 1.76 (s, 3H), 1.03 (d, J = 7.1, 3H), 0.99 (d, J = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 148.2, 131.6, 128.1, 123.4, 92.2, 35.2, 26.6, 21.6, 16.2, 15.5. IR: 3110, 2989, 2970, 1703, 1544, 1506, 1338, 1110, 863. HRMS (ESI$^+$): m/z calcd for $C_{14}H_{17}N_3O_4Na^+$ 314.111 13; found 314.110 87. Data for the crystal structure have been deposited at the Cambridge Crystallographic Data Centre, reference no. CCDC 871602.

*2-Isopropyl-1,2-dimethyl-4-(4-methyl-3-nitrophenyl)-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7e**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and 4-bromo-2-nitrotoluene (238 mg, 1.1 mmol): 2 h; white solid (300 mg, 98%). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 106−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, J = 1.7, 1H), 8.95 (dd, J = 8.2, 1.7, 1H), 7.44 (d, J = 8.2, 1H), 3.10 (s, 3H), 2.64 (s, 3H), 2.43 (qq, J = 7.1, 6.8, 1H), 1.74 (s, 3H), 1.02 (d, J = 7.1, 3H), 0.98 (d, J = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 149.3, 135.7, 132.6, 131.0, 128.7, 125.0, 123.1, 91.8, 35.0, 26.5, 21.5, 20.5, 16.2, 15.5. IR: 3113, 2978, 2882, 1702, 1566, 1514, 1343, 1154, 843. Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.28; N, 13.77. Found: C, 59.36; H, 6.57; N, 13.96.

*2-Isopropyl-4-(4-(methoxycarbonyl)phenyl)-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7f**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and methyl 4-bromobenzoate (240 mg, 1.1 mmol): 1 h; white solid (260 mg, 85%). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 96−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, J = 8.2, 2H), 8.12 (d, J = 8.2, 2H), 3.94 (s, 3H), 3.10 (s, 3H), 2.43 (qq, J = 7.1, 6.7, 1H), 1.74 (s, 3H), 1.03 (d, J = 7.1, 3H), 0.98 (d, J = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 162.7, 131.5, 129.8, 129.3, 127.2, 91.7, 52.2, 35.1, 26.6, 21.5, 16.2, 15.5 (one quaternary C remained undetected). IR: 2945, 2883, 1718, 1699, 1549, 1364, 1280, 1110, 859. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.15; H, 6.63; N, 9.21. Found: C, 63.30; H, 6.83; N, 9.30.

*2-Isopropyl-4-(2-(methoxycarbonyl)phenyl)-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7g**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and methyl 2-bromobenzoate (240 mg, 1.1 mmol): 1 h; white solid (281 mg, 92%). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 97−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 7.8, 1.1, 1H), 7.80 (dd, J = 7.8, 1.0, 1H), 7.61 (td, J = 7.6, 1.4, 1H), 7.52 (td, J = 7.7, 1.3, 1H), 3.84 (s, 3H), 3.09 (s, 3H), 2.43 (qq, J = 7.2, 6.8, 1H), 1.74 (s, 3H), 1.08 (d, J = 7.2, 1H), 1.04 (d, J = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 162.3, 133.7, 131.7, 131.6, 130.2, 130.1, 130.1, 124.4, 92.0, 52.5, 34.62, 26.6, 21.4, 16.3, 15.6. IR: 3375, 3072, 2975, 2939, 1728, 1697, 1560, 1361, 1255, 1127, 774. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.15; H, 6.63; N, 9.21. Found: C, 63.52; H, 6.60; N, 9.20.

*4-(5-Formyl-2,4-dimethoxyphenyl)-2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7h**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and 5-bromo-2,4-dimethoxybenzaldehyde (273 mg, 1.1 mmol): 2.7 h; white solid (227 mg, 68%). An analytical sample was obtained by washing the solid with diethyl ether under sonication. Mp: 289−290 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 7.94 (s, 1H), 6.50 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.07 (s, 3H), 2.38 (qq, J = 7.1, 6.8, 1H), 1.72 (s, 3H), 1.05 (d, J = 7.1, 3H), 1.02 (d, J = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 187.5, 165.2, 164.4, 162.6, 132.7, 131.8, 118.7, 107.2, 95.0, 92.1, 56.2, 55.9, 34.7, 26.7, 21.6, 16.2, 15.5. IR: 3123, 2977, 2853, 1699, 1670, 1607, 1570, 1359, 1283, 1022, 821. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.64; N, 8.38. Found: C, 60.92; H, 6.86; N, 8.25.

*(2S,2′S)-4,4′-(1,2-Phenylene)bis(2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-oxide) (**7i**).* The title compound was prepared according to general procedure A from (*S*)-MiPNO (189 mg, 1.11 mmol) and 1,2-dibromobenzene (132 mg, 0.56 mmol): 2 h; yellow solid (183 mg, 79%). An analytical sample was obtained by washing the solid with diethyl ether under sonication. Mp: 224−226 °C. $[\alpha]_D^{25}$ = +293° (*c* 0.99, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04−7.97 (m, 2H), 7.62−7.55 (m, 2H), 3.09 (s, 6H), 2.31 (qq, *J* = 7.1, 6.8, 2H), 1.74 (s, 6H), 1.00 (d, *J* = 7.1, 6H), 0.89 (d, *J* = 6.8, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 134.7, 130.2, 129.9, 123.9, 91.6, 34.8, 26.8, 21.8, 16.3, 15.5. IR: 3082, 2974, 2876, 1694, 1571, 1571, 1430, 1356, 1223, 1123, 789. Anal. Calcd for $C_{22}H_{30}N_4O_4$: C, 63.75; H, 7.30; N, 13.52. Found: C, 64.00; H, 7.49; N, 13.18.

*(S)-4-(2-Bromophenyl)-2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7i′**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72−7.63 (m, 1H), 7.45−7.37 (m, 2H), 6.93−6.81 (m, 1H), 3.11 (s, 3H), 2.51−2.36 (m, 1H), 1.77 (s, 1H), 1.16−1.00 (m, 6H).

*(2S,2′S)-4,4′-(1,3-Phenylene)bis(2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-oxide) (**7j**).* The title compound was prepared according to general procedure A from (*S*)-MiPNO (476 mg, 2.8 mmol) and 1,3-dibromobenzene (340 mg, 1.4 mmol): 0.5 h; white solid (497 mg, 86%). An analytical sample was obtained by washing the solid with diethyl ether under sonication. Mp: 159−162 °C. $[\alpha]_D^{25}$ = +174° (*c* 1.17, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.33 (t, *J* = 1.6, 1H), 8.88 (dd, *J* = 8.1, 1.7, 2H), 7.58 (t, *J* = 8.1, 1H), 3.10 (s, 6H), 2.44 (qq, *J* = 7.1, 6.8, 2H), 1.73 (s, 6H), 1.03 (d, *J* = 7.1, 6H), 0.97 (d, *J* = 6.8, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8, 130.0, 129.4, 128.2, 126.5, 126.1, 91.3, 35.0, 26.6, 21.6, 16.3, 15.6. IR: 3101, 3082, 2977, 2885, 1694, 1548, 1354, 1279, 1040, 808, 691. Anal. Calcd for $C_{22}H_{30}N_4O_4$: C, 63.75; H, 7.30; N, 13.52. Found: C, 63.82; H, 7.65; N, 13.56.

*(R)-2-Isopropyl-1,2-dimethyl-5-oxo-4-(pyridin-3-yl)-2,5-dihydro-1H-imidazole 3-Oxide (**7k**).* The title compound was prepared according to general procedure A from (*R*)-MiPNO (850 mg, 5.0 mmol) and 3-bromopyridine (869 mg, 5.5 mmol): 2 h; yellow oil (1.05 g, 85%). $[\alpha]_D^{25}$ = −85.5° (*c* 0.93, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (d, *J* = 1.6, 1H), 9.08 (dd, *J* = 8.2, 1.6, 1H), 8.67 (dd, *J* = 4.9, 1.6, 1H), 7.39 (ddd, *J* = 8.2, 4.9, 0.7, 1H), 3.09 (s, 3H), 2.41 (qq, *J* = 7.1, 6.8, 1H), 1.73 (s, 3H), 1.02 (d, *J* = 7.1, 3H), 0.98 (d, *J* = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.6, 151.2, 148.6, 134.2, 128.9, 123.2, 122.8, 92.0, 35.2, 26.7, 21.7, 16.3, 15.6. IR: 3378, 3092, 2978, 2877, 1697, 1553, 1378, 1364, 1287, 1113, 809, 703. HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{17}N_3O_2Na^+$ 270.121 30; found 270.121 37.

*2-Isopropyl-1,2-dimethyl-5-oxo-4-(pyridin-4-yl)-2,5-dihydro-1H-imidazole 3-Oxide (**7l**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and 4-bromopyridine (213 mg, 1.1 mmol): 1 h; white solid (249 mg, quantitative). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 127−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (dd, *J* = 4.7, 1.6, 2H), 8.63 (dd, *J* = 4.7, 1.7, 2H), 3.10 (s, 3H), 2.41 (qq, *J* = 7.1, 6.8, 1H), 1.74 (s, 3H), 1.02 (d, *J* = 7.1, 3H), 0.98 (d, *J* = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 150.3, 132.6, 120.2, 92.3, 35.1, 26.6, 21.6, 16.2, 15.5. IR: 3110, 2970, 2939, 1696, 1555, 1399, 1365, 1319, 992, 829. HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{18}N_3O_2^+$ 248.139 35; found 248.139 34.

*4-(Anthracen-9-yl)-2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7m**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and 9-bromoanthracene (283 mg, 1.1 mmol): 3 h; yellow crystals (240 mg, 70%). Mp: 243−244 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.09−8.01 (m, 2H), 7.83−7.76 (m, 1H), 7.56−7.41 (m, 5H), 3.24 (s, 3H), 2.56 (qq, *J* = 7.0, 1H), 2.00 (s, 3H), 1.24 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 134.6, 131.5, 131.4, 131.2, 131.0, 130.0, 129.3, 129.1, 127.1, 127.0, 125.4, 125.4, 125.1, 124.7, 117.6, 93.1, 34.5, 26.8, 22.8, 16.6, 16.0. IR: 3047, 3025, 2971, 2870, 1691, 1557, 1366, 741. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.41; N, 8.09. Found: C, 76.36; H, 6.46; N, 8.28.

*2-Isopropyl-1,2-dimethyl-5-oxo-4-(pyridin-2-yl)-2,5-dihydro-1H-imidazole 3-Oxide (**7n**).* The title compound was prepared according to general procedure B from MiPNO (170 mg, 1.0 mmol) and 2-bromopyridine (174 mg, 1.1 mmol): 1.5 h; orange oil (238 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, *J* = 4.8, 1H), 8.43 (d, *J* = 7.9, 1H), 7.81 (td, *J* = 7.9, 1.8, 1H), 7.33 (ddd, *J* = 7.6, 4.9, 0.7, 1H), 3.11 (s, 3H), 2.44 (qq, *J* = 7.1, 6.8, 1H), 1.76 (s, 3H), 1.05 (d, *J* = 7.1, 3H), 1.02 (d, *J* = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.9, 150.1, 145.4, 136.2, 131.0, 124.5, 124.4, 92.1, 35.0, 26.6, 21.6, 16.2, 15.5. IR: 3573, 3060, 2968, 2879, 1698, 1549, 1361, 1283, 789. HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{17}N_3O_2Na^+$ 270.121 30; found 270.121 16.

*4-(4-(Dimethylamino)phenyl)-2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7o**).* The title compound was prepared according to general procedure A from MiPNO (170 mg, 1.0 mmol) and 4-bromo-*N*,*N*-dimethylaniline (225 mg, 1.1 mmol): 0.75 h; yellow solid (285 mg, 99%). An analytical sample was obtained by washing the solid with diethyl ether under sonication. Mp: 158−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, *J* = 9.3, 2H), 6.73 (d, *J* = 9.3, 2H), 3.07 (s, 3H), 3.04 (s, 6H), 2.42 (qq, *J* = 7.2, 6.8, 1H), 1.70 (s, 3H), 1.01 (d, *J* = 7.2, 3H), 0.95 (d, *J* = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.6, 151.6, 130.6, 129.0, 114.0, 111.0, 89.8, 40.0, 34.9, 26.5, 21.4, 16.4, 15.6. IR: 3370, 3085, 2968, 2923, 1693, 1603, 1521, 1357, 1303, 1216, 947, 824. Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.42; H, 8.02; N, 14.53. Found: C, 66.29; H, 7.87; N, 14.43.

*4-(4-Aminophenyl)-2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-Oxide (**7p**).* The title compound was prepared according to general procedure B from MiPNO (170 mg, 1.0 mmol) and 4-bromoaniline (190 mg, 1.1 mmol): 1 h; brown solid (200 mg, 77%). An analytical sample was obtained by washing the solid with diethyl ether under sonication. Mp: 146−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 8.0, 2H), 6.71 (d, *J* = 8.0, 2H), 3.06 (s, 3H), 2.41 (qq, *J* = 7.1, 6.7, 1H), 1.69 (s, 3H), 1.01 (d, *J* = 7.1, 3H), 0.95 (d, *J* = 6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 130.5, 129.3, 116.3, 114.0, 90.0, 34.9, 26.5, 21.4, 16.3, 15.6 (one quaternary C remained undetected). IR: 3453, 3344, 3217, 2974, 2879, 1683, 1627, 1601, 1558, 1508, 1353, 1294, 1187, 838. Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.43; H, 7.49; N, 15.92.

*(2S,2′S)-4,4′-(Pyridine-2,6-diyl)bis(2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-oxide) (**7q**).* The title compound was prepared according to general procedure B from (*S*)-MiPNO (175 mg, 1.1 mmol) and 2,6-dibromopyridine (120 mg, 0.5 mmol): 1 h; white solid (175 mg, 84%). Mp: 218−219 °C. $[\alpha]_D^{25}$ = +119° (*c* 1.97, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 7.9, 2H), 7.84 (t, *J* = 7.9, 1H), 3.03 (s, 6H), 2.37 (qq, *J* = 7.0, 6.7, 2H), 1.66 (s, 6H), 0.98 (d, *J* = 7.0, 6H), 0.93 (d, *J* = 6.7, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 145.9, 136.6, 130.8, 124.8, 92.1, 35.1, 26.6, 21.5, 16.4, 15.7. IR: 3069, 2960, 2933, 1710, 1566, 1357, 1229, 812. Anal. Calcd for $C_{21}H_{29}N_5O_4 \cdot {}^1/_3H_2O$: C, 59.84; H, 7.09; N, 16.62. Found: C, 60.00; H, 7.05; N, 16.39.

*(2S,2′S)-4,4′-(Thiophene-2,5-diyl)bis(2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1H-imidazole 3-oxide) (**7r**).* The title compound was prepared according to general procedure B from (*S*)-MiPNO (196 mg, 1.1 mmol) and 2,5-dibromothiophene (121 mg, 0.5 mmol): 1 h; the crude product was filtered over Celite, and **7r** was recrystallized from ethyl acetate; orange crystals (160 mg, 76%). Same experiment with general procedure A: 52% after 19 h. Mp: 203−204 °C. $[\alpha]_D^{25}$ = +120° (*c* 1.03, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 3.10 (s, 3H), 2.47−2.33 (m, 1H), 1.73 (s, 3H), 0.99 (d, *J* = 6.8, 3H), 0.97 (d, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 129.3, 129.3, 128.5, 91.0, 35.0, 26.4, 21.4, 16.1, 15.5. IR: 3113, 3094, 2971, 2939, 1703, 1560, 1427, 1353, 1236, 1126, 1045, 907, 821. Anal. Calcd for $C_{20}H_{28}N_4O_4S$: C, 57.13; H, 6.72; N, 13.33. Found: C, 57.12; H, 6.65; N, 13.47.

*2,2′-Diisopropyl-1,1′,2,2′-tetramethyl-5,5′-dioxo-2,2′,5,5′-tetrahydro-1H,1′H-[4,4′-biimidazole] 3-Oxide (**8**).* The title compound was prepared according to general procedure B, *except that* Pd and triphenylphosphine were omitted, starting from *rac*-MiPNO (170 mg, 1.0 mmol) and 4-bromotoluene (181 mg, 1.1 mmol): 1 h; white solid (153 mg, 95%, ca. 1/1 mixture of diastereomers). Mp: 201−202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 3H), 2.93 (s, 3H), 2.46−2.29 (m, 1H), 2.28−2.10 (m, 1H), 1.76 and 1.72 (s, 3H), 1.57 (s, 3H), 1.21 and 1.19 (d, *J* = 6.8, 3H), 1.11−1.05 (m, 6H), 0.65 and 0.64 (d, *J* = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.8, 127.8, 94.1, 91.2,

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35.0, 34.5, 26.6, 26.1, 22.0, 21.5, 17.6, 16.1, 15.5, 15.3. IR: 2970, 2939, 1698, 1557, 1434, 1381, 1256, 1119, 1082, 1051, 931, 711. Anal. Calcd for $C_{16}H_{26}N_4O_3$: C, 59.61; H, 8.13; N, 17.38. Found: C, 59.29; H, 7.98; N, 17.28.

*5-(Anthracen-9-yl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-Oxide (**9a**).* The title compound was prepared according to general procedure A from DMPO (48 mg, 0.42 mmol) and 9-bromoanthracene (148 mg, 0.55 mmol): 1.5 h; orange crystals (115 mg, 95%). Mp: 160−161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.03 (d, J = 8.1, 2H), 7.68 (d, J = 8.4, 2H), 7.57−7.41 (m, 4H), 3.12 (t, J = 7.2, 2H), 2.45 (t, J = 7.2, 2H), 1.73 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.0, 131.5, 129.4, 129.1, 128.9, 126.8, 125.4, 124.6, 124.5, 74.8, 33.6, 30.5, 25.9. IR: 3047, 2967, 2866, 1576, 1361, 1238, 1179, 888, 786, 731. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.02; H, 6.62; N, 4.85. Found: C, 82.82; H, 6.68; N, 4.89.

*5-(4-Methoxyphenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-Oxide (**9b**).* The title compound was prepared according to general procedure A from DMPO (56 mg, 0.50 mmol) and 4-bromoanisole (100 mg, 0.55 mmol): 1 h; white solid (93 mg, 85%). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 122−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 8.4, 2H), 6.95 (d, J = 8.4, 2H), 3.85 (s, 3H), 3.00 (t, J = 7.2, 2H), 2.09 (t, J = 7.2, 2H), 1.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.7, 137.4, 129.1, 122.8, 113.7, 75.18, 55.3, 31.9, 26.8, 25.6. IR: 3091, 2974, 2838, 1601, 1545, 1509, 1367, 1239, 1024, 831. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.82; N, 6.39. Found: C, 71.33; H, 8.08; N, 6.47. Data for the crystal structure have been deposited at the Cambridge Crystallographic Data Centre, reference no. CCDC 871603.

*5-(2-(Methoxycarbonyl)phenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-Oxide (**9c**).* The title compound was prepared according to general procedure A from DMPO (56 mg, 0.50 mmol) and methyl 2-bromobenzoate (113 mg, 0.55 mmol): 1.5 h; yellow oil (97 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 7.7, 1H), 7.54 (t, J = 7.5, 1H), 7.46−7.34 (m, 2H), 3.87 (s, 3H), 3.00 (t, J = 7.1, 2H), 2.18 (t, J = 7.1, 2H), 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 139.0, 131.4, 131.4, 130.2, 129.8, 129.2, 128.5, 74.4, 52.5, 32.8, 28.4, 25.2. IR: 3063, 2974, 2949, 1723, 1558, 1362, 1290, 113, 916, 722. HRMS (ESI$^+$): m/z calcd for $C_{14}H_{17}NO_3Na^+$ 270.110 06; found 270.110 03.

*5-(4-(Methoxycarbonyl)phenyl)-2,2-dimethyl-3,4-dihydro-2H-pyrrole 1-Oxide (**9d**).* The title compound was prepared according to general procedure A (run performed with 5 mol % Pd/PPh_3) from DMPO (56 mg, 0.5 mmol) and methyl 4-bromobenzoate (124 mg, 0.6 mmol): 1 h; white solid (113 mg, 90%). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 102−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, J = 8.0, 2H), 8.09 (d, J = 8.0, 2H), 3.93 (s, 3H), 3.07 (t, J = 7.3, 2H), 2.15 (t, J = 7.3, 2H), 1.50 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 136.8, 133.7, 130.7, 129.6, 126.8, 76.3, 52.2, 31.9, 26.7, 25.6. IR: 3094, 2984, 2949, 1714, 1534, 1364, 1274, 1102, 1016, 855, 767. Anal. Calcd for $C_{14}H_{17}NO_3 \cdot {}^1/_3H_2O$: C, 66.39; H, 7.03; N, 5.53. Found: C, 66.36; H, 6.93; N, 5.54.

*3,3-Dimethyl-1-(p-tolyl)-3,4-dihydroisoquinoline 2-Oxide (**10a**).* The title compound was prepared according to general procedure A from **3** (175 mg, 1.0 mmol) and 4-bromotoluene (187 mg, 1.1 mmol): 1.5 h; white solid (195 mg, 74%). An analytical sample was obtained by recrystallization from *tert*-butyl methyl ether. Mp: 110−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.6, 2H), 7.30−7.18 (m, 4H), 7.14 (t, J = 7.2, 1H), 6.85 (d, J = 7.8, 1H), 3.15 (s, 2H), 2.40 (s, 3H), 1.50 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 138.7, 130.9, 130.7, 130.0, 129.1, 128.9, 128.3, 127.5, 126.9, 126.4, 66.9, 41.9, 24.7, 21.5. IR: 3050, 3031, 3005, 2972, 2939, 1479, 1235. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.26; H, 7.20; N, 4.95. Data for the crystal structure have been deposited at the Cambridge Crystallographic Data Centre, reference no. CCDC 871604.

*3,3-Dimethyl-1-(3,4,5-trimethoxyphenyl)-3,4-dihydroisoquinoline 2-Oxide (**10b**).* The title compound was prepared according to general procedure A from **3** (175 mg, 1.0 mmol) and 1-bromo-3,4,5-trimethoxybenzene (272 mg, 1.1 mmol): 1.5 h; orange oil (330 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−7.12 (m, 3H), 6.89 (d, J = 7.6, 1H), 6.72 (s, 1H), 3.90 (s, 2H), 3.84 (s, 3H), 3.17 (s, 1H), 2.04 (s, 1H), 1.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.2, 140.9, 138.5, 130.9, 130.6, 128.5, 127.6, 127.4, 127.0, 126.5, 107.4, 67.2, 60.9, 56.3, 41.9, 24.7. IR: 3063, 2965, 2933, 2834, 1584, 1451, 1410, 1355, 1233, 1120, 1002, 761. HRMS (ESI$^+$): m/z calcd for $C_{20}H_{23}NO_4Na^+$ 364.151 93; found 364.151 89.

*1-(4-(Methoxycarbonyl)phenyl)-3,3-dimethyl-3,4-dihydroisoquinoline 2-Oxide (**10c**).* The title compound was prepared according to general procedure A from **3** (85 mg, 0.50 mmol) and methyl 4-bromobenzoate (118 mg, 0.55 mmol); 2 h; colorless crystals (117 mg, 76%). Mp: 128−129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18−8.10 (m, 2H), 7.63−7.56 (m, 2H), 7.31−7.20 (m, 2H), 7.20−7.10 (m, 1H), 6.75 (d, J = 7.8, 1H), 3.95 (s, 3H), 3.18 (s, 2H), 1.52 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 140.1, 136.9, 130.8, 130.3, 130.3, 130.1, 129.5, 128.7, 127.7, 127.1, 125.9, 67.4, 52.2, 41.8, 24.6. IR: 3183, 3050, 2974, 2889, 1711, 1660, 1481, 1363, 1278, 1177, 1110, 761. HRMS (ESI$^+$): m/z calcd for $C_{19}H_{19}NO_3Na^+$ 332.125 71; found 332.125 33.

Preparation of Deuterated MiPNO: 4-Deuterio-2-isopropyl-1,2-dimethyl-5-oxo-2,5-dihydro-1*H*-imidazole 3-Oxide (*d*-1). In a CEM Discover 10 mL vial, racemic MiPNO **1** (0.543 g, 3.2 mmol) was dissolved in 1 mL of d_6-acetone. The sealed vial was heated at 140 °C for 30 min under microwave irradiation in a CEM Discover S-class apparatus (external surface sensor, maximum power 140 W, 2 min to reach set temperature, maximum pressure 6 bar), and then the solvent was evaporated to yield 0.545 g of pure *d*-**1** (pale yellow solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (s, 3H), 2.31 (hept, J = 7.0, 1H), 1.67 (s, 3H), 1.01 (d, J = 7.1, 3H), 0.99 (d, J = 6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.55, 124.48 (t, J = 33), 93.88, 34.16, 26.19, 21.27, 15.89, 15.25. IR: 2972, 2803, 2300 (ν_{C-D}), 1701, 1542, 1265. HRMS (ESI$^+$): m/z calcd for $C_8H_{14}DN_2O_2^+$ 172.119 08; found 172.119 18.

Kinetic Isotope Effect Experiments. Two experiments were conducted separately, one with nitrone **1** (1 mmol) and one with the deuterated analogue *d*-**1** (1 mmol). Both reactions were performed according to general procedure A, using 4-bromotoluene **6** and $PdCl_2(PPh_3)_2$ (0.2 mol %). The corresponding rate constants k_H and k_D were thus determined, and a k_H/k_D ratio of 3 was found.[38]

Ab Initio Calculations. These calculations were performed using the same functional and basis set as Gorelsky and Fagnou[26] in order to have comparable data and accordingly a fruitful discussion. Density functional theory (DFT) calculations were performed using the Gaussian 03 program.[42] The structures of all species were optimized at the B3LYP exchange-correlation (XC) level[43,44] using the mixed double-/triple-ζ basis set (DZVP[45] on Pd and TZVP[46] on all other atoms). Tight SCF convergence criteria (10^{-8} au) were used for all calculations. Harmonic frequency calculations with the analytic evaluation of force gradients were used to determine the nature of the stationary points i.e. minima and transition states. See the Supporting Information for detailed results.

Synthesis of Enantiopure α-Methyl α-Arylglycine Esters. *General Procedure. Methylation.* The aryl nitrone **7** was dissolved in anhydrous THF (20 mL) and cooled to 0 °C, and methylmagnesium chloride in THF (22 wt %, 3 equiv) was added. The mixture was then kept at room temperature. After 1 h, a saturated aqueous solution of NH_4Cl (15 mL) was added, followed by ethyl acetate (60 mL) and water (15 mL). The aqueous layer was separated and extracted with ethyl acetate (60 mL). The gathered organic layers were washed with brine (60 mL), dried over anhydrous $MgSO_4$, and filtered. The solvents were removed under reduced pressure to furnish the desired hydroxylamine product **11**, which was used in the next step without further purification.

Reduction. The crude hydroxylamine **11** was suspended in glacial acetic acid (20 mL), and zinc dust (30 equiv) was added. The reaction mixture was heated for 3−7 h at 80 °C under sonication. The excess zinc was then filtered off and rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure. A saturated aqueous solution of Na_2CO_3 (30 mL) was added and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and evaporated under reduced pressure to yield the

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imidazolidinone **13**, which was used in the next step without further purification.

Hydrolysis. In a 20 mL pressure vessel were introduced the imidazolidinone **13** and a 6 N aqueous solution of hydrochloric acid (5 mL). The reaction mixture was heated for the indicated time at 160 °C. After evaporation under reduced pressure, an equimolar mixture of amino acid hydrochloride **14** and methylamine hydrochloride was obtained, which was directly used in the next step.

Esterification. The mixture of amino acid hydrochloride **14** and methylamine hydrochloride was dissolved in MeOH (10 mL). Thionyl chloride (1.5 mL) was added at room temperature without cooling, and then the reaction mixture was heated for 3 h at reflux. The solvent was removed under reduced pressure, and ethyl acetate (10 mL) was added. The organic layer was washed with a saturated aqueous solution of Na_2CO_3 (10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent cyclohexane/AcOEt 10/0 to 0/10) to yield the amino ester **12**.

*(R)-Methyl 2-Amino-2-p-tolylpropanoate (**12a**).* The title compound was prepared according to the general procedure from **7a** (1.136 g, 4.4 mmol): yellow oil (560 mg; 66%). $[\alpha]_D^{25} = -18.1°$ (*c* 5.1, MeOH) (lit.[47] $[\alpha]^{20}_D = -19.8°$ (*c* 0.5, MeOH)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.3, 2H), 7.15 (d, *J* = 8.0, 2H), 3.70 (s, 3H), 2.33 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.8, 141.3, 137.1, 129.2, 125.0, 60.5, 52.6, 27.5, 21.0. HRMS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{16}NO_2^+$ 194.117 56; found 194.117 48.

Characterization Data for Intermediates. (2*S*,5*R*)-1-Hydroxy-2-isopropyl-2,3,5-trimethyl-5-*p*-tolyl-imidazolidin-4-one (**11a**): pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.2, 2H), 7.16 (d, *J* = 8.0, 2H), 4.37 (s, 1H), 2.81 (s, 3H), 2.33 (s, 3H), 1.92 (hept, *J* = 6.8, 1H), 1.72 (s, 3H), 1.57 (s, 3H), 1.10 (d, *J* = 6.9, 3H), 0.84 (d, *J* = 6.6, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 140.3, 137.0, 129.9, 126.6, 84.2, 69.3, 36.3, 25.8, 21.2, 20.3, 18.3, 18.0, 17.1. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.54; H, 8.76; N, 10.14. Found: C, 69.59; H, 8.85; N, 10.13. Data for the crystal structure have been deposited at the Cambridge Crystallographic Data Centre, reference no. CCDC 871605.

(2*S*,5*R*)-2-Isopropyl-2,3,5-trimethyl-5-*p*-tolyl-imidazolidin-4-one (**13a**): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.2, 2H), 7.12 (d, *J* = 8.0, 2H), 2.79 (s, 3H), 2.31 (s, 3H), 1.85 (hept, *J* = 6.8, 1H,), 1.75 (broad s, 1H), 1.64 (s, 3H), 1.47 (s, 3H), 0.96 (d, *J* = 6.8, 3H), 0.54 (d, *J* = 6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6, 141.8, 136.3, 128.7, 125.8, 78.8, 63.1, 35.0, 31.4, 26.1, 25.7, 21.0, 16.9, 16.8.

(*R*)-2-Amino-2-*p*-tolylpropanoic acid hydrochloride (**14a**). ^{1}H NMR (400 MHz, D_2O): δ 7.33 (d, *J* = 8.1, 2H), 7.22 (d, *J* = 8.0, 2H), 2.21 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, D_2O): δ 173.5, 140.4, 132.2, 130.0, 125.6, 61.6, 21.1, 20.2.

*(R)-Methyl 2-Amino-2-(4-hydroxyphenyl)propanoate (**12b**).* The title compound was prepared according to the general procedure from **7b** (1.232 g, 4.5 mmol): yellow oil (421 mg, 48%). $[\alpha]_D^{25} = -36°$ (*c* 0.4, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7, 2H), 6.69 (d, *J* = 8.8, 2H), 3.70 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 155.8, 135.1, 126.5, 115.8, 60.2, 52.8, 26.9. HRMS (ESI$^+$): *m*/*z* calcd for $C_{10}H_{14}NO_3^+$ 196.096 82; found 196.096 74.

Characterization Data for Intermediates. (2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-(4-methoxyphenyl)-2,3,5-trimethylimidazolidin-4-one (**11b**): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.9, 2H), 6.88 (d, *J* = 8.9, 2H), 4.46 (s, 1H), 3.79 (s, 3H), 2.81 (s, 3H), 1.90 (hept, *J* = 6.7, 1H), 1.70 (s, 3H), 1.56 (s, 3H), 1.10 (d, *J* = 6.8, 3H), 0.84 (d, *J* = 6.6, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 158.9, 135.5, 127.9, 113.7, 84.1, 69.1, 55.4, 36.3, 25.8, 20.3, 18.3, 17.9, 17.1. HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{25}N_2O_3^+$ 293.185 97; found 293.185 82.

(2*S*,5*R*)-2-Isopropyl-5-(4-methoxyphenyl)-2,3,5-trimethylimidazolidin-4-one (**13b**): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.9, 2H), 6.84 (d, *J* = 8.9, 2H), 3.77 (s, 3H), 2.79 (s, 3H), 1.84 (hept, *J* = 6.7, 1H), 1.78 (broad s, 1H), 1.63 (s, 3H), 1.46 (s, 3H), 0.96 (d, *J* = 6.7, 3H), 0.54 (d, *J* = 6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7, 158.5, 137.1, 127.2, 113.4, 78.9, 63.0, 55.3, 35.1, 31.5, 26.2, 25.8, 17.0, 16.9.

(*R*)-2-Amino-2-(4-hydroxyphenyl)propanoic acid hydrochloride (**14b**). ^{1}H NMR (400 MHz, D_2O): δ 7.02 (d, *J* = 8.8, 2H), 6.57 (d, *J* = 8.8, 2H), 1.59 (s, 3H). ^{13}C NMR (101 MHz, D_2O): δ 173.1, 156.5, 127.3, 127.1, 126.5, 115.8, 61.1, 20.8.

*(S)-Methyl 2-Amino-2-(pyridin-3-yl)propanoate (**12k**).* The title compound was prepared according to the general procedure from **7k** (1.018 g, 4.1 mmol): yellow oil (317 mg, 43%). $[\alpha]_D^{25} = +32°$ (*c* 1.9, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, *J* = 2.2, 1H), 8.52 (dd, *J* = 4.8, 1.6, 1H), 7.85 (ddd, *J* = 8.0, 2.2, 1.6, 1H), 7.27 (dd, *J* = 8.0, 4.8, 1H), 3.73 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.9, 148.7, 147.3, 139.5, 133.1, 123.1, 59.4, 52.8, 27.6. HRMS (ESI$^+$): *m*/*z* calcd for $C_9H_{13}N_2O_2^+$ 181.097 15; found 181.097 14.

Characterization Data for Intermediates. (2*R*,5*S*)-1-Hydroxy-2-isopropyl-2,3,5-trimethyl-5-pyridin-3-ylimidazolidin-4-one (**11k**): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74−9.31 (br m, 1H), 8.72 (br s, 1H), 8.64−8.35 (br m, 1H), 8.12 (br. d, *J* = 7.8, 1H), 7.48−7.28 (br m, 1H), 3.82 (s, 3H), 2.81 (s, 3H), 1.93 (hept, *J* = 6.8, 1H), 1.72 (s, 3H), 1.64 (s, 3H), 1.13 (d, *J* = 6.9, 3H), 0.82 (d, *J* = 6.5, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 147.3, 147.2, 139.6, 136.0, 123.6, 84.5, 68.2, 36.1, 25.8, 21.6, 18.8, 17.3, 17.2. HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_{22}N_3O_2^+$ 264.170 65; found 264.170 73.

(2*R*,5*S*)-2-Isopropyl-2,3,5-trimethyl-5-pyridin-3-ylimidazolidin-4-one (**13k**): colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (d, *J* = 2.2, 1H), 8.46 (dd, *J* = 4.6, 1.5, 1H), 8.17 (ddd, *J* = 8.2, 2.2, 1.5, 1H), 7.20 (dd, *J* = 8.2, 4.6, 1H), 2.78 (s, 3H), 1.79 (hept, *J* = 6.7, 1H), 1.65 (s, 3H), 1.60 (broad s, 1H), 1.50 (s, 3H), 0.97 (d, *J* = 6.7, 3H), 0.47 (d, *J* = 6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 148.2, 148.1, 140.2, 133.8, 122.8, 79.2, 61.9, 35.2, 32.2, 26.5, 25.8, 17.0, 16.9.

(*S*)-2-Amino-2-(pyridin-3-yl)propanoic acid hydrochloride (**14k**). ^{1}H NMR (400 MHz, D_2O): δ 8.80 (d, *J* = 2.3, 1H), 8.65 (d, *J* = 5.6, 1H), 8.53 (ddd, *J* = 8.4, 2.3, 1.3, 1H), 7.95 (dd, *J* = 8.4, 5.9, 1H), 1.84 (s, 3H). ^{13}C NMR (101 MHz, D_2O): δ 170.3, 144.8, 142.3, 139.8, 135.6, 128.0, 59.9, 21.7.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, tables, and CIF files giving ^{1}H and ^{13}C NMR spectra for all new compounds, determination of optical purity for **12a**, KIE experiments, results of DFT calculations, and crystallographic data for compounds **7d**, **9b**, **10a**, and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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