CHAPTER 1

Development of a Nickel-Catalyzed N–N Cross-Coupling for the Synthesis of Hydrazides †

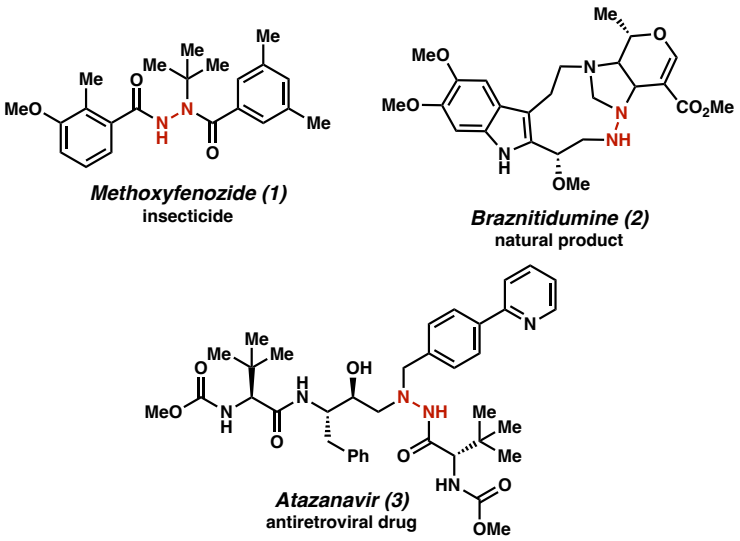
1.1 INTRODUCTION

Nitrogen–nitrogen bonds are prevalent motifs in biologically active small molecules and natural products and feature prominently in pharmaceutical and agricultural compounds (Figure 1.1).[1-5] Moreover, a variety of druglike heterocyclic scaffolds can be accessed from hydrazines and hydrazides.[2,6] The synthesis of N–N containing compounds typically entails a linear, stepwise process of hydrazine protection and derivatization, which hampers rapid access to highly-substituted products.[2] Improved methods for the convergent cross-coupling of two complex nitrogen-containing compounds would not only simplify the preparation of known hydrazines and hydrazides, but also accelerate access to

† This work was performed in collaboration with Dr. Vaishnavi N. Nair, Kimberly R. Sharp, Dr. Trevor D. Lohrey, Dr. Sara E. Dibrell, Dr. Tejas K. Shah, Dr. Martin J. Walsh, Dr Sarah E. Reisman and Dr. Brian M. Stoltz. Portions of this chapter have been reproduced with permission from Nair, V. N.; Sharp, K. S.; Lohrey, T. D.; Dibrell, S. E.; Shah, T. K.; Walsh, M. J.; Reisman, S. E.; Stoltz, B. M. Development of a Nickel-Catalyzed N–N Coupling for the Synthesis of Hydrazides. *J. Am. Chem. Soc*. **2023**, *145*, 15071–15077.

new chemical space. For these reasons, new N–N bond forming reactions are of high value to the synthetic chemistry community.

Figure 1.1 *Compounds featuring N–N bonds.*



1.2 N–N BOND FORMING STRATEGIES

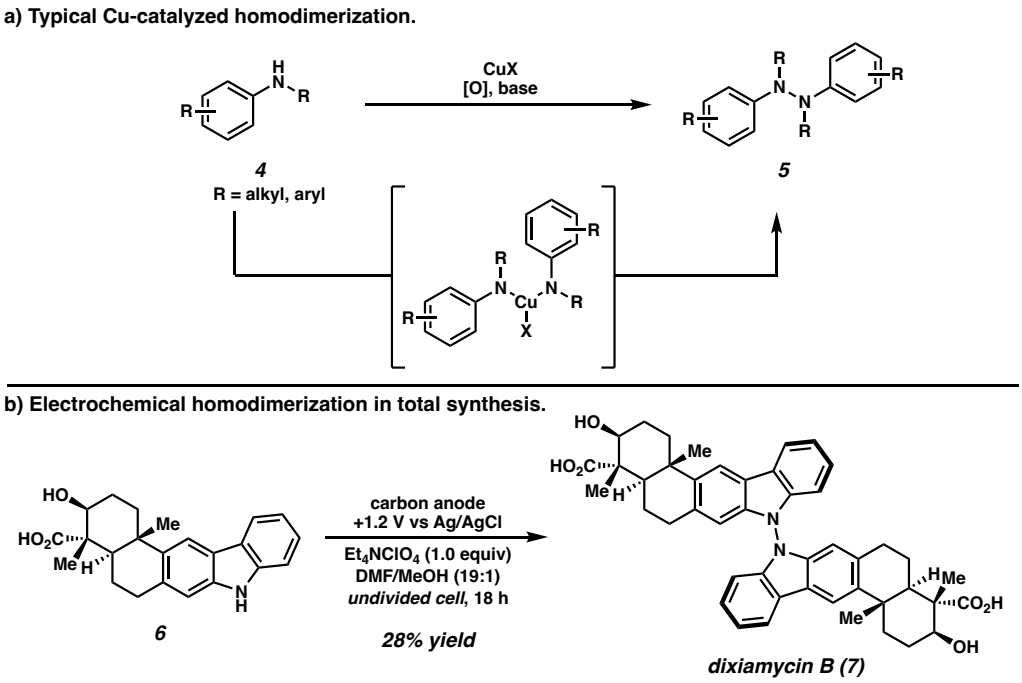
N–N cross-couplings can generally be broken into three categories: oxidative, reductive, and electrophilic. A brief discussion of the existing methodologies disclosed at the time we began this investigation is disclosed *vide infra.*

1.2.1 Oxidative N–N Cross-Couplings

Due to the difficult of chemically differentiating two amine coupling partners, oxidative N–N bond forming strategies are largely limited to the homodimerization of anilines or carbazoles.[2] Aside from the use of stoichiometric oxidizing reagents[7]—such as Ag_2O, $KMnO_4$, or $Na_2Cr_2O_7$—copper-catalyzed or electrochemical methods are the predominate technologies for N–N dimerization (Figure 1.2).[8,9] Cu-catalyzed dehydrogenative dimerizations typically invoke a Cu(I)/Cu(III) catalytic cycle and

necessitate the inclusion of an exogenous oxidant (Figure 1.2a).[8] The first electrochemical oxidative N–N dimerization was disclosed in 2014 from Baran and coworkers for the total synthesis of dixiamycin B (Figure 1.2b).[9a] Since this seminal report, several other electrochemical N–N couplings have been developed.[9b,c]

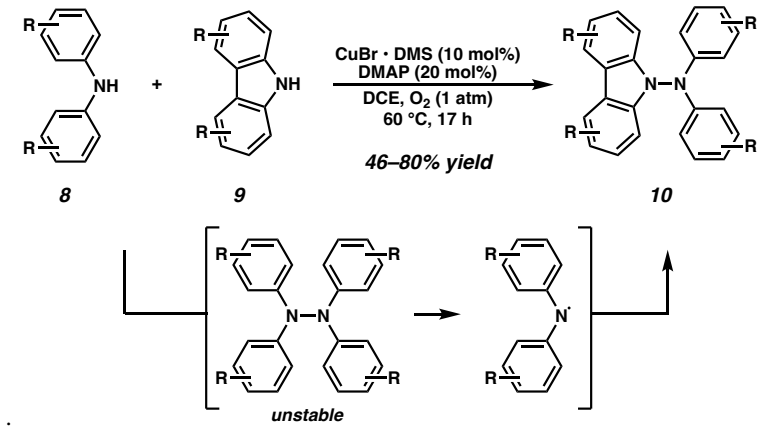
Figure 1.2 *Cu-catalyzed and electrochemical N–N homodimerizations.*



Despite the inherent challenges, cross-selective oxidative N–N couplings have also been achieved.[10] In 2018, Stahl and coworkers published an impressive Cu-catalyzed cross-selective coupling of biaryl anilines and carbazoles (Figure 1.3).[10a] Mechanistically, they propose the cross-selectivity originates from the kinetic dimerization of biaryl anilines to form tetra-arylhydrazines. Under the reaction conditions, these tetra-arylhydrazine intermediates were found to be unstable and underwent homolytic cleavage to deliver reactive aminyl radicals that could then undergo bond formation with a carbazole, delivering the thermodynamically preferred cross-coupled product. These assertions are

supported by ^{1}H NMR and EPR studies, which confirm the formation and disappearance of a tetra-arylhydrazine derived from dimerization of **8** and the presence of aminyl radicals in the reaction mixture, respectively.

Figure 1.3 *Cross-selective oxidative N–N couplings.*



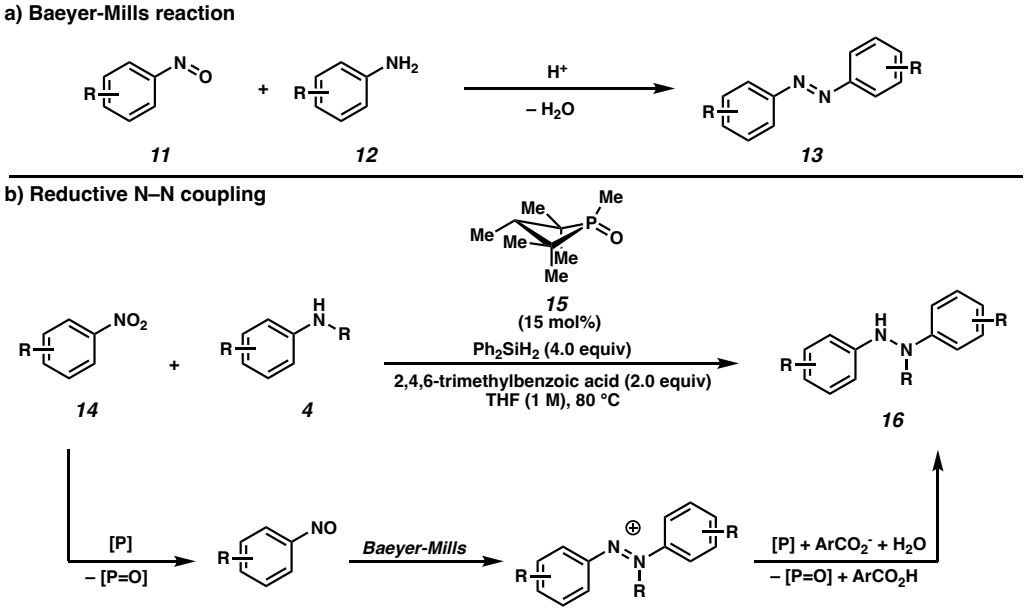
Outside of this mechanistic paradigm, other cross-selective N–N couplings typically rely upon stoichiometric biasing to achieve high yields of heterocoupled hydrazine. The development of more robust cross-selective oxidative couplings remains an ongoing challenge, and with the exception of one report,[11] these transformations are limited to diarylamine and carbazole coupling partners.

1.2.2 Reductive N–N Cross-Couplings

Reductive N–N cross-coupling strategies are derived from the Baeyer-Mills reaction, first developed in 1874, in which an amine is condensed with an aryl nitroso in the presence of catalytic acid to afford an azo product (Figure 1.4a).[12a] In collaboration with Merck, the Radosevich group developed a method expanding upon the Baeyer–Mills reaction,[12b] whereby commercially available aryl nitro compounds can be reduced *in situ* to the corresponding nitroso, followed by a Baeyer–Mills condensation and further reduction of the azo by the phosphine catalyst to generate hydrazine products in a one-pot

transformation (Figure 1.4b). Reduction of the phosphine oxide catalyst to turnover the catalytic cycle is mediated by stoichiometric amounts of a silane additive. While reductive N–N coupling strategies are generally more amenable to the synthesis of nonsymmetrical hydrazine derivatives, to date, this strategy is still limited to aryl substrates.

Figure 1.4 *Reductive N–N cross-coupling.*

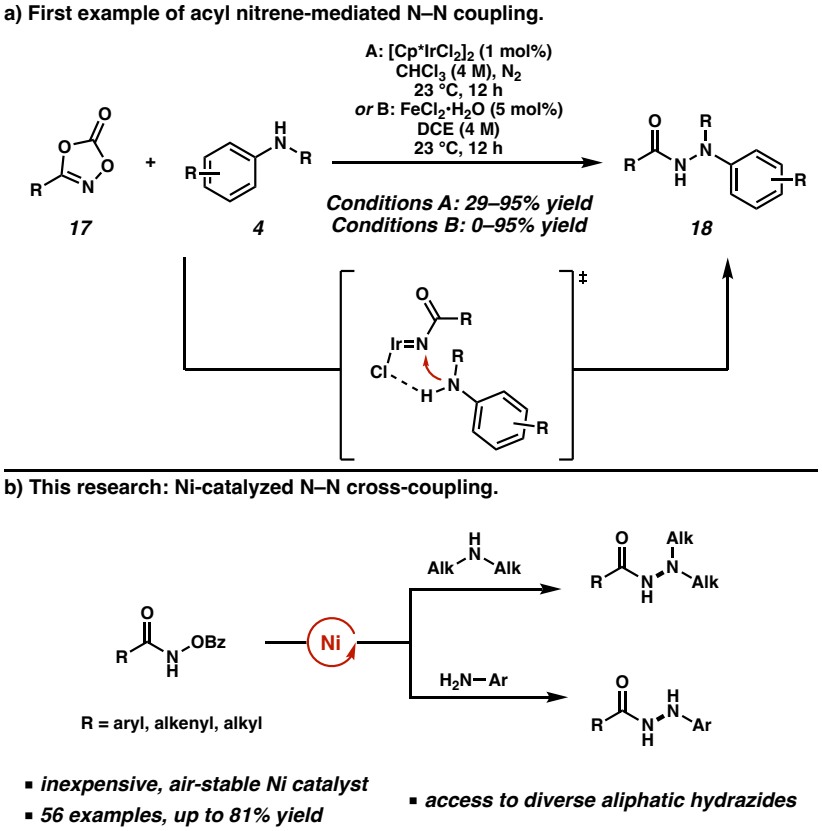


1.2.3 Electrophilic N–N Cross-Couplings

Electrophilic N–N forming strategies encompass reactions utilizing either umpolung aminating reagents, like chloramines,[13] or nitrenoid precursors, such as dioxazolones, hydroxamic esters and azides.[14] Transition metal-catalyzed nitrene insertion chemistry has gained significant attention as a potential tool for N–N bond formation. In 2021, the Chang group reported the first N–N coupling for the formation of hydrazides utilizing either iron or iridium catalysis (Figure 1.5a).[15] Mechanistically, Chang proposed the reaction initiates via decarboxylation of the dioxazolone to form a metal-bound acyl nitrene that is subject to outer-sphere attack by a secondary aniline to deliver the hydrazide product. Only primary and secondary aliphatic dioxazolones and secondary aniline

nucleophiles were demonstrated to be compatible with this chemistry. Moreover, reaction concentrations of 4 M were required to abate undesired acyl nitrene rearrangement. Although the required reaction concentrations prove environmentally friendly, they greatly limit the scope of this transformation with respect to the solubility of more challenging coupling partners.

Figure 1.5 *Acyl nitrene-mediated N–N bond formation.*



While the method developed by Chang and Chen enables efficient coupling of a wide array of aliphatic electrophiles and secondary anilines, other classes of amine nucleophiles—most notably aliphatic amines—remain incompatible. As part of an industrial-academic collaboration aimed at developing new modular approaches for N–N coupling, we pursued the development of a new acyl nitrene-mediated N–N cross-coupling

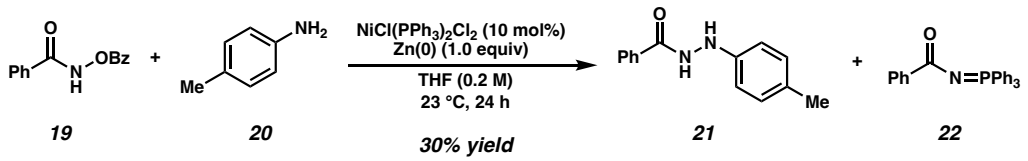
with the goal of accessing diverse hydrazides from both aryl and aliphatic coupling partners (Figure 1.5b).

1.3 REACTION OPTIMIZATION

1.3.1 Initial Reaction Discovery

After a wide survey of potential transition metal catalysts, we were pleased to discover that reaction with N-(benzoyloxy)benzamide **19** and p-toluidine (**20**) in the presence of Zn(0) and catalytic $Ni(PPh_3)_2Cl_2$ resulted in a 30% yield of the desired hydrazide product **21** (Table 1.1). Iminophosphorane **22** was observed as a side product of this reaction, which is suggestive of the intermediacy of a nitrenoid species.[16] Surprisingly, we observed no urea formation, indicating robust stabilization of the hydroxamate against Lossen-type rearrangement.[17]

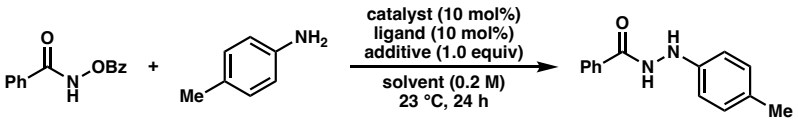
Figure 1.6 *Initial reaction discovery.*



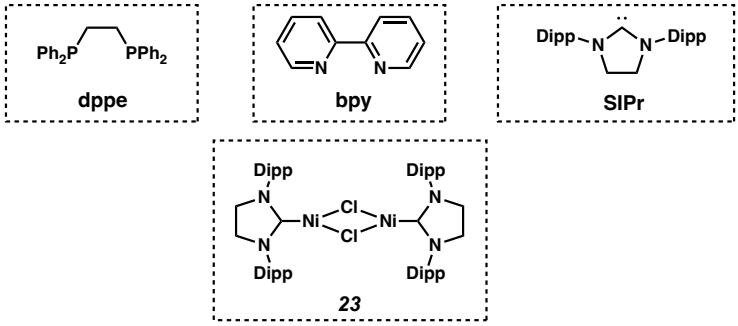
In the absence of Zn, poor conversion was observed, providing a similar 30% yield of **21** only after extended reaction time and with significant unconsumed starting material (Table 1.1). We postulate that Ni(II) may be effecting the desired transformation via an alternative mechanism, such as Lewis acid activation. Use of $Ni(cod)_2$ yielded no reaction, suggesting that a Ni(0) species is not capable of initiating the catalytic cycle. Use of bidentate ligands dppe or bpy resulted in a complete loss of reactivity; however, strongly σ-donating N-heterocyclic carbene (NHC) SIPr afforded a 32% yield of **21** with no observed nitrene transfer to the ligand. Use of alternative NHC ligands resulted in

diminished yields. Given the stark difference in reactivity observed between monodentate and bidentate ligands, we hypothesized that the catalyst must be coordinatively unsaturated to effect the desired chemistry.

Table 1.1 *Initial reaction optimization.*[a]



entry	catalyst	ligand	additive	yield (%)
1	$Ni(PPh_3)_2Cl_2$	—	Zn	30
2	$Ni(PPh_3)_2Cl_2$	—	—	30[b]
3	$Ni(cod)_2$	PPh_3	—	0
4	$NiCl_2$·glyme	dppe	Zn	0
5	$NiCl_2$·glyme	bpy	Zn	0
6	$NiCl_2$·glyme	SIPr	Zn	32
7	*23*	—	—	0
8	*23*	—	Zn	0
9	$NiCl_2$·glyme	SIPr	$PhSiH_3$	34-82[c]



[a] Reactions performed on 0.05 mmol scale. [b] 72 h. [c] Excess **19** (1.5 equiv). [d] Dipp = 2,6-diisopropylphenyl.

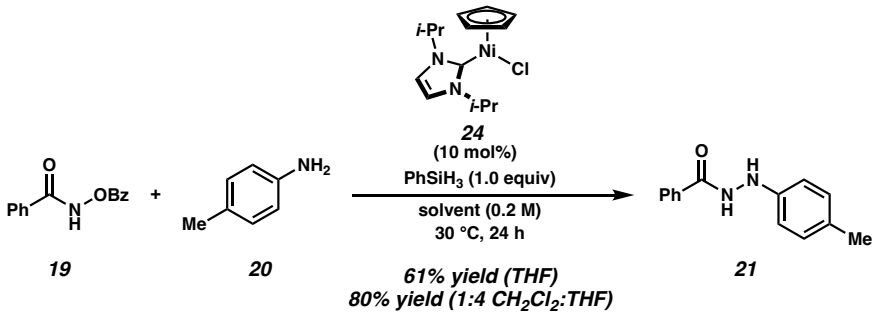
Having identified a more suitable ligand, we reexamined the role of Zn as an additive. Previous reports have demonstrated the ability of Ni(I) dimer **23** to form a bridged Ni-nitrene; we considered the possibility that Zn-mediated reduction may be forming a similar species in situ.[18] Unfortunately, examination of **23** both with and without Zn resulted in no reactivity, leading us to hypothesize a mononuclear Ni(I) complex as the active catalyst.[19] While further exploration of reductants ultimately revealed that phenylsilane improved reactivity, yields were highly variable across batches of starting

materials and reagents. Despite an extensive effort to assess the purity of our reagents, we were ultimately unable to identify the cause of irreproducibility.

1.3.2 Revised Catalyst Framework

Aiming to achieve more consistent results, we explored well-defined Ni complexes and were intrigued by reports of NHC-ligated Ni(II) half-sandwich catalysts, which have recently been utilized for catalytic oxidative N–N coupling of ammonia to dinitrogen.[20-23] These easily synthesized and air-stable complexes have been implicated to undergo hydride-mediated reduction to Ni(I),[20,21] and the cyclopentadienyl (Cp) ligand has been suggested to undergo surprisingly facile equilibration among η^5, η^3, and η^1 binding modes, which we imagined could satisfy the previously observed requirement for a coordinatively unsaturated catalyst.[20,22]

Figure 1.7 *Revised catalyst.*[a]



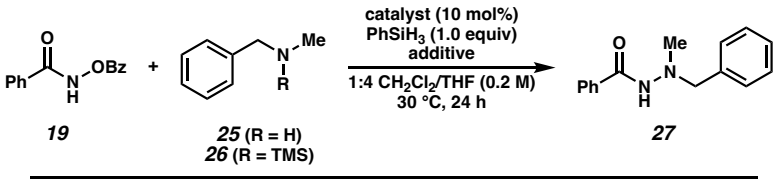
[a] Reactions performed on 0.05 mmol scale.

Excitingly, use of **24** generated a 61% yield of the desired product, which was found to be reproducible across all batches of starting materials, catalyst, and silane (Figure 1.7). Further exploration of solvent effects revealed that a 1:4 mixture of CH_2Cl_2/THF further improved the yield to 80%.

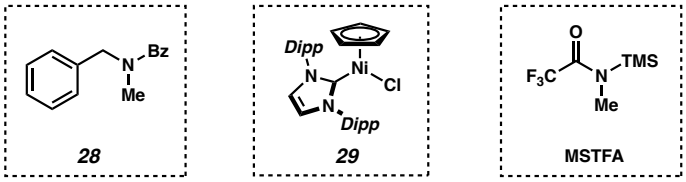
1.3.3 Aliphatic Amine Nucleophiles

Having identified optimal conditions for aryl amine nucleophiles, we sought to expand the scope of the transformation to aliphatic amines. Reaction with unprotected secondary aliphatic amine **25** resulted in significant *O*-to-*N* benzoyl transfer from the hydroxamate to the amine, yielding product **28** and minimal formation of the desired hydrazide (Table 1.2).

Table 1.2 *Optimization of aliphatic amine nucleophiles.*[a]



entry	catalyst	nucleophile	additive	yield (%)
1	*24*	*25*	–	6[b]
2	*24*	*26*	–	27[b]
3	*24*	*26* (1.1 equiv)	–	43
4	*24*	*26* (1.5 equiv)	–	57
5	*29*	*26* (1.5 equiv)	–	69
6	*29*	*25* (1.5 equiv)	MSTFA (1.5 equiv)	59



[a] Reactions performed on 0.05 mmol scale. [b] Excess **19** (1.5 equiv). [c] Dipp = 2,6-diisopropylphenyl.

Surmising that silylation of these more challenging nucleophiles might serve as a transient protection strategy until either transmetallation with the catalyst or benzoate-mediated desilylation, we explored reactivity with silylamine **26**.[24] To our satisfaction, reaction of **26** with excess **19** afforded the desired product **27** in 27% yield. Use of excess amine was found to improve the product distribution, with 1.5 equiv **26** resulting in a 57% yield. Gratifyingly, use of IPr-substituted catalyst **29** afforded a 69% yield of the desired hydrazide **27**, minimizing formation of undesired side-product **28**. We posit the *O*-to-*N*

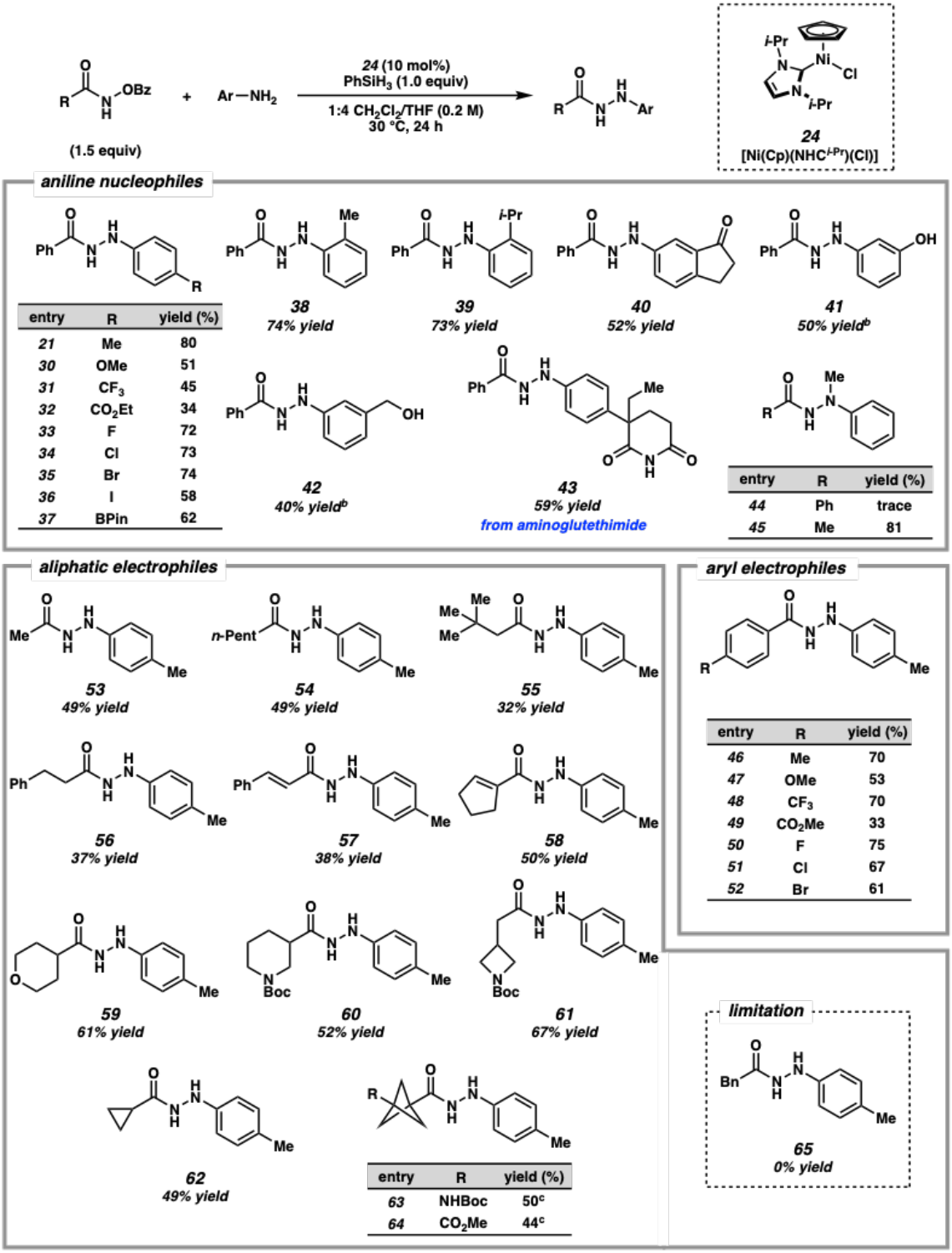
benzoyl transfer may be accelerated within the coordination sphere of the catalyst, and that increasing steric hinderance around the metal center may block this competing pathway. Although satisfied with the efficiency of these conditions utilizing pre-silylated amines, a more operationally expedient route was developed via *in situ* silylation of amine **25** with MSTFA, affording 59% yield of product in a single synthetic step.

1.4 SUBSTRATE SCOPE

With optimized conditions in hand, we examined the scope of compatible coupling partners. An electron-rich aniline derivative provided the desired product in good yields (**30**), while electron-deficient amines gave slightly diminished yields (**31** and **32**). Halide substituents on the arene (**33**–**36**) were well tolerated under the reaction conditions and showed no signs of protodehalogenation. Functional handles for further derivatization, such as an aryl iodide (**36**) and boronic ester (**37**), remained intact under the reaction conditions. Sterically hindered *ortho*-substituted aniline derivatives afforded products **38** and **39** in good yields. Amines bearing unprotected ketone (**40**) and hydroxyl (**41** and **42**) moieties were also found to be compatible. Moreover, aminoglutethimide, a drug used in the treatment of Cushing's disease,[25] was efficiently derivatized to the corresponding hydrazine (**43**), highlighting the potential use of this method for late-stage functionalization of complex molecules.

Although exploration of a secondary aniline in the reaction with **19** yielded only trace hydrazide (**44**), we observed an 81% yield of product when using *N*-(benzoyloxy)acetamide as an electrophile (**45**). We postulate the difference in reactivity between aryl and aliphatic hydroxamates with secondary anilines may reveal the balance

Figure 1.8 *Scope of aniline nucleophiles with various hydroxamates.*[a]



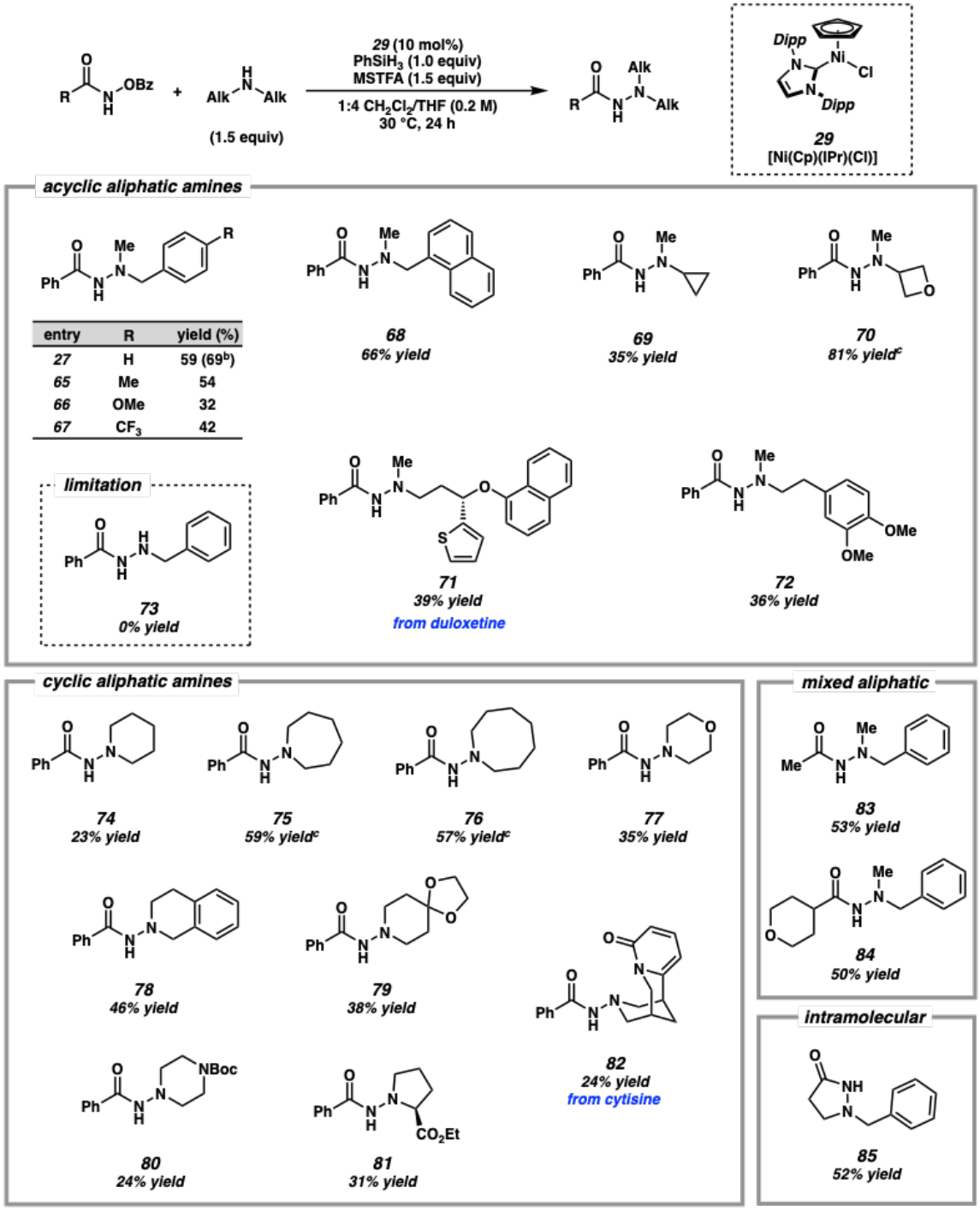
[a] Reactions performed on 0.2 mmol scale. [b] Protected as TBS ether for isolation. [c] 72 h.

between steric and electronic constraints for this transformation—although secondary anilines are more nucleophilic than primary anilines,[21] the increased steric bulk may bar their reactivity with more encumbered aryl electrophiles.

Hydroxamates with a variety of electron-donating and electron-withdrawing *para*-substituents on the aryl ring furnished the N–N products with moderate to high yields (**46**–**52**). Additionally, primary, secondary, and tertiary aliphatic hydroxamates were compatible with this chemistry (**53**–**56**). We were pleased to observe styrenyl and alkenyl functional groups did not participate in undesired C-H insertion, hydroamidation, reduction, or aziridination processes, affording moderate yields of products **57** and **58**, respectively.[19,2729] Additionally, several saturated heterocyclic compounds, such tetrahydropyran-, piperidine-, and azetidine-derived hydroxamates (**59–61**) afforded products in 52–67% yields. Hydroxamates featuring phenyl isostere [1.1.1]-bicyclopentane (BCP) derivatives were also compatible in this transformation (**63** and **64**).[30] Surprisingly, a benzylic hydroxamate remained inert under the reaction conditions (**65**).

N-methylbenzylamine derivatives with both electron-donating and electron-withdrawing substituents on the aryl ring afforded modest yields of the desired products (Figure 1.9, **65**–**67**). Replacement of the benzyl group with a variety of acyclic and cyclic moieties (**68**–**72**), including a formamide isostere (**70**), resulted in efficient product formation.[31] Reaction with duloxetine, an antidepressant, yielded the corresponding hydrazide derivative **71** in synthetically useful yield.[32] Although broadly useful with secondary aliphatic amines, primary aliphatic amines remain incompatible with this transformation, instead yielding undesired amine acylation arising from *O*-to-*N* benzoyl transfer and only trace product (**73**).

Figure 1.9. *Scope of aliphatic amine nucleophiles and mixed aliphatic substrates.*[a]

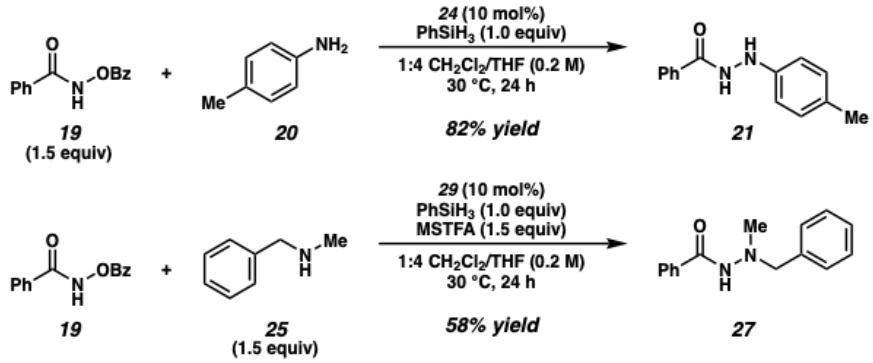


[a] Reactions performed on 0.2 mmol scale. [b] Silylamine **26** used. [c] 48 h.

Cyclic aliphatic amines were competent coupling partners in this chemistry (**74**–**82**), albeit affording products in diminished yields due to the greater propensity of these

nucleophiles to generate *O*-to-*N* benzoyl transfer side products. Cytisine, a smoking cessation agent, was able to be derivatized to the corresponding hydrazide in a synthetically useful yield (**82**),[33] and we were able to access fully aliphatic hydrazides (**83** and **84**), including saturated heterocycle **85** resulting from intramolecular bond formation. Lastly, both sets of conditions were demonstrated to be scalable, with hydrazides **21** and **27** obtained in near identical yields from 2.0 mmol scale reactions (Figure 1.10).

Figure 1.10. *Large-scale reactions.*[a]



[a] Reactions performed on 2.0 mmol scale.

1.5 REACTION MECHANISM

To investigate the role of the silane additive, Ni(I) half sandwich **87** was independently synthesized, and its catalytic competence was examined.[22] Reaction in the presence and absence of phenylsilane afforded similar product yields with near identical reaction times, supporting the notion that the active catalyst is a Ni(I) species formed via reduction with silane (Figure 1.11).[20,34] With this evidence in hand, we suggest the following mechanism (Figure 1.12): phenylsilane can reduce **24** or **29** to a Ni(I) species via formation of a Ni(II) hydride. Reaction with a hydroxamate starting material can form a putative Ni-nitrenoid with net loss of benzoic acid, which may be enabled by transient

slippage of the Cp ligand.[20,22] The Ni-nitrenoid can then undergo outer sphere N–N bond formation with an amine, which following proton transfer yields a metal bound hydrazide. Dissociation of product regenerates the active catalyst.

Figure 1.11. *Mechanistic experiments.*

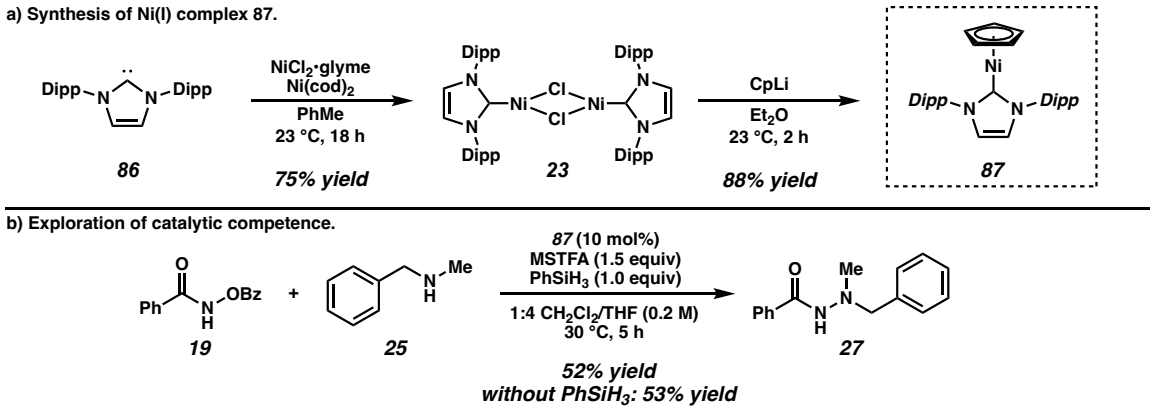
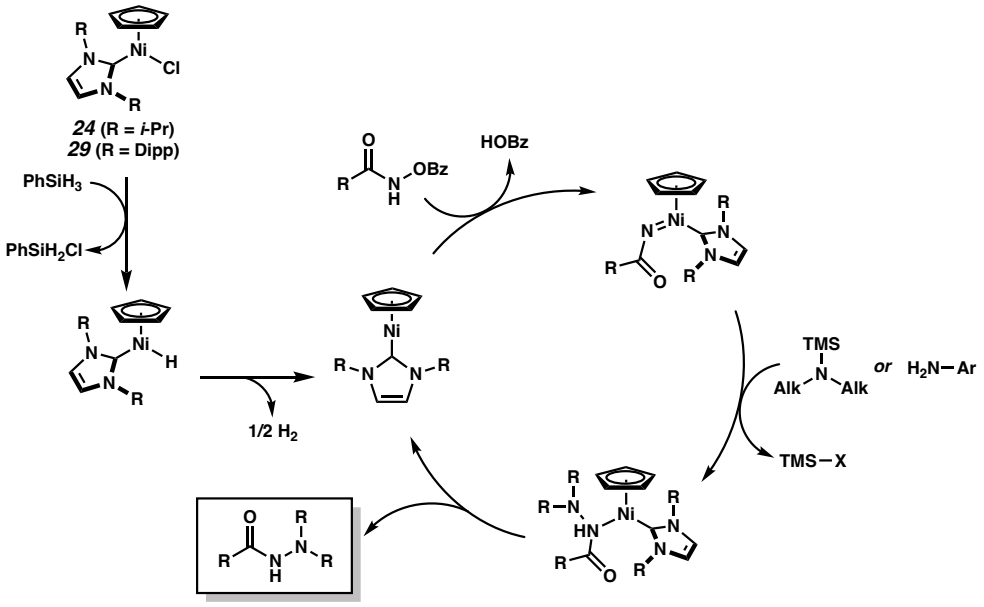


Figure 1.12. *Potential catalytic cycle.*



1.6 CONCLUSIONS

In summary, we have developed a Ni-catalyzed N–N cross-coupling enabling the convenient formation of complex hydrazides. This transformation is effected by an easily

synthesized and air-stable Ni(II) half-sandwich precatalyst. *In situ* silylation enables unprecedented access to secondary aliphatic amines in transition-metal catalyzed N–N coupling methodology. This reaction tolerates an impressive breadth of functionality, including handles for further derivatization. Preliminary mechanistic investigation suggests a mononuclear Ni(I) species as the active catalyst.

1.7 EXPERIMENTAL SECTION

1.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[35] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, iodine, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for silica gel flash chromatography. Teledyne Isco RediSep Gold High Performance C18 columns were used for reverse phase flash chromatography. ^{1}H NMR spectra were recorded on Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (101 MHz) and are reported relative to residual $CHCl_3$ (δ 77.16 ppm).^{19}F NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (282 MHz) and referenced to an external standard (hexafluorobenzene; ^{19}F NMR (282 MHz, $CDCl_3$) δ -161.64; ^{19}F NMR (282 MHz, CD_3OD) δ -165.37).[36] ^{11}B NMR spectra were recorded on a Bruker 400 MHz spectrometer

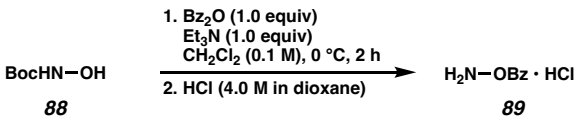
(128 MHz) and referenced to an external standard (boron trifluoride diethyl etherate; ^{11}B NMR (128 MHz, $CDCl_3$) δ 0.0).[37] Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR, ^{11}B and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a ThermoScientific Nicolet iS50 FT-IR spectrometer, or a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Center for Catalysis and Chemical Synthesis, using an Agilent 6230 Series TOF LC/MS with an Agilent Jet Stream source in electrospray mode (ESI), and the Caltech Mass Spectral Facility, using a JEOL JMS-T2000 AccuTOF GC-Alpha time-of-flight mass spectrometer using Field Desorption (FD) ionization (ions detected are $M^{+\bullet}$).

1.7.1.1 Preparation of Known Compounds

Reagents were purchased from commercial sources and used as received unless otherwise stated. *N*-(benzoyloxy)-*N*-methylbenzamide (**112**),[38] *N*-(pivaloyloxy)benzamide (**113**),[39] *N*-acetoxybenzamide (**114**),[40] *N*-methoxybenzamide (**115**),[41] *N*-hydroxybenzamide (**116**),[42] 3-phenyl-1,4,2-dioxazol-5-one (**117**),[43] *tert*-butyl (3-((benzoyloxy)amino)-3-oxopropyl)(benzyl)carbamate (**110**),[44] [Ni(Cp)(IPr)(Cl)] (**29**),[45] [Ni(Cp)(IPr)] (**87**),[46] [Ni(Cp)(SIPr)(Cl)] (**125**),[47] [Ni(Cp)($NHC^{Me,n\text{-}Bu}$)(Cl)] (**126**),[48] and [Ni(Cp)(IMes)(Cl)] (**124**)[49] were prepared according to literature procedures.

1.7.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

1.7.2.1 Synthesis of Hydroxamate Starting Materials



_O_-benzoylhydroxylamine hydrochloride (89)

To *N*-Boc-hydroxylamine (13.3 g, 100 mmol, 1.0 equiv) and triethylamine (14 mL, 100 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 M) at 0 °C was added benzoic anhydride (22.6 g, 100 mmol, 1.0 equiv) portionwise over five minutes. The reaction was continued at 0 °C for 2 hours, then diluted with saturated $NaHCO_3$, transferred to a separatory funnel, and extracted with dichloromethane three times. The combined organics were washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide crude *tert*-butyl-(benzoyloxy)carbamate. The crude material was then dissolved in 4 M HCl in dioxane (200 mL, 8 equiv) and stirred for 1 hour. The precipitated product was filtered from solution, washed with diethyl ether, and dried under vacuum to afford **89** (17 g, 98% yield) as a white solid.

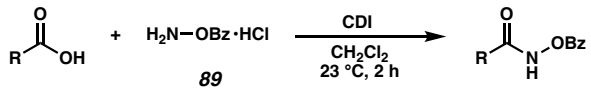
^{1}H NMR (400 MHz, CD_3OD): δ 8.11–8.02 (m, 2H), 7.82–7.71 (m, 1H), 7.66–7.49 (m, 2H).

^{13}C NMR (101 MHz, CD_3OD): δ 164.5, 136.5, 131.0, 130.4, 126.2.

IR (neat film): 1739, 1647, 1450, 1371, 1273, 1243, 1084, 1059, 907, 862, 705 cm^{-1}.

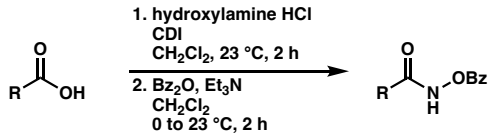
HRMS (ESI+): m/z calc'd for $C_7H_8NO_2$ $[M+H]^+$: 138.0550, found 138.0556.

Preparation of Hydroxamate Starting Materials: General Procedure A



To a round bottom flask containing carboxylic acid (1.0 equiv) dissolved in dichloromethane (0.2 M) was added 1,1'-carbonyldiimidazole (1.1 equiv). The reaction mixture was stirred for 30 minutes, and then *O*-benzoylhydroxylamine hydrochloride (**89**) (1.1 equiv) was added. The reaction was continued for an additional 2 hours, or until reaction reached completion as determined by monitoring with TLC. The crude mixture was diluted with water and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel flash chromatography to provide the desired hydroxamic ester.

Preparation of Hydroxamate Starting Materials: General Procedure B

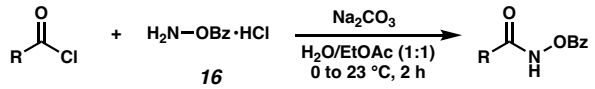


To a round bottom flask containing carboxylic acid (1.0 equiv) dissolved in dichloromethane (0.2 M) was added 1,1'-carbonyldiimidazole (1.1 equiv). The reaction mixture was stirred for 30 minutes, and then hydroxylamine hydrochloride (1.1 equiv) was added. The reaction was continued for an additional 2 hours, or until reaction reached completion as determined by TLC. The crude mixture was diluted with water and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and used without further purification.

The crude hydroxamic acid was dissolved in dichloromethane (0.2 M), and triethylamine (1.0 equiv) was added. The reaction mixture was cooled to 0 °C, and benzoic anhydride (1.0 equiv) was added portionwise over 5 minutes. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired hydroxamic ester.

Note: all reaction yields for the preparation of hydroxamate starting materials are unoptimized.

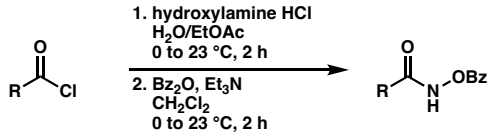
Preparation of Hydroxamate Starting Materials: General Procedure C



To a round bottom flask containing *O*-benzoylhydroxylamine hydrochloride (**16**) (1.5 equiv) and sodium carbonate (2.0 equiv) was added water and ethyl acetate (1:1, 0.2 M). The biphasic mixture was cooled to 0 °C, and the acid chloride (1.0 equiv) was added dropwise. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired hydroxamic ester.

Note: all reaction yields for the preparation of hydroxamate starting materials are unoptimized.

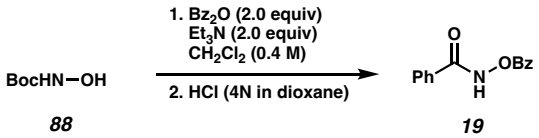
Preparation of Hydroxamate Starting Materials: General Procedure D



To a round bottom flask containing hydroxylamine hydrochloride (1.5 equiv) and sodium carbonate (2.0 equiv) was added water and ethyl acetate (1:1, 0.2 M). The biphasic mixture was cooled to 0 °C, and the acid chloride (1.0 equiv) was added dropwise. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and used without further purification.

The crude hydroxamic acid was dissolved in dichloromethane (0.2 M), and triethylamine (1.0 equiv) was added. The reaction mixture was cooled to 0 °C, and benzoic anhydride (1.0 equiv) was added portionwise over 5 minutes. The reaction continued and was allowed to slowly warm to room temperature over 2 hours, after which the mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired hydroxamic ester.

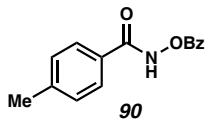
Note: all reaction yields for the preparation of hydroxamate starting materials are unoptimized.



N-(benzoyloxy)benzamide (19)

To *N*-Boc-hydroxylamine (26.6 g, 200 mmol, 1.0 equiv) and triethylamine (56 mL, 400 mmol, 2.0 equiv) in CH_2Cl_2 (0.4 M) was added benzoic anhydride (90.5 g, 400 mmol, 2.0 equiv) portionwise over five minutes. The reaction was stirred at 23 °C for 2 hours, then diluted with saturated $NaHCO_3$, transferred to a separatory funnel, and extracted with dichloromethane three times. The combined organics were washed with saturated $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4, filtered through a short silica pad (~2 inches), and concentrated to provide crude *tert*-butyl benzoyl(benzoyloxy)carbamate. The crude material was then dissolved in 4 M HCl in dioxane (400 mL, 8 equiv) and stirred for 1 hour. The precipitated product was filtered from solution, washed with diethyl ether, and dried under vacuum to afford **19** (37.6 g, 78% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.21 – 8.13 (m, 2H), 7.92 – 7.85 (m, 2H), 7.80 – 7.64 (m, 1H), 7.62 – 7.55 (m, 1H), 7.54 – 7.40 (m, 4H); all characterization data match those reported in the literature.[47]



90

***N*-(benzoyloxy)-4-methylbenzamide (90)**

Prepared according to general procedure D using 4-methylbenzoyl chloride (15.0 mmol). Purification by column chromatography (10–25 % EtOAc in hexanes) yielded **90** (1.025 g, 27% yield) as a white solid.

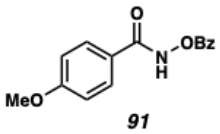
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.20 – 8.13 (m, 2H), 7.82 – 7.74 (m, 2H), 7.70 – 7.61 (m, 1H), 7.55 – 7.46 (m, 2H), 7.33 – 7.25 (m, 2H), 2.42 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 165.5, 143.6, 134.4, 130.2, 129.6, 128.8, 128.1,

127.7, 126.8, 21.7.

IR (neat film): 3174, 2957, 1766, 1651, 1483, 1236, 1041, 1019, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{13}NO_3Na$ $[M+Na]^+$: 278.0788, found 278.0788.



91

***N*-(benzoyloxy)-4-methoxybenzamide (91)**

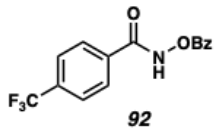
Prepared according to general procedure D using 4-methoxybenzoyl chloride (2.0 mmol). Purification by column chromatography (10–25 % EtOAc in hexanes) yielded **91** (341 mg, 63% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.20 – 8.13 (m, 2H), 7.90 – 7.80 (m, 2H), 7.70 – 7.61 (m, 1H), 7.55 – 7.44 (m, 2H), 7.01 – 6.93 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 165.6, 163.4, 134.4, 130.2, 129.7, 128.9, 126.8, 123.1, 114.3, 55.6.

IR (neat film): 3198, 2937, 1769, 1647, 1605, 1489, 1261, 1238, 1023, 707 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{13}NO_4Na$ $[M+Na]^+$: 294.0737, found 294.0739.



92

***N*-(benzoyloxy)-4-(trifluoromethyl)benzamide (92)**

Prepared according to general procedure A using N-hydroxy-4-(trifluoromethyl)benzamide (3.0 mmol). Purification by column chromatography (10–50% EtOAc in hexanes) yielded **92** (400 mg, 43% yield) as a white solid.

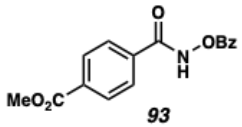
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.20 – 8.13 (m, 2H), 8.00 (d, J = 7.7 Hz, 2H), 7.76 (d, J = 7.9 Hz, 2H), 7.71 – 7.63 (m, 1H), 7.57 – 7.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 134.6, 134.2, 134.1, 130.5, 130.1, 128.8, 128.1, 126.3, 125.9 (q, J = 3.8 Hz), 123.5 (q, J = 272.7 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -63.3.

IR (neat film): 3144, 1775, 1659, 1326, 1237, 1123, 1067, 1016, 855, 704 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{15}H_9F_3NO_3$ $[M–H]^-$: 308.0540, found 308.0536.



93

Methyl 4-((benzoyloxy)carbamoyl)benzoate (93)

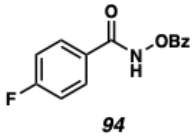
Prepared according to general procedure C from the corresponding acid chloride (3.84 mmol). Purification by column chromatography (2.5% to 10% EtOAc in CH_2Cl_2) provided **93** (525 mg, 46% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (brs, 1H), 8.17 – 8.13 (m, 4H), 7.94 (d, J = 8.6 Hz, 2H), 7.69 – 7.65 (m, 1H), 7.54 – 7.50 (m, 2H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.7, 165.3, 134.8, 134.6, 134.0, 130.2, 130.2, 129.0, 127.8, 126.5, 52.7.

IR (neat film): 3142, 2964, 1776, 1717, 1654, 1282, 1252, 1108, 1018, 911, 734, 704, 592, 417 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{16}H_{12}NO_5$ $[M–H]^-$: 298.0721, found 298.0720.



94

***N*-(benzoyloxy)-4-fluorobenzamide (94)**

Prepared according to general procedure D using 4-fluorobenzoyl chloride (10.0 mmol). A solid precipitated upon benzoylation; filtration yielded **94** (1.84 g, 71% yield).

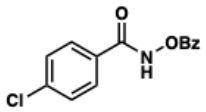
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.20 – 8.10 (m, 2H), 7.95 – 7.83 (m, 2H), 7.66 (ddt, *J* = 8.0, 7.1, 1.3 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.23 – 7.10 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 165.5 (d, *J* = 254.0 Hz), 165.4, 134.6, 130.2 (d, *J* = 9.2 Hz), 130.2, 128.9, 127.1 (d, *J* = 3.2 Hz), 126.6, 116.2 (d, *J* = 21.9 Hz).

^{19}F NMR (282 MHz, CD_3OD): δ -108.8.

IR (neat film): 3189, 1767, 1659, 1602, 1490, 1236, 1045, 849, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{10}FNO_3Na$ $[M+Na]^+$: 282.0537, found 282.0537.



95

***N*-(benzoyloxy)-4-chlorobenzamide (95)**

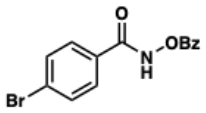
Prepared according to general procedure C using 4-chlorobenzoyl chloride (2.0 mmol). Purification by trituration with 30% EtOAc in hexanes yielded **95** (194 mg, 35% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.19 – 8.12 (m, 2H), 7.87 – 7.78 (m, 2H), 7.71 – 7.62 (m, 1H), 7.56 – 7.41 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8, 165.4, 139.4, 134.6, 130.2, 129.3, 129.3, 129.1, 128.9, 126.5.

IR (neat film): 3161, 1765, 1654, 1597, 1482, 1238, 1094, 1045, 1003, 844, 703 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{10}ClNO_3Na$ $[M+Na]^+$: 298.0241, found 298.0237.



96

***N*-(benzoyloxy)-4-bromobenzamide (96)**

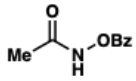
Prepared according to general procedure C using 4-bromobenzoyl chloride (2.0 mmol). Purification by trituration with 30% EtOAc in hexanes yielded **96** (235.5 mg, 37% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 8.19 – 8.12 (m, 2H), 7.79 – 7.71 (m, 2H), 7.70 – 7.60 (m, 3H), 7.56 – 7.47 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 165.4, 134.6, 132.3, 130.2, 129.8, 129.2, 128.9, 127.9, 126.5.

IR (neat film): 3150, 2972, 1764, 1652, 1589, 1478, 1237, 1044, 1011, 841, 702 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{14}H_9BrNO_3$ $[M–H]^-$: 317.9771, found 317.9764.

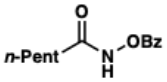


97

N-(benzoyloxy)acetamide (97)

Prepared according to general procedure C using acetyl chloride (3 mmol), providing **97** (335 mg, 61% yield) as a white solid after work up.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.14 – 8.07 (m, 2H), 7.64 (m, 1H), 7.49 (t, *J* = 7.9 Hz, 2H), 2.14 (s, 3H); all characterization data match those reported in the literature.[47]



98

N-(benzoyloxy)hexanamide (98)

Prepared according to general procedure D using hexanoyl chloride (6.0 mmol). Purification by column chromatography (10–20% EtOAc in hexanes) yielded **98** (810 mg, 57% yield) as a white solid.

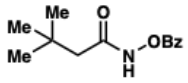
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.10 (d, *J* = 7.1 Hz, 2H), 7.68 – 7.59 (m,

1H), 7.49 (t, *J* = 7.8 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.43 – 1.27 (m, 4H), 0.97 – 0.85 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 165.1, 134.3, 130.1, 128.8, 126.7, 33.1, 31.4, 24.9, 22.4, 14.0.

IR (neat film): 3162, 2957, 2930, 2870, 1767, 1663, 1237, 1075, 1053, 986, 702 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1281, found 236.1289.



99

***N*-(benzoyloxy)-3,3-dimethylbutanamide (99)**

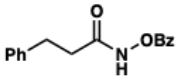
Prepared according to general procedure B using 3,3-dimethylbutanoic acid (1.0 mmol). Purification by column chromatography (30–50% EtOAc in hexanes) yielded **99** (136 mg, 58% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.15 – 8.05 (m, 2H), 7.68 – 7.58 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 2.21 (s, 2H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 165.2, 134.4, 130.3, 130.1, 128.8, 128.6, 126.7, 31.2, 29.9.

IR (neat film): 3167, 2955, 2869, 1768, 1660, 1452 1234, 1064, 997, 703 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1281, found 236.1288.

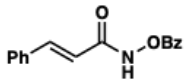


100

***N*-(benzoyloxy)-3-phenylpropanamide (100)**

Prepared according to general procedure C using 3-phenylpropanoyl chloride (2 mmol). Purification by column chromatography (2% EtOAc in CH_2Cl_2) provided **100** (419 mg, 78% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.12 – 8.06 (m, 2H), 7.69 – 7.59 (m, 1H), 7.53 – 7.44 (m, 2H), 7.36 – 7.27 (m, 2H), 7.27 – 7.18 (m, 3H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H); all characterization data match those reported in the literature.[48]



101

***N*-(benzoyloxy)cinnamamide (101)**

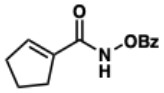
Prepared according to general procedure C using cinnamoyl chloride (5 mmol). Purification by column chromatography (2% EtOAc in CH_2Cl_2) provided **101** (643 mg, 48% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 – 8.11 (m, 2H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.58 – 7.44 (m, 4H), 7.39 (dd, *J* = 4.6, 1.8 Hz, 3H), 6.57 (d, *J* = 15.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 144.4, 134.5, 134.3, 130.6, 130.2, 129.1, 128.9, 128.3, 126.7, 115.4.

IR (neat film): 3163, 2971, 1768, 1667, 1631, 1577, 1507, 1338, 1075, 972, 756 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{13}NO_3Na$ $[M+Na]^+$: 290.0788, found 290.0783.



102

***N*-(benzoyloxy)cyclopent-1-ene-1-carboxamide (102)**

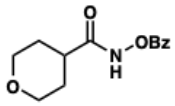
Prepared according to general procedure D from the corresponding acid chloride (2.23 mmol). Purification by column chromatography (0–50% EtOAc in hexanes) provided **102** (144 mg, 28% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (brs, 1H), 8.14 – 8.11 (m, 2H), 7.65 – 7.61 (m, 1H), 7.51 – 7.45 (m, 2H), 6.77 – 6.75 (m, 1H), 2.65 (ddt, *J* = 7.8, 6.9, 2.4 Hz, 2H), 2.53 (dtd, *J* = 9.6, 5.2, 2.6 Hz, 2H), 2.05 – 1.97 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 164.5, 141.8, 135.7, 134.3, 133.6, 130.2, 130.1, 128.8, 128.6, 126.8, 33.5, 31.4, 23.2.

IR (neat film): 3176, 2959, 1767, 1662, 1490, 1239, 1044, 1018, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{13}NNaO_3$ $[M+Na]^+$: 254.0788, found 254.0788.



103

***N*-(benzoyloxy)tetrahydro-2*H*-pyran-4-carboxamide (103)**

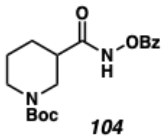
Prepared according to general procedure A from the corresponding carboxylic acid (4.00 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **103** (718 mg, 72% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (brs, 1H), 8.09 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.66 – 7.61 (m, 1H), 7.51 – 7.45 (m, 2H), 4.03 (ddd, *J* = 11.6, 4.3, 2.4 Hz, 2H), 3.44 (td, *J* = 11.6, 2.4 Hz, 2H), 2.61 – 2.53 (m, 1H), 1.95 (dtd, *J* = 13.5, 11.4, 4.4 Hz, 2H), 1.85 – 1.78 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 165.2, 134.5, 130.1, 128.9, 126.6, 67.1, 39.6, 28.9.

IR (neat film): 3180, 2953, 2846, 1773, 1665, 1506, 1239, 1119, 1039, 980 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1074, found 250.1069.



104

***Tert*-butyl 3-((benzoyloxy)carbamoyl)piperidine-1-carboxylate (104)**

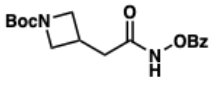
Prepared according to general procedure A using 1-(*tert*-butoxycarbonyl)piperidine-3carboxylic acid (1 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **104** (170 mg, 49% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.06 (m, 2H), 7.67 – 7.58 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 3.92 – 3.28 (m, 3H), 2.56 (s, 1H), 2.15 (d, *J* = 12.3 Hz, 1H), 1.89 (s, 1H), 1.76 – 1.65 (m, 2H), 1.63 – 1.48 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 164.8, 155.4, 134.1, 130.1, 128.7, 126.9, 80.5, 45.0, 40.3, 28.5, 27.5, 23.9.

IR (neat film): 3182, 2976, 1766, 1659, 1450, 1239, 1147, 1054, 729, 702 cm^{-1}.

HRMS (ESI–): m/z calc'd for $C_{18}H_{23}N_2O_5$ $[M–H]^-$: 347.1612, found 347.1611.



105

***Tert*-butyl 3-(2-((benzoyloxy)amino)-2-oxoethyl)azetidine-1-carboxylate (105)**

Prepared according to general procedure A from the corresponding carboxylic acid (4.00 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **105** (814 mg, 61% yield) as a white solid.

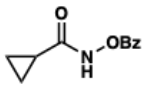
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (brs, 1H), 8.09 – 8.05 (m, 2H), 7.64 – 7.60 (m, 1H), 7.49 – 7.44 (m, 2H), 4.11 (dd, *J* = 8.5, 8.5 Hz, 2H), 3.67 (dd, *J* = 8.9, 5.3 Hz, 2H), 3.04 – 2.91 (m, 1H), 2.63 (d, *J* = 7.7 Hz, 2H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9, 156.5, 134.5, 130.1, 128.9, 126.6, 79.8, 54.4, 37.2,

28.5, 25.5.

IR (neat film): 3164, 2975, 1767, 1698, 1670, 1414, 1241, 1155, 1060, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{17}H_{22}N_2NaO_5$ $[M+Na]^+$: 357.1437, found 357.1431.



106

***N*-(benzoyloxy)cyclopropanecarboxamide (106)**

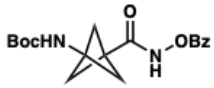
Prepared according to general procedure C from the corresponding acid chloride (6.28 mmol). Purification by column chromatography (5–10% EtOAc in CH_2Cl_2) provided **106** (445 mg, 34% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.11 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.51 – 7.47 (m, 2H), 1.63 (s, 1H), 1.13 – 1.09 (m, 2H), 0.93 – 0.88 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 134.4, 130.1, 128.8, 126.8, 11.9, 8.4.

IR (neat film): 3155, 2984, 2901, 1766, 1657, 1515, 1398, 1240, 1053, 705, 600 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{11}NNaO_3$ $[M+Na]^+$: 228.0631, found 228.0631.



107

***Tert*-butyl (3-((benzoyloxy)carbamoyl)bicyclo[1.1.1]pentan-1-yl)carbamate (107)**

Prepared according to general procedure A from the corresponding carboxylic acid (2.00 mmol). Purification by column chromatography (15–20% EtOAc in CH_2Cl_2) provided **107** (391 mg, 56% yield) as a white solid.

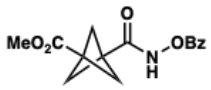
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (brs, 1H), 8.10 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.49 (dd, *J* = 8.3, 7.4 Hz, 2H), 5.00 (brs, 1H), 2.38 (s, 6H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 165.0, 154.8, 134.5, 130.1, 128.9, 126.6, 80.2,

54.3, 46.0, 34.8, 28.5.

IR (neat film): 3648, 3327, 2981, 1775, 1689, 1499, 1368, 1251, 1168, 1011, 943 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{23}N_2O_5$ $[M+H]^+$: 347.1601, found 347.1604.



108

Methyl 3-((benzoyloxy)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (108)

Prepared according to general procedure A from the corresponding carboxylic acid (1.00 mmol). Purification by column chromatography (10–30% EtOAc in CH_2Cl_2) provided **108** (121 mg, 42% yield) as a white solid.

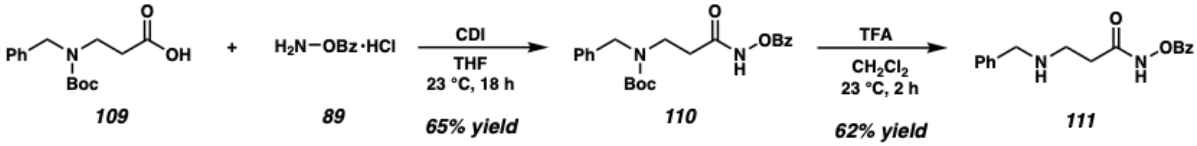
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 7.5, 1.1 Hz, 2H), 7.66 – 7.62 (m, 1H),), 7.50 – 7.46 (m, 2H), 3.70 (s, 3H), 2.40 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.4, 166.7, 164.9, 134.5, 130.1, 128.9, 126.5, 52.9, 52.1, 38.0, 37.2.

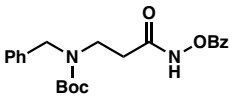
IR (neat film): 3150, 3001, 1769, 1732, 1673, 1502, 1452, 1240, 1219, 1037, 1018, 839, 705 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{16}NO_5$ $[M+H]^+$: 290.1025, found 290.1036.

*Preparation of N-(benzoyloxy)-3-(benzylamino)propenamide (**111**)*



Note: subsequent reactions for substrate preparation are unoptimized.



110

***Tert*-butyl (3-((benzoyloxy)amino)-3-oxopropyl)(benzyl)carbamate (110)**

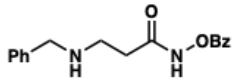
Prepared according to general procedure A, using 3-(benzyl(*tert*-butoxycarbonyl)amino)propanoic acid[42] (**109**) (715 mg, 2.56 mmol). Purification by column chromatography (20–40% EtOAc in hexanes) provided **110** (660 mg, 65% yield) as a clear oil, characterized as a mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 – 8.04 (m, 2H), 7.66 – 7.57 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.31 (dd, *J* = 8.8, 5.9 Hz, 2H), 7.28 – 7.14 (m, 3H), 4.48 (s, 2H, major rotamer), 4.42 (s, 2H, minor rotamer), 4.44 (s, 2H), 3.58 (m, 2H), 2.63 (m, 2H), 1.51 (s, 9H, minor rotamer), 1.46 (s, 9H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 164.7, 156.5, 152.4, 138.1, 134.2, 130.1, 128.8, 128.7, 127.5, 81.0, 51.3, 42.8, 32.9, 28.5, 27.7.

IR (neat film): 3164, 2979, 2320, 1767, 1690, 1459, 1429, 1241, 1161, 889, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{22}H_{27}N_2O_5$ $[M+H]^+$: 399.1914, found 399.1923.



111

N-(benzoyloxy)-3-(benzylamino)propenamide (111)

To a 20-mL scintillation vial containing *tert*-butyl (3-((benzoyloxy)amino)-3oxopropyl)(benzyl)carbamate (**110**) (655 mg, 1.64 mmol, 1 equiv) was added CH_2Cl_2 (3 mL, 0.5 M), followed by trifluoroacetic acid (1 mL). The reaction was stirred at 23 °C for two hours, then added to a separatory funnel and washed with saturated sodium bicarbonate, dried with Na_2SO_4, filtered and concentrated to afford **111** (304 mg, 62% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.99 (d, *J* = 7.7 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.41 (m, 4H), 7.37 (d, *J* = 3.1 Hz, 3H), 4.17 (s, 2H), 3.31 – 3.26 (m, 2H), 2.87 – 2.81 (m, 2H).

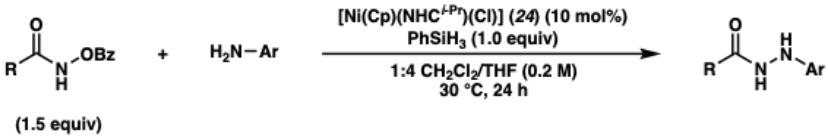
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 165.9, 134.6, 130.3, 130.0, 129.9, 129.5, 128.8, 126.3, 52.1, 44.0, 29.8.

IR (neat film): 3164, 2979, 1848, 2320, 1767, 1690, 1429, 1366, 1241, 1161, 1003, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{17}H_{19}N_2O_3$ $[M+H]^+$: 299.1390, found 299.1387.

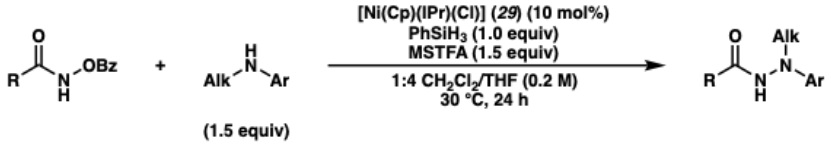
1.7.2.2 Synthesis of Hydrazide Products

Preparation of Aniline-Derived Hydrazides: General Procedure E

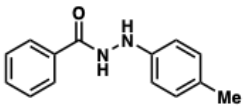


In a nitrogen-filled glovebox, a 2-dram vial is charged with hydroxamic ester (0.30 mmol, 1.5 equiv). A solution of amine (0.20 mmol, 1.0 equiv) in THF (0.8 mL) is added, followed by a solution of **24** (0.020 mmol, 10 mol%) and phenylsilane (0.20 mmol, 1.0 equiv) in dichloromethane (0.20 mL). The reaction is sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 30 °C for 24 h unless otherwise noted. After 24 h, the reaction is quenched with sat. $NaHCO_3$ (2 mL), extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by either silica gel flash chromatography or C18 reverse phase chromatography to provide the desired hydrazide product.

Preparation of Aliphatic Amine-Derived Hydrazides: General Procedure F



In a nitrogen-filled glovebox, a 2-dram vial is charged with aliphatic amine (0.30 mmol, 1.5 equiv). THF (0.80 mL) is added to the reaction vial, followed sequentially by MSTFA (0.30 mmol, 1.5 equiv), a solution of **29** (0.020 mmol, 10 mol%) and phenylsilane (0.20 mmol, 1.0 equiv) in dichloromethane (0.20 mL), and then solid hydroxamate (0.20 mmol, 1.0 equiv). The reaction is sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 30 °C for 24 h unless otherwise noted. After 24 h, the reaction is quenched with sat. $NaHCO_3$ (2 mL), extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by either silica gel flash chromatography or C18 reverse phase chromatography to provide the desired hydrazide product.



21

***N*'-(*p*-tolyl)benzohydrazide (21)**

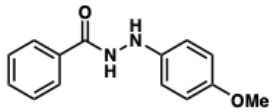
Prepared according to general procedure E using **19** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **21** (36 mg, 80% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.82 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 8.1 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 9.2 Hz, 2H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 145.6, 132.5, 132.4, 131.1, 129.9, 128.9, 127.3, 114.3, 20.7.

IR (neat film): 3246, 3062, 3007, 2919, 2864, 1642, 1511, 1323, 1241, 930, 817, 731, 700 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1179, found 227.1179.



30

***N*'-(4-methoxyphenyl)benzohydrazide (30)**

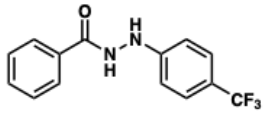
Prepared according to general procedure E using **19** (0.3 mmol) and 4-methoxyaniline (0.2 mmol). Purification by column chromatography (2% acetone in CH_2Cl_2) provided **30** (24.9 mg, 51% yield) as a gray solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.90 – 7.73 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 6.94 – 6.86 (m, 2H), 6.85 – 6.76 (m, 2H), 6.31 (s, 1H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 155.0, 141.7, 132.5, 132.4, 128.9, 127.2, 116.0, 114.8, 55.8.

IR (neat film): 3260, 1651, 1508, 1235, 1150, 1036, 826, 694 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{15}N_2O_2$ $[M+H]^+$: 243.1128, found 243.1134.



31

_N_'-(4-(trifluoromethyl)phenyl)benzohydrazide (31)

Prepared according to general procedure E using **19** (0.3 mmol) and 4-(trifluoromethyl)aniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **31** (25.1 mg, 45% yield) as a gray solid.

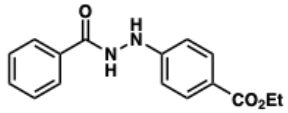
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.85 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.53 – 7.37 (m, 4H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.56 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 151.0, 132.8, 131.9, 129.1, 127.3, 126.8 (q, *J* = 3.8 Hz), 125.9, 123.3 (q, *J* = 32.7 Hz), 113.2.

^{19}F (282 MHz, $CDCl_3$): δ -61.6.

IR (neat film): 3270, 1652, 1617, 1521, 1477, 1324, 1263, 1157, 1110, 1063, 832, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$: 281.0896, found 281.0900.



32

Ethyl 4-(2-benzoylhydrazineyl)benzoate (32)

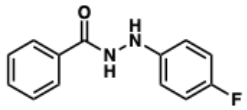
Prepared according to general procedure E using **19** (0.3 mmol) and ethyl 4-aminobenzoate (0.2 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **32** (19.1 mg, 34% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 3.2 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.85 – 7.71 (m, 2H), 7.65 – 7.52 (m, 1H), 7.45 (dd, *J* = 8.4, 7.0 Hz, 2H), 6.88 – 6.80 (m, 2H), 6.63 (d, *J* = 3.3 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.35.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 166.7, 152.1, 132.6, 132.0, 131.4, 129.0, 127.4, 123.0, 112.5, 60.7, 14.5.

IR (neat film): 3281, 2982, 1667, 1604, 1511, 1476, 1259, 1170, 1105, 1025, 900, 844, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O_3$ $[M+H]^+$: 285.1234, found 285.1238.



33

***N*'-(4-fluorophenyl)benzohydrazide (33)**

Prepared according to general procedure E using **19** (0.3 mmol) and 4-fluoroaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **33** (33.1 mg, 72% yield) as a white solid.

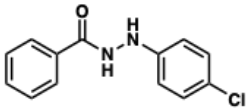
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.76 (m, 3H), 7.71 – 7.55 (m, 1H), 7.53 – 7.39 (m, 2H), 7.01 – 6.87 (m, 4H), 6.31 – 6.26 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.0, 158.2 (d, J = 238.8 Hz), 144.2 (d, J = 2.2 Hz), 132.6, 132.2, 129.0, 127.2, 115.9 (d, J = 22.8 Hz), 115.4 (d, J = 7.9 Hz).

^{19}F (282 MHz, $CDCl_3$): δ -123.2.

IR (neat film): 3255, 1648, 1503, 1324, 1211, 1102, 912, 833, 693 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{10}FN_2O$ $[M–H]^–$: 231.0928, found 229.0782.



34

***N*'-(4-chlorophenyl)benzohydrazide (34)**

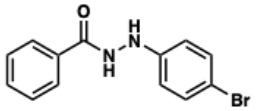
Prepared according to general procedure E using **19** (0.3 mmol) and 4-chloroaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **34** (36.1 mg, 73% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.80 (m, 3H), 7.66 – 7.56 (m, 1H), 7.54 – 7.45 (m, 2H), 7.25 – 7.17 (m, 2H), 6.96 – 6.84 (m, 2H), 6.33 – 6.27 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 146.8, 132.6, 132.1, 129.3, 129.0, 127.3, 126.4, 115.2.

IR (neat film): 3240, 1731, 1646, 1596, 1489, 1325, 1244, 1109, 913, 851, 693, 650 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{12}ClN_2O$ $[M+H]^+$: 247.0633, found 247.0634.



35

N'-(4-bromophenyl)benzohydrazide (35)

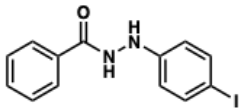
Prepared according to general procedure E using **19** (0.3 mmol) and 4-bromoaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **35** (35.4 mg, 74% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.89 – 7.79 (m, 2H), 7.66 – 7.53 (m, 1H), 7.52 – 7.43 (m, 2H), 7.33 (dt, *J* = 8.9, 2.4 Hz, 2H), 6.85 – 6.76 (m, 2H), 6.34 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 132.6, 132.2, 132.1, 129.0, 127.3, 115.6, 113.6.

IR (neat film): 3241, 1646, 1594, 1486, 1245, 1109, 913, 834, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{12}BrN_2O$ $[M+H]^+$: 291.0128, found 291.0127.



36

***N*'-(4-iodophenyl)benzohydrazide (36)**

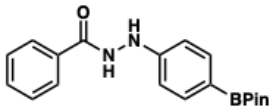
Prepared according to general procedure E using **19** (0.3 mmol) and 4-iodoaniline (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **36** (39.2 mg, 58% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.83 (d, *J* = 7.1 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.54 – 7.32 (m, 4H), 6.71 (d, *J* = 8.3 Hz, 2H), 6.32 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 148.1, 138.1, 132.7, 132.1, 129.1, 127.3, 116.1, 83.5.

IR (neat film): 3234, 1728, 1647, 1590, 1525, 1482, 1243, 1176, 913, 822, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{12}IN_2O$ $[M+H]^+$: 338.9989, found 338.9973.



37

***N*'-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzohydrazide (37)**

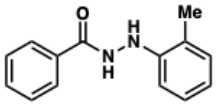
Prepared according to general procedure E using **19** (0.3 mmol) and 4-(4,4,5,5-tetramethyl1,3,2-dioxaborolan-2-yl)aniline (0.2 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **37** (41.8 mg, 62% yield) as a white solid.

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 150.8, 136.4, 132.5, 132.4, 129.0, 127.3, 112.8, 83.6, 29.9, 25.0.

^{11}B NMR (128 MHz): δ 31.41.

IR (neat film): 3284, 1728, 1655, 1511, 1474, 1299, 1246, 1155, 1011, 898, 801, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{19}H_{24}BN_2O_3$ $[M+H]^+$: 338.1911, found 338.1908.



38

***N*'-(*o*-tolyl)benzohydrazide (38)**

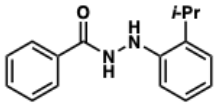
Prepared according to general procedure E using **19** (0.3 mmol) and *o*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **38** (33.5 mg, 74% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.0 Hz, 2H), 7.80 (s, 1H), 7.65 – 7.54 (m, 1H), 7.54 – 7.34 (m, 2H), 7.17 – 7.10 (m, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.87 (td, *J* = 7.4, 1.3 Hz, 1H), 6.28 – 6.23 (m, 1H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 145.9, 132.5, 132.4, 130.8, 129.0, 127.2, 127.1, 123.7, 121.4, 112.4, 17.2.

IR (neat film): 3277, 3058, 1642, 1516, 1488, 1249, 1114, 899, 745, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1179, found 227.1173.



39

***N*'-(2-isopropylphenyl)benzohydrazide (39)**

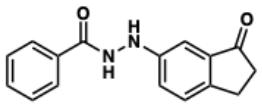
Prepared according to general procedure E using **19** (0.3 mmol) and 2-isopropylaniline (0.2 mmol). Purification by column chromatography (20% EtOAc in hexanes) provided **39** (37.3 mg, 73% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 1.5 Hz, 1H), 7.16 – 7.07 (m, 1H), 7.03 – 6.90 (m, 2H), 6.52 (d, *J* = 4.6 Hz, 1H), 3.14 (hept, *J* = 6.7 Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 144.6, 134.3, 132.4, 132.4, 129.0, 127.2, 126.7, 125.5, 121.8, 113.0, 27.3, 22.7.

IR (neat film): 3344, 3285, 3057, 2959, 1643, 1537, 1312, 1239, 1037, 904, 749 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1492, found 255.1494.



40

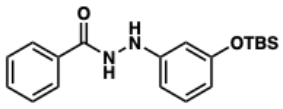
***N*'-(3-oxo-2,3-dihydro-1*H*-inden-5-yl)benzohydrazide (40)**

Prepared according to general procedure E using **19** (0.3 mmol) and 6-amino-2,3-dihydro1H-inden-1-one (0.2 mmol). Purification by column chromatography (5% acetone in CH_2Cl_2) provided **40** (27.5 mg, 52% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.96 – 7.80 (m, 2H), 7.67 – 7.54 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.21 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 3.23 – 2.93 (m, 2H), 2.82 – 2.59 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 207.3, 167.9, 148.7, 148.2, 138.2, 132.6, 132.0, 129.0, 127.4, 127.3, 122.1, 106.9, 37.0, 25.3.

IR (neat film): 3280, 2958, 2924, 1701, 1601, 1489, 1293, 1177, 693 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$: 267.1128, found 267.1128.



41

***N*'-(3-((*tert*-butyldimethylsilyl)oxy)phenyl)benzohydrazide (41)**

Prepared according to a modified version of general procedure E using **19** (0.3 mmol) and 3-aminophenol (0.2 mmol). Prior to purification, the crude mixture was dissolved in dichloromethane (1 mL, 0.2 M), and imidazole (41 mg, 0.6 mmol) and TBSCl (45 mg, 0.3

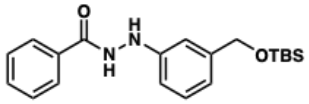
mmol) were added. The reaction was stirred at 23 °C for two hours, then diluted with water, extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (20% EtOAc in hexanes), providing **41** (28.2 mg, 50% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 3.6 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.74 – 7.53 (m, 1H), 7.51 – 7.43 (m, 3H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.69 – 6.51 (m, 1H), 6.49 – 6.35 (m, 2H), 6.29 (d, *J* = 3.9 Hz, 1H), 0.96 (s, 9H), 0.17 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 156.8, 149.5, 132.4, 132.3, 130.1, 128.9, 127.3, 113.2, 107.0, 105.9, 25.8, 18.3, -4.3.

IR (neat film): 3277, 2955, 2923, 2857, 1651, 1600, 1485, 1288, 1253, 1204, 1149, 997, 836, 779, 688 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{19}H_{27}N_2O_2Si$ $[M+H]^+$: 343.1836, found 343.1846.



42

***N*'-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)benzohydrazide (42)**

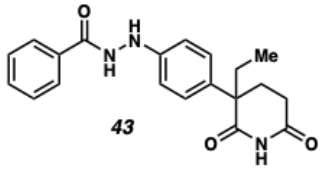
Prepared according to a modified version of general procedure E using **19** (0.3 mmol) and (3-aminophenyl)methanol (0.2 mmol). Prior to purification, the crude mixture was dissolved in dichloromethane (1 mL, 0.2 M), and imidazole (41 mg, 0.6 mmol) and TBSCl (45 mg, 0.3 mmol) were added. The reaction was stirred at 23 °C for two hours, then diluted with water, extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (20% EtOAc in hexanes), providing **42** (28.2 mg, 40% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.88 – 7.81 (m, 2H), 7.61 – 7.52 (m, 1H), 7.48 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.87 – 6.73 (m, 2H), 6.36 (d, *J* = 3.6 Hz, 1H), 4.69 (s, 2H), 0.91 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 148.2, 143.0, 132.5, 132.4, 129.2, 129.0, 127.3, 119.1, 112.5, 111.3, 64.9, 26.1, 18.5, -5.1.

IR (neat film): 3299, 2954, 2928, 2856, 1640, 1596, 1533, 1471, 1255, 1107, 836, 781, 692 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{20}H_{29}N_2O_2Si$ $[M+H]^+$: 357.1993, found 357.1992.



***N*'-(4-(3-ethyl-2,6-dioxopiperidin-3-yl)phenyl)benzohydrazide (43)**

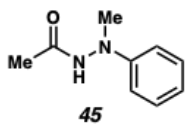
Prepared according to general procedure E using **19** (0.3 mmol) and aminoglutethimide (0.2 mmol). Purification by column chromatography (20% EtOAc in CH_2Cl_2) provided **43** (51.7 mg, 59% yield) as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 – 7.85 (m, 1H), 7.69 – 7.56 (m, 1H), 7.54 – 7.45 (m, 1H), 7.20 – 7.11 (m, 1H), 6.95 – 6.78 (m, 1H), 2.63 – 2.44 (m, 1H), 2.42 – 2.25 (m, 1H), 2.24 – 2.07 (m, 1H), 2.00 – 1.80 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (101 MHz, CD_3OD): δ 178.1, 175.5, 170.3, 149.5, 134.1, 133.2, 131.8, 129.7, 128.5, 128.2, 114.4, 51.6, 33.9, 30.3, 28.0, 9.4.

IR (neat film): 3210, 2967, 1690, 1611, 1515, 1353, 1268, 1197, 835, 713 cm^{-1}.

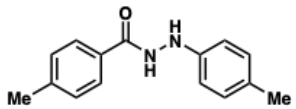
HRMS (ESI+): m/z calc'd for $C_{20}H_{22}N_3O_3$ $[M+H]^+$: 352.1656, found 352.1664.



_N_'-methyl-_N_'-phenylacetohydrazide (45)

Prepared according to general procedure E using **19** (0.3 mmol) and *N*-methyl aniline (0.2 mmol). Purification by column chromatography (25% acetone in hexanes) provided **45** (26.5 mg, 81% yield) as a white solid, characterized as a mixture of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (brs, 1H, major rotamer), 7.30 (m, 2H, major rotamer), 7.24 (m, 2H, minor rotamer), 6.98 (brs, 1H, minor rotamer), 6.94 (m, 1H, major rotamer), 6.86 (m, 3H), 6.82 (d, 2H, minor rotamer), 3.18 (s, 3H, minor rotamer), 3.16 (s, 3H, major rotamer), 2.08 (s, 3H, major rotamer), 2.05 (s, 3H, minor rotamer); all characterization data match those reported in the literature.[50]



46

4-methyl-_N_'-(*p*-tolyl)benzohydrazide (46)

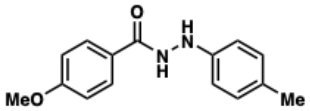
Prepared according to general procedure E using **90** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **46** (33.6 mg, 70% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 4.1 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 9.7 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.27 (d, J = 4.2 Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 145.9, 142.9, 129.9, 129.7, 129.6, 127.2, 114.2, 21.7, 20.7.

IR (neat film): 3354, 3243, 2981, 2918, 1648, 1613, 1539, 1512, 1250, 812 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1335, found 241.1335.



47

4-methoxy-*N′*-(*p*-tolyl)benzohydrazide (47)

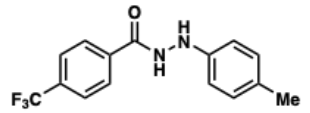
Prepared according to general procedure E using **91** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (20–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **47** (27.1 mg, 53% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.20 – 8.13 (m, 2H), 7.90 – 7.80 (m, 2H), 7.70 – 7.61 (m, 1H), 7.55 – 7.44 (m, 2H), 7.01 – 6.93 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 162.8, 145.8, 130.8, 129.7, 129.0, 124.6, 114.1, 114.0, 55.5, 20.6.

IR (neat film): 3280, 1648, 1607, 1511, 1254, 1178, 1029, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{17}N_2O_2$ $[M+H]^+$: 257.1285, found 257.1287.



48

***N*'-(*p*-tolyl)-4-(trifluoromethyl)benzohydrazide (48)**

Prepared according to general procedure E using **92** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **48** (41.0 mg, 70% yield) as a white solid.

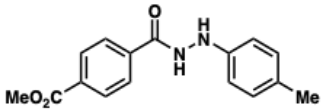
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.91 (m, 3H), 7.74 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.28 (d, J = 4.3 Hz, 1H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, ($(CD_3)_2CO$): δ 166.3, 148.0, 138.0, 133.4 (q, J = 32.2 Hz), 130.1, 129.8, 129.0, 126.4 (q, J = 3.6 Hz), 125.0 (q, J = 270.2 Hz), 114.3, 20.5.

^{19}F NMR (282 MHz, CD_3OD): δ -64.5.

IR (neat film): 3264, 1650, 1512, 1328, 1168, 1128, 860, 812 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{14}F_3N_2O$ $[M+H]^+$: 295.1053, found 295.1057.



49

Methyl 4-(2-(*p*-tolyl)hydrazine-1-carbonyl)benzoate (49)

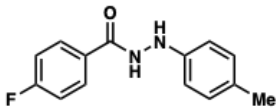
Prepared according to general procedure E using **93** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (1% MeOH in CH_2Cl_2) provided **49** (18.8 mg, 33% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.94 – 7.86 (m, 3H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.28 (s, 1H), 3.96 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 166.3, 145.5, 136.4, 133.5, 131.3, 130.2, 129.9, 127.3, 114.3, 52.6, 20.7.

IR (neat film): 3289, 2952, 1724, 1658, 1513, 1436, 1280, 1110, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O_3$ $[M+H]^+$: 285.1234, found 284.1235.



50

4-fluoro-*N*'-(*p*-tolyl)benzohydrazide (50)

Prepared according to general procedure E using **94** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **50** (36.7 mg, 75% yield) as a white solid.

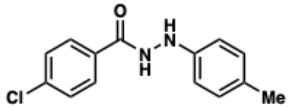
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.80 (m, 3H), 7.15 (t, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.26 (s, 1H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 165.3 (d, *J* = 253.2 Hz), 145.7, 131.2, 129.9, 129.6 (d, *J* = 9.0 Hz), 128.7 (d, *J* = 3.2 Hz), 116.1 (d, *J* = 22.0 Hz), 114.2, 20.7.

^{19}F NMR (282 MHz, CD_3OD): δ -109.9.

IR (neat film): 3341, 3234, 3070, 1648, 1511, 1232, 856, 815, 668 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{14}FN_2O$ $[M+H]^+$: 245.1085, found 245.1088.



51

4-chloro-*N*'-(*p*-tolyl)benzohydrazide (51)

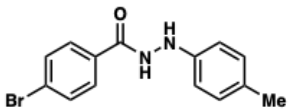
Prepared according to general procedure E using **95** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **51** (34.9 mg, 67% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.81 – 7.74 (m, 2H), 7.49 – 7.41 (m, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.28 – 6.22 (m, 1H), 2.27 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 145.6, 138.7, 131.3, 130.9, 129.9, 129.3, 128.7, 114.2, 20.7.

IR (neat film): 3341, 3237, 1647, 1510, 1093, 852, 813 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{14}ClN_2O$ $[M+H]^+$: 261.0789, found 261.0791.



52

4-bromo-*N*'-(*p*-tolyl)benzohydrazide (52)

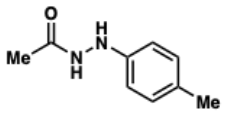
Prepared according to general procedure E using **96** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) provided **52** (37.5 mg, 61% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.24 (d, *J* = 4.3 Hz, 1H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 145.6, 132.3, 131.3, 131.3, 129.9, 128.8, 127.2, 114.3, 20.7.

IR (neat film): 3246, 1647, 1589, 1511, 1009, 812 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{14}BrN_2O$ $[M+H]^+$: 305.0284, found 305.0279.



53

***N*'-(*p*-tolyl)acetohydrazide (53)**

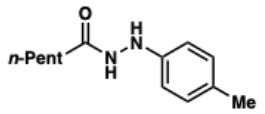
Prepared according to general procedure E using **97** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (5–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **53** (16.1 mg, 49% yield) as a white solid, characterized as a mixture of 2:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 2H, minor rotamer), 7.03 (d, *J* = 7.8 Hz, 2H, major rotamer), 6.74 (d, *J* = 8.0 Hz, 2H, major rotamer), 6.67 (d, *J* = 7.9 Hz, 2H, minor rotamer), 6.13 (s, 1H, major rotamer), 5.74 (s, 1H, minor rotamer), 2.28 (s, 3H, minor rotamer), 2.26 (s, 3H, major rotamer), 2.11 (s, 3H, minor rotamer), 2.04 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 145.6, 144.8, 130.8, 130.1, 129.8, 114.0, 112.7, 21.1, 20.7, 20.6, 19.3.

IR (neat film): 3261, 3025, 2922, 1658, 1510, 1371, 1244, 996, 813, 714, 600 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_9H_{13}N_2O$ $[M+H]^+$: 165.1022, found 165.1022.



54

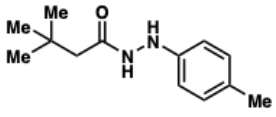
_N_'-(_p_-tolyl)hexanehydrazide (54)

Prepared according to general procedure E using **98** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0.5% MeOH in CH_2Cl_2) followed by preparative thin layer chromatography (50% EtOAc in hexanes) provided **54** (12.9 mg, 29% yield) as a white solid, characterized as a mixture of unresolved rotamers.

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2, 145.8, 145.0, 130.9, 130.8, 130.1, 129.8, 114.0, 112.7, 34.6, 31.7, 31.6, 25.3, 22.6, 22.5, 20.7, 14.1.

IR (neat film): 3261, 3025, 2958, 2925, 2859, 1645, 1615, 1514, 975, 813 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{21}N_2O$ $[M+H]^+$: 221.1648, found 221.1645.



55

3,3-dimethyl-_N_'-(_p_-tolyl)butanehydrazide (55)

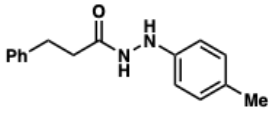
Prepared according to general procedure E using **99** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (1% MeOH in CH_2Cl_2) followed by preparative thin layer chromatography (10% EtOAc in CH_2Cl_2) provided **55** (14.1 mg, 32% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H), 7.08 (d, *J* = 8.2 Hz, 2H, minor rotamer), 7.03 (d, *J* = 8.7 Hz, 2H, major rotamer), 6.77 (d, *J* = 8.5 Hz, 2H, major rotamer), 6.69 (d, *J* = 8.3 Hz, 2H, minor rotamer), 2.63 – 1.72 (m, 5H), 1.07 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 145.9, 130.8, 130.1, 129.8, 114.1, 112.9, 48.2, 42.8, 31.2, 30.0, 20.7.

IR (neat film): 3266, 3025, 2953, 2867, 1659, 1513, 1476, 1366, 1237, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{21}N_2O$ $[M+H]^+$: 221.1648, found 221.1649.



56

3-phenyl-*N*'-(*p*-tolyl)propanehydrazide (56)

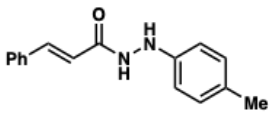
Prepared according to general procedure E using **100** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (0–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **56** (18.7 mg, 37% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 4.0 Hz, 1H, major rotamer), 7.35 – 7.14 (m, 5H), 7.02 (d, *J* = 8.2 Hz, 2H, minor rotamer), 6.97 (d, *J* = 8.5 Hz, 2H, major rotamer), 6.61 – 6.49 (m, 2H), 6.04 (d, *J* = 4.1 Hz, 1H, major rotamer), 5.47 (s, 1H, minor rotamer), 2.97 (m, 2H), 2.75 (m, 2H, minor rotamer), 2.53 (t, *J* = 7.5 Hz, 2H, major rotamer), 2.30 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 172.3, 145.5, 144.7, 141.2, 140.5, 130.8, 130.7, 130.0, 129.7, 128.8, 128.6, 128.6, 128.6, 128.5, 126.6, 126.3, 113.8, 112.7, 36.3, 33.1, 31.5, 30.8, 20.7, 20.6.

IR (neat film): 3257, 3026, 2920, 1655, 1510, 1453, 1239, 994, 812, 698 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1492, found 255.1493.



57

***N*'-(*p*-tolyl)cinnamohydrazide (57)**

Prepared according to general procedure E using **101** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (0–75% MeCN in H_2O with

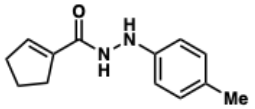
0.1% TFA, C18 column) provided **57** (19.2 mg, 38% yield) as a white solid, characterized as a ratio of 2:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 15.9 Hz, 1H, minor rotamer), 7.72 (d, *J* = 15.7 Hz, 1H, major rotamer), 7.67 (d, *J* = 4.2 Hz, 1H), 7.51 (m, 5H, minor rotamer), 7.38 – 7.37 (m, 3H, major rotamer), 7.34 (m, 2H, major rotamer), 7.15 (d, *J* = 15.9 Hz, 1H, minor rotamer), 7.08 (d, *J* = 8.1 Hz, 2H, minor rotamer), 7.04 (d, *J* = 8.1 Hz, 2H, major rotamer), 6.80 (d, *J* = 8.2 Hz, 2H, major rotamer), 6.74 (d, *J* = 8.1 Hz, 2H, minor rotamer), 6.48 (d, *J* = 15.7 Hz, 1H, major rotamer), 6.28 (d, *J* = 4.3 Hz, 1H), 5.77 (s, 1H, minor rotamer), 2.28 (s, 3H, minor rotamer), 2.26 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 166.3, 145.6, 145.1, 144.6, 142.9, 135.1, 134.6, 131.1, 130.9, 130.2, 130.2, 130.1, 129.9, 129.0, 128.9, 128.4, 128.1, 117.6, 115.4, 114.2, 113.2, 20.7.

IR (neat film): 3227, 3025, 2917, 1661, 1626, 1510, 1449, 1349, 1217, 1177, 977, 810, 726, 650 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1335, found 253.1335.



58

***N*'-(*p*-tolyl)cyclopent-1-ene-1-carbohydrazide (58)**

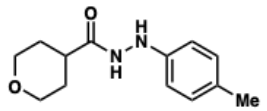
Prepared according to general procedure E using **102** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (15% EtOAc in CH_2Cl_2) provided **58** (21.6 mg, 50% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (brs, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.67 – 6.64 (m, 1H), 6.19 (brs, 1H), 2.60 (ddt, *J* = 10.3, 7.4, 2.3 Hz, 2H), 2.54 – 2.48 (m, 2H), 2.26 (s, 3H), 2.06 – 1.97 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6, 145.8, 140.1, 137.1, 130.8, 129.8, 114.2, 33.3, 31.4, 23.4, 20.7.

IR (neat film): 3276, 2953, 2853, 1652, 1614, 1512, 1470, 1294, 1122, 813, 658 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{17}N_2O$ $[M+H]^+$: 217.1335, found 217.1330.



59

***N*'-(*p*-tolyl)tetrahydro-2*H*-pyran-4-carbohydrazide (59)**

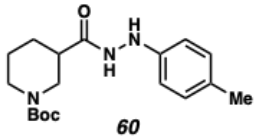
Prepared according to general procedure E using **103** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (30–50% EtOAc in CH_2Cl_2) provided **59** (28.6 mg, 61% yield) as a white solid, characterized as a ratio of 4:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H, minor rotamer), 7.49 (d, *J* = 4.3 Hz, 1H, major rotamer), 7.08 (d, *J* = 8.1 Hz, 2H, minor rotamer), 7.03 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.72 (d, *J* = 8.5 Hz, 2H, major rotamer), 6.69 (d, *J* = 8.6 Hz, 2H, minor rotamer), 6.13 (d, *J* = 4.4 Hz, 1H, major rotamer), 5.67 (s, 1H, minor rotamer), 4.03 (ddd, *J* = 10.7, 4.0, 1.9 Hz, 2H, major rotamer), 3.97 (ddd, *J* = 12.0, 4.5, 2.4 Hz, 2H, minor rotamer), 3.47 –3.35 (m, 2 x 2H), 3.08 (tt, *J* = 11.5, 3.9 Hz, 1H, minor rotamer), 2.44 (tt, *J* = 11.4, 4.2 Hz, 1H, major rotamer), 2.28 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer), 1.93 – 1.81 (m, 2 x 2H), 1.81 – 1.73 (m, 2 x 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 180.1, 174.4, 145.7, 131.3, 131.0, 130.2, 113.9, 112.9, 67.3, 67.2, 67.1, 42.4, 40.6, 36.4, 29.1, 28.6, 28.6, 20.7, 20.6.

IR (neat film): 3285, 2954, 2848, 1743, 1682, 1513, 1277, 1243, 1135, 1087, 815 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{19}N_2O_2$ $[M+H]^+$: 235.1441, found 235.1437.



60

***Tert*-butyl 3-(2-(*p*-tolyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (60)**

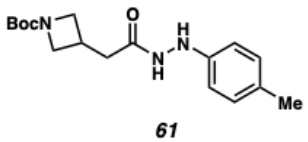
Prepared according to general procedure E using **104** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by reverse phase flash chromatography (0–75% MeCN in H_2O with 0.1% TFA, C18 column) provided **60** (34.5 mg, 52% yield) as a white solid, characterized as a mixture of unresolved rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 – 6.98 (m, 2H), 6.76 – 6.65 (m, 2H), 3.94 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.74 (s, 1H), 3.28 (t, *J* = 10.3 Hz, 1H), 3.06 (s, 1H), 2.40 (s, 1H), 2.32 – 2.19 (m, 3H), 1.89 (s, 2H), 1.74 – 1.61 (m, 1H), 1.46 (s, 9H), 1.43 – 1.34 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.4, 173.1, 154.8, 145.8, 145.0, 130.7, 130.1, 129.8, 113.9, 112.9, 80.3, 79.7, 77.5, 77.4, 77.2, 76.8, 45.7, 41.3, 34.0, 32.0, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 28.6, 28.5, 27.6, 27.4, 25.0, 24.2, 22.8, 20.7, 20.6, 14.3.

IR (neat film): 3266, 2922, 2857, 1660, 1512, 1424, 1364, 1242, 1148, 909, 813 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{28}N_3O_3$ [M+H]+: 332.1980, found 332.1980.



61

***Tert*-butyl 3-(2-oxo-2-(2-(*p*-tolyl)hydrazineyl)ethyl)azetidine-1-carboxylate (61)**

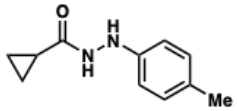
Prepared according to general procedure E using **105** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (0–5% MeOH in CH_2Cl_2) provided **61** (42.8 mg, 67% yield) as a white solid, characterized as a ratio of 1.8:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 4.1 Hz, 1H, major rotamer), 7.07 (d, *J* = 8.6 Hz, 2H, minor rotamer), 7.02 (d, *J* = 8.1 Hz, 2H, major rotamer), 6.69 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.66 (d, *J* = 8.4 Hz, 2H, minor rotamer), 6.09 (d, *J* = 4.2 Hz, 1H, major rotamer), 5.76 (s, 1H, minor rotamer), 4.07 (dd, *J* = 8.5, 8.5 Hz, 2 x 2H), 3.62 (dd, *J* = 8.8, 5.4 Hz, 2H, major rotamer), 3.56 (dd, *J* = 8.8, 5.2 Hz, 2H, minor rotamer), 2.96 – 2.88 (m, 1H, major rotamer), 2.86 – 2.83 (m, 1H, minor rotamer), 2.75 (d, *J* = 7.8 Hz, 2H, minor rotamer), 2.53 (d, *J* = 7.8 Hz, 2H, major rotamer), 2.28 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer), 1.43 (s, 9H, major rotamer); 1.41 (s, 9H, minor rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 171.0, 156.5, 156.4, 145.6, 144.7, 131.1, 130.9, 130.2, 129.9, 113.9, 112.6, 79.7, 79.5, 54.5, 41.7, 38.4, 36.0, 28.5, 25.6, 24.9, 24.6, 20.7, 20.6.

IR (neat film): 3278, 2976, 1675, 1513, 1408, 1145, 814, 731 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{17}H_{26}N_3O_3$ $[M+H]^+$: 320.1969, found 320.1973.



62

***N*'-(*p*-tolyl)cyclopropanecarbohydrazide (62)**

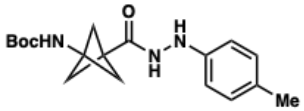
Prepared according to general procedure E using **106** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (25% EtOAc in CH_2Cl_2) provided **62** (18.6 mg, 49% yield) as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ 6.99 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 2.22 (s, 3H), 1.66 (tt, *J* = 7.9, 4.7 Hz, 1H), 0.92 – 0.87 (m, 2H), 0.85 – 0.77 (m, 2H).

^{13}C NMR (101 MHz, CD_3OD): δ 176.5, 147.7, 130.6, 130.4, 114.3, 113.7, 20.6, 13.1, 9.9, 8.4, 7.3.

IR (neat film): 3295, 2414, 2358, 1622, 1606, 1513, 1462, 1100, 952, 814 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{14}N_2NaO$ $[M+Na]^+$: 213.0998, found 213.1001.



63

***Tert*-butyl (3-(2-(*p*-tolyl)hydrazine-1-carbonyl)bicyclo[1.1.1]pentan-1-yl)carbamate (63)**

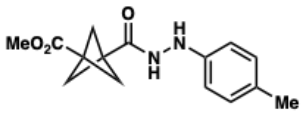
Prepared according to general procedure E using **107** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (10–40% EtOAc in CH_2Cl_2) provided **63** (33.1 mg, 50% yield) as a white solid, characterized as a ratio of 7.3:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 4.3 Hz, 1H, major rotamer), 7.05 (d, *J* = 4.1 Hz, 2H, minor rotamer), 7.02 (d, *J* = 7.8 Hz, 2H, major rotamer), 6.71 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.63 (d, *J* = 8.4 Hz, 2H, minor rotamer), 6.07 (d, *J* = 4.4 Hz, 1H, major rotamer), 5.62 (s, 1H, minor rotamer), 5.05 (s, 1H, major rotamer), 4.94 (s, 1H, minor rotamer), 2.33 (s, 6H, minor rotamer), 2.30 (s, 6H, major rotamer), 2.27 (s, 3H, minor rotamer), 2.25 (s, 3H, major rotamer), 1.45 (s, 9H, major rotamer) 1.40 (s, 9H, minor rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6, 169.2, 145.4, 144.9, 131.0, 130.8, 130.1, 129.8, 114.1, 112.8, 80.1, 54.7, 54.1, 53.9, 46.4, 45.6, 35.7, 28.5, 28.5, 20.7, 20.6.

IR (neat film): 3278, 2980, 2920, 1694, 1513, 1366, 1251, 1168, 1051, 814, 703 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{26}N_3O_3$ $[M+H]^+$: 332.1969, found 332.1972.



64

Methyl 3-(2-(*p*-tolyl)hydrazine-1-carbonyl)bicyclo[1.1.1]pentane-1-carboxylate (64)

Prepared according to general procedure E using **108** (0.3 mmol) and *p*-toluidine (0.2 mmol). Purification by column chromatography (10–30% EtOAc in CH_2Cl_2) provided **64**

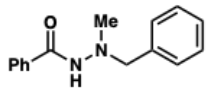
(11 mg, 44% yield) as a white solid, characterized as a ratio of 5:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 4.3 Hz, 1H, major rotamer), δ 7.07 (d, *J* = 8.4 Hz, 2H, minor rotamer), 7.04 (d, *J* = 8.6 Hz, 2H, major rotamer), 6.89 (s, 1H, minor rotamer), 6.73 (d, *J* = 8.4 Hz, 2H, major rotamer), 6.66 (d, *J* = 8.4 Hz, 2H, minor rotamer), 5.99 (d, *J* = 4.4 Hz, 1H, major rotamer), 5.62 (s, 1H, minor rotamer), 3.71 (s, 3H, major rotamer), 3.63 (s, 3H, minor rotamer), 2.36 (s, 6H, major rotamer), 2.34 (s, 6H, minor rotamer), 2.28 (s, 3H, minor rotamer), 2.26 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 172.3, 169.6, 168.8, 146.2, 145.3, 131.2, 130.2, 129.9, 114.2, 112.8, 53.5, 52.6, 52.1, 51.9, 38.6, 38.1, 37.5, 20.7, 20.6.

IR (neat film): 3274, 1732, 1658, 1513, 1312, 1277, 1063, 910, 814, 711 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{19}N_2O$ $[M+H]^+$: 275.1390, found 275.1389.



27

***N*'-benzyl-*N*'-methylbenzohydrazide (27)**

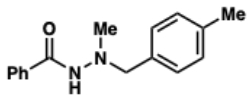
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (0–30% EtOAc in CH_2Cl_2) provided **27** (28.4 mg, 59% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.57 (m, 2H), 7.49 – 7.44 (m, 1H), 7.39 – 7.28 (m, 7H), 6.90 (s, 1H), 4.11 (s, 2H), 2.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 135.9, 134.0, 131.7, 129.7, 128.7, 128.6, 127.9, 127.0, 62.6, 44.7.

IR (neat film): 3235, 3061, 2848, 1645,1542, 1448, 1306, 1108, 1006, 921, 742 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1335, found 241.1338.



65

***N*'-methyl-*N*'-(4-methylbenzyl)benzohydrazide (65)**

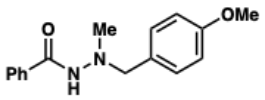
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methyl-1-(*p*tolyl)methanamine (0.3 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **65** (27.5 mg, 54% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.59 (m, 2H), 7.49 – 7.44 (m, 1H), 7.40 – 7.35 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.86 (brs, 1H), 4.06 (s, 2H), 2.77 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 137.6, 134.0, 132.6, 131.6, 129.7, 129.3, 128.7, 127.0, 62.3, 44.6, 21.3.

IR (neat film): 3228, 2848, 1648, 1578, 1448, 1306, 1108, 1004, 802, 693 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1492, found 255.1495.



66

***N*'-(4-methoxybenzyl)-*N*'-methylbenzohydrazide (66)**

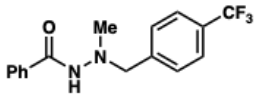
Prepared according to general procedure F, using **19** (0.2 mmol) and 1-(4-methoxyphenyl)*N*-methylmethanamine (0.3 mmol). Purification by column chromatography (20% EtOAc in CH_2Cl_2) provided **66** (17.4 mg, 32% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.57 (m, 2H), 7.51 – 7.41 (m, 1H), 7.40 – 7.32 (m, 2H), 7.32 – 7.21 (m, 2H), 6.92 – 6.81 (m, 3H), 4.04 (s, 2H), 3.79 (s, 3H), 2.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 159.3, 134.0, 131.6, 130.9, 128.7, 127.8, 127.0, 113.9, 61.9, 55.4, 44.6.

IR (neat film) 3223, 2953, 2836, 1768, 1651, 1511, 1449, 1240, 1174, 1035, 909, 853, 701 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$: 271.1441, found 271.1446.



67

***N*'-(4-methoxybenzyl)-*N*'-methylbenzohydrazide (67)**

Prepared according to general procedure F, using **19** (0.2 mmol) and *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (0.3 mmol). Purification by column chromatography (20% EtOAc in CH_2Cl_2) provided **67** (25.7 mg, 42% yield) as a white solid.

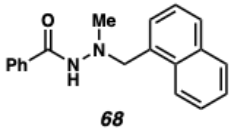
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.54 (m, 4H), 7.48 (dd, *J* = 20.8, 7.7 Hz, 3H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.05 (s, 1H), 4.18 (s, 2H), 2.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 140.9, 133.7, 131.8, 123.0 (q, *J* = 32.3 Hz), 129.5, 128.8, 125.5 (q, *J* = 3.5 Hz), 124.3 (q, *J* = 272.0 Hz), 122.9, 120.2, 62.0, 45.0.

^{19}F (282 MHz, $CDCl_3$): δ -62.5.

IR (neat film): 3214, 1640, 1538, 1324, 1165, 1115, 1066, 1019, 913, 858, 817, 724, 691, 648 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{16}F_3N_2O$ $[M+H]^+$: 309.1108, found 309.1121.



68

***N*'-methyl-*N*'-(naphthalen-1-ylmethyl)benzohydrazide (68)**

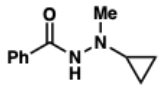
Prepared according to general procedure F, using **19** (0.2 mmol) and *N*-methyl-1-(naphthalen-1-yl)-methanamine (0.3 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **68** (36.6 mg, 66% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.54 (m, 3H), 7.53 – 7.50 (m, 1H), 7.49 – 7.32 (m, 5H), 7.07 (s, 1H), 4.58 (s, 2H), 2.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 134.0, 134.0, 132.6, 132.6, 131.6, 128.8, 128.7, 128.6, 128.3, 127.0, 126.5, 126.0, 125.3, 124.8, 60.2, 44.5.

IR (neat film): 3218, 3056, 1640, 1538, 1324, 1165, 1114, 1067, 907, 799, 725 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{19}H_{19}N_2O$ $[M+H]^+$: 291.1492, found 291.1479.



69

***N*'-cyclopropyl-*N*'-methylbenzohydrazide (9h)**

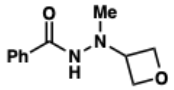
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methyl-cyclopropanamine (0.3 mmol). Purification by column chromatography (0–30% EtOAc in CH_2Cl_2) provided **69** (16.4 mg, 43% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.42 (ddd, *J* = 8.4, 6.5, 1.5 Hz, 2H), 7.23 (s, 1H), 2.84 (s, 3H), 2.49 (tt, *J* = 6.7, 3.4 Hz, 1H), 0.79 – 0.67 (m, 2H), 0.60 – 0.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 134.1, 131.7, 128.7, 127.1, 45.3, 39.8, 6.8.

IR (neat film): 3238, 3061, 2954, 1647, 1578, 1541, 1490, 1448, 1300, 1142, 1018, 915, 888, 712, 693 cm^{-1}.

HRMS (ESI+) m/z calc'd for $C_{11}H_{15}N_2O$ $[M+H]^+$: 191.1179, found 191.118.



70

_N_'-methyl-_N_'-(oxetan-3-yl)benzohydrazide (70)

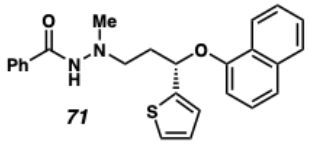
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (20–33% acetone in CH_2Cl_2) provided **70** (33.4 mg, 81% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.51 (dd, *J* = 7.5, 7.3 Hz, 1H), 7.42 (dd, *J* = 7.6, 7.4 Hz, 2H), 7.30 (s, 1H), 4.71 (dd, *J* = 6.6, 2.1 Hz, 4H), 4.32 (dt, *J* = 6.6, 6.3 Hz, 1H), 2.71 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 133.4, 132.0, 128.8, 127.2, 74.8, 60.5, 41.9.

IR (neat film): 3229, 2953, 2878, 1648, 1536, 1490, 1289, 1069, 975, 921, 898 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1128, found 207.1129.



71

(_S_)-_N_'-methyl-_N_'-(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)benzohydrazide (71)

Prepared according to general procedure F, using **19** (0.2 mmol) and duloxetine (0.3 mmol). Purification by column chromatography (10% EtOAc in hexanes) provided **71** (32.7 mg, 39% yield) as a white solid.

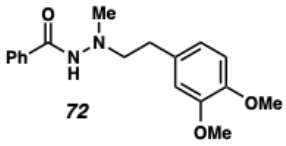
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 6.3, 3.4 Hz, 1H), 7.78 (dd, *J* = 6.1, 3.3 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.53 – 7.43 (m, 3H), 7.43 – 7.35 (m, 3H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.10 (d, *J* = 2.8 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.92

(dd, *J* = 5.1, 3.5 Hz, 1H), 6.79 (s, 1H), 6.03 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.21 – 2.89 (m, 2H), 2.72 (s, 3H), 2.57 – 2.23 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 153.4, 145.2, 134.7, 133.8, 131.7, 128.7, 127.6, 127.1, 126.7, 126.3, 126.0, 125.3, 124.9, 124.8, 122.2, 120.7, 107.4, 74.2, 55.9, 46.7, 36.8.

IR (neat film): 3220, 3054, 2957, 1643, 1578, 1396, 1264, 1235, 1094, 908, 727 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{25}H_{25}N_2O_2S$ $[M+H]^+$: 417.1631, found 417.1647.



72

***N*'-(3,4-dimethoxyphenethyl)-*N*'-methylbenzohydrazide (72)**

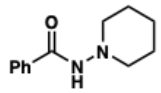
Prepared according to general procedure F using **19** (0.2 mmol) and 2-(3,4dimethoxyphenyl)-*N*-methylethan-1-amine (0.3 mmol). Purification by reverse phase flash chromatography (10%–100% MeCN in H_2O with 0.1% TFA, C18 column), and basic workup of the resulting TFA salt of **72** with saturated $NaHCO_3$ solution, provided **72** (22.6 mg, 36% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.0 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.42 (dd, *J* = 8.2, 6.7 Hz, 2H), 6.79 – 6.73 (m, 4H, N–H & aromatic C–H), 3.84 (s, 3H), 3.83 (s, 3H), 3.10 (dd, *J* = 8.5, 6.7 Hz, 2H), 2.87 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.79 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 149.1, 147.6, 133.8, 132.4, 131.8, 128.7, 127.1, 120.6, 112.2, 111.4, 61.1, 56.0, 56.0, 46.4, 33.7.

IR (neat film): 3240, 2927, 2851, 1648, 1515, 1464, 1261, 1236, 1156, 1141, 1028, 805, 715, 695 cm^{-1}.

HRMS (ESI+) m/z calc'd for $C_{18}H_{23}N_2O$ $[M+H]^+$: 315.1703, found 315.1692.



74

***N*-(piperidin-1-yl)benzamide (74)**

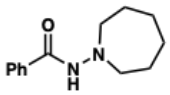
Prepared according to general procedure F using **19** (0.2 mmol) and piperidine (0.3 mmol). Purification by column chromatography (0–25% acetone in hexanes) provided **74** (9.4 mg, 23% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.1 Hz, 2H), 7.49 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.41 (dd, *J* = 7.7, 7.3 Hz, 1H), 6.79 (s, 1H), 2.87 (t, *J* = 5.4 Hz, 4H), 1.80 – 1.75 (m, 4H), 1.48 – 1.43 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 134.2, 131.6, 128.7, 127.1, 57.3, 25.5, 23.4.

IR (neat film): 3191, 3031, 2938, 2811, 1653, 1638, 1570, 1472, 1316, 1143, 1085, 918, 725 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1335, found 205.1342.



75

***N*-(azepan-1-yl)benzamide (75)**

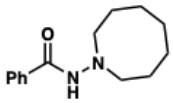
Prepared according to general procedure F using **19** (0.2 mmol) and azepane (0.3 mmol). Purification by column chromatography (25% EtOAc in CH_2Cl_2) provided **75** (25.8 mg, 59% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.51 – 7.46 (m, 1H), 7.41 (dd, *J* = 7.6, 7.1 Hz, 2H), 7.30 (s, 1H), 3.20 – 3.14 (m, 4H), 1.78 – 1.72 (m, 4H), 1.68 – 1.63 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 134.2, 131.6, 128.7, 127.1, 58.3, 27.2, 26.4.

IR (neat film): 3191, 3031, 2811, 1653, 1638, 1570, 1316, 1143, 1085, 1038, 918, 725, 695 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492, found 219.1499.



76

***N*-(azocan-1-yl)benzamide (76)**

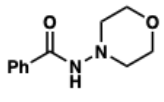
Prepared according to general procedure F using **19** (0.2 mmol) and azocane (0.3 mmol). Purification by column chromatography (10–15% EtOAc in CH_2Cl_2) provided **76** (26.5 mg, 57% yield) as a white solid, characterized as a ratio of 7.8:1 rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 6.9 Hz, 2H, major rotamer), 7.66 (d, *J* = 7.3 Hz, 2H, minor rotamer), 7.51 – 7.46 (m, 2 x 1H), 7.45 – 7.39 (m, 2 x 2H), 3.15 (t, *J* = 5.3 Hz, 4H, major rotamer), 2.90 – 2.85 (m, 4H, minor rotamer), 1.73 – 1.64 (m, 10H, major rotamer), 1.53 – 1.50 (m, 10H, minor rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 134.3, 131.6, 128.7, 128.3, 127.7, 127.1, 58.9, 56.4, 27.1, 27.0, 26.5, 26.3, 25.5.

IR (neat film): 3251, 2910, 1649, 1545, 1308, 1167, 1015, 927, 891, 649 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1648, found 233.1655.



77

***N*-morpholinobenzamide (77)**

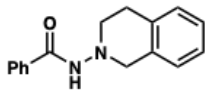
Prepared according to general procedure F, using **19** (0.2 mmol) and morpholine (0.3 mmol). Purification by reverse phase flash chromatography (0–50% MeCN in H_2O with 0.1% TFA, C18 column) provided **77** (14.5 mg, 35% yield) as a white solid.

^{1}H NMR (400 MHz, CD_3OD): δ 7.83 – 7.76 (m, 2H), 7.59 – 7.51 (m, 1H), 7.46 (dd, *J* = 8.2, 6.7 Hz, 2H), 3.85 – 3.78 (m, 4H), 2.95 – 2.88 (m, 4H).

^{13}C NMR (101 MHz, CD_3OD): δ 168.4, 134.6, 132.9, 129.6, 128.4, 67.5, 56.3.

IR (neat film): 2954, 2848, 2320, 1631, 1577, 1432, 1381, 1264, 1108, 1104, 889 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1128, found 207.1128.



78

***N*-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (78)**

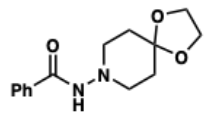
Prepared according to general procedure F, using **19** (0.2 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.3 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) provided **78** (23.2 mg, 46% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.21 (s, 1H), 7.19 – 7.10 (m, 3H), 7.07 – 6.98 (m, 1H), 4.20 (s, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 6.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 133.9, 133.1, 133.0, 131.8, 128.8, 128.8, 127.2, 127.0, 126.9, 126.2, 57.4, 52.9, 27.8.

IR (neat film): 3191, 3029, 2927, 1644, 1558, 1313, 940, 905, 738, 707 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1335, found 253.1343.



79

_N_-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzamide (79)

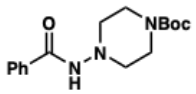
Prepared according to general procedure F using **19** (0.2 mmol) and 1,4-dioxa-8azaspiro[4.5]decane (0.3 mmol). Purification by reverse phase flash chromatography (10%–100% MeCN in H_2O with 0.1% TFA, C18 column), and basic workup of the resulting TFA salt of **79** with saturated $NaHCO_3$ solution, provided **79** (19.9 mg, 38% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.1 Hz, 2H), 7.51 – 7.45 (m, 1H), 7.41 (dd, *J* = 8.2, 6.6 Hz, 2H), 6.87 (brs, 1H), 3.95 (s, 4H), 3.01 (t, *J* = 5.6 Hz, 4H), 1.92 (t, *J* = 5.7 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 133.9, 131.7, 128.7, 127.2, 106.2, 64.5, 54.1, 34.2.

IR (neat film): 3224, 2930, 1648, 1549, 1294, 1223, 1144, 1071, 1037, 963, 846 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1390, found 263.1400.



80

***Tert*-butyl 4-benzamidopiperazine-1-carboxylate (80)**

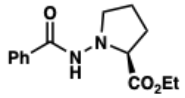
Prepared according to general procedure F, using **19** (0.2 mmol) and *tert*-butyl piperazine1-carboxylate (0.3 mmol). Purification by reverse phase flash chromatography (0–50% MeCN in H_2O with 0.1% TFA, C18 column) provided **80** (14.5 mg, 24% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.82 – 7.76 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 3.68 (t, *J* = 5.1 Hz, 4H), 3.31 (t, *J* = 5.1 Hz, 4H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 154.4, 132.8, 132.0, 129.1, 127.4, 81.1, 54.4, 42.5, 28.5.

IR (neat film): 2980, 2319, 1650, 1428, 1263, 1173, 1138, 998, 889, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{16}H_{24}N_3O_3$ $[M+H]^+$: 306.1812, found 306.1813.



81

Ethyl benzamido-(*L*)-prolinate (81)

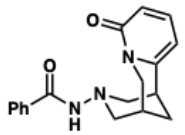
Prepared according to general procedure F using **19** (0.2 mmol) and ethyl (*L*)-prolinate (0.3 mmol). Purification by column chromatography (30% EtOAc in CH_2Cl_2) provided **81** (16.3 mg, 31% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.73 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.44 – 7.39 (m, 2H), 4.24 – 4.13 (m, 3H, N–H & CH_2), 3.50 (td, *J* = 8.0, 5.6 Hz, 1H), 3.24 (td, *J* = 8.2, 5.7 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.08 – 1.96 (m, 2H), 1.95 – 1.86 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 166.5, 133.7, 131.8, 128.7, 127.1, 63.7, 61.0, 53.1, 28.3, 22.0, 14.3.

IR (neat film): 3248, 2980, 1733, 1652, 1579, 1539, 1375, 1294, 1184, 1026, 929, 860, 801, 694 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1390, found 263.1401; $[\alpha]_D^{21.7}$ – 53.62 (*c* 1.26, $CHCl_3$).



82

***N*-((1*S*,5*S*)-8-oxo-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-3(4*H*)-yl)benzamide (82)**

Prepared according to general procedure F, using **19** (0.2 mmol) and cytisine (0.3 mmol).

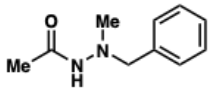
Purification by reverse phase flash chromatography (0–95% MeCN in H_2O with 0.1% TFA, C18 column) provided **82** (15 mg, 24% yield) as a white solid, characterized as a mixture of unresolved rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.61 (m, 2H), 7.54 – 7.37 (m, 3H), 7.37 – 7.27 (m, 1H), 7.16 (m, 1H, major rotamer), 6.87 (s, 1H, minor rotamer), 6.74 (d, *J* = 8.9 Hz, 1H, major rotamer), 6.65 (d, *J* = 9.0 Hz, 1H, minor rotamer), 6.30 (d, *J* = 7.0 Hz, 1H, major rotamer), 6.12 (d, *J* = 7.0 Hz, 1H, minor rotamer), 4.24 (d, *J* = 15.7 Hz, 1H, major rotamer), 4.06 – 3.92 (m, 2H), 3.91 – 3.74 (m, 1H, minor rotamer), 3.13 (d, *J* = 25.9 Hz, 3H), 2.81 (dd, *J* = 17.0, 10.4 Hz, 1H, minor rotamer), 2.60 (s, 1H, major rotamer), 2.54 (s, 1H, minor rotamer), 2.07 – 1.51 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 164.1, 151.6, 140.6, 139.9, 133.2, 132.1, 131.6, 128.8, 127.9, 127.6, 126.9, 116.8, 115.9, 108.2, 107.3, 63.3, 59.8, 59.6, 50.9, 50.1, 36.1, 35.4, 28.5, 28.2, 24.7, 24.6.

IR (neat film): 3234, 2948, 1644, 1546, 1192, 1143, 907, 802, 729, 712 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{18}H_{20}N_3O_2$ $[M+H]^+$: 310.1550, found 310.1554.



83

***N*'-benzyl-*N*'-methylacetohydrazide (83)**

Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (25–50% acetone in hexanes) provided **83** (18.9 mg, 53% yield) as a white solid, characterized as a ratio of 2.7:1 rotamers.

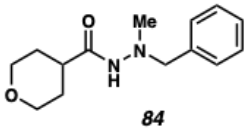
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 2 x 5H), 6.45 (s, 1H, major rotamer), 6.30

(s, 1H, minor rotamer), 3.97 (s, 2H, minor rotamer), 3.74 (s, 2H, major rotamer), 2.67 (s, 3H, minor rotamer), 2.54 (s, 3H, major rotamer), 1.94 (s, 3H, minor rotamer), 1.82 (s, 3H, major rotamer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5, 168.4, 135.8, 135.8, 129.8, 129.5, 128.6, 128.5, 128.0, 127.8, 65.1, 62.6, 46.3, 44.8, 21.7, 19.9.

IR (neat film): 3212, 3062, 2954, 2849, 1652, 1547, 1495, 1446, 1368, 1325, 1297, 1112, 997, 891, 746, 698, 526 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{10}H_{15}N_2O$ $[M+H]^+$: 179.1179, found 179.1176.



84

***N*'-benzyl-*N*'-methyltetrahydro-2*H*-pyran-4-carbohydrazide (84)**

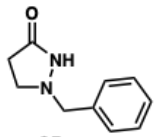
Prepared according to general procedure F using **19** (0.2 mmol) and *N*-methylbenzylamine (0.3 mmol). Purification by column chromatography (25–50% acetone in hexanes) provided **84** (24.8 mg, 50% yield) as a white solid, characterized as a 1.3:1 ratio of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 2 x 5H), 6.27 (s, 1H, minor rotamer), 6.03 (s, 1H, major rotamer), 3.99 (s, 2H, major rotamer), 3.96 – 3.91 (m, 2H, major rotamer), 3.91 – 3.85 (m, 2H, minor rotamer), 3.80 (d, J = 12.3 Hz, 1H, minor rotamer), 3.66 (d, J = 12.2 Hz, 1H, minor rotamer), 3.45 – 3.38 (m, 2H, minor rotamer), 3.32 (td, J = 11.7, 2.3 Hz, 2H, major rotamer), 2.95 (tt, J = 11.7, 3.9 Hz, 1H), 2.72 (s, 3H, minor rotamer), 2.58 (s, 3H, major rotamer), 2.11 (tt, J = 11.5, 3.9 Hz, 1H, minor rotamer), 1.78 – 1.49 (m, 2 x 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.8, 172.6, 136.2, 135.6, 130.0, 129.6, 128.7, 128.5, 128.2, 127.8, 67.4, 67.3, 65.5, 62.4, 47.1, 44.9, 41.0, 36.9, 29.1, 29.0, 28.0.

IR (neat film): 3225, 3061, 2951, 2846, 1660, 1533, 1445, 1297, 1127, 1088, 1016, 984, 859, 741, 700 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{14}H_{21}N_2O_2$ $[M+H]^+$: 249.1598, found 249.1600.



85

1-benzylpyrazolidin-3-one (85)

Prepared according to general procedure F, using *N*-(benzoyloxy)-3(benzylamino)propenamide (**19**) (0.2 mmol). Purification by reverse phase flash chromatography (0–50% MeCN in H_2O with 0.1% TFA, C18 column) provided **85** (18.4 mg, 52% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.47 – 7.33 (m, 5H), 4.14 (s, 2H), 3.59 – 3.55 (m, 2H), 2.54 (t, J = 8.1 Hz, 2H).

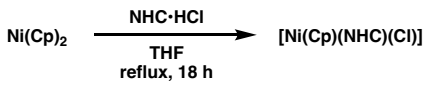
^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 131.3, 130.4, 129.6, 129.4, 63.0, 50.7, 29.5.

IR (neat film): 3030, 2848, 2319, 1678, 1630, 1576, 1429, 1263, 1197, 1132, 889, 712, 694 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{10}H_{13}N_2O$ $[M+H]^+$: 177.1022, found 177.1016.

1.7.2.3 Synthesis of Ni Half-Sandwich Catalyst

*Preparation of [Ni(Cp)(NHC$^{i\text{-}Pr}$)(Cl)] (**24**): General Procedure G*



A procedure was adapted from the literature.[43]

In a nitrogen-filled glovebox, nickelocene (1.13 g, 1.0 equiv) and 1,3-diisopropyl-1*H*imidazol-3-ium chloride (1.13 g, 1.0 equiv) were weighed into a Schlenk tube and dissolved in THF (50 mL, 0.12 M). The tube was sealed, removed from the glovebox, and the green solution was heated to reflux overnight, during which the solution turned from dark green to maroon. After 18 hours, the reaction mixture was passed through a Celite plug eluting with CH_2Cl_2, concentrated, and purified with silica gel chromatography (0–25% EtOAc in CH_2Cl_2), collecting only the maroon fractions, to provide **24** (1.41 g, 75% yield) as a dark red solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 2H), 6.42 (p, *J* = 6.8 Hz, 2H), 5.22 (s, 5H), 1.53 (dd, *J* = 41.1, 6.8 Hz, 12H).

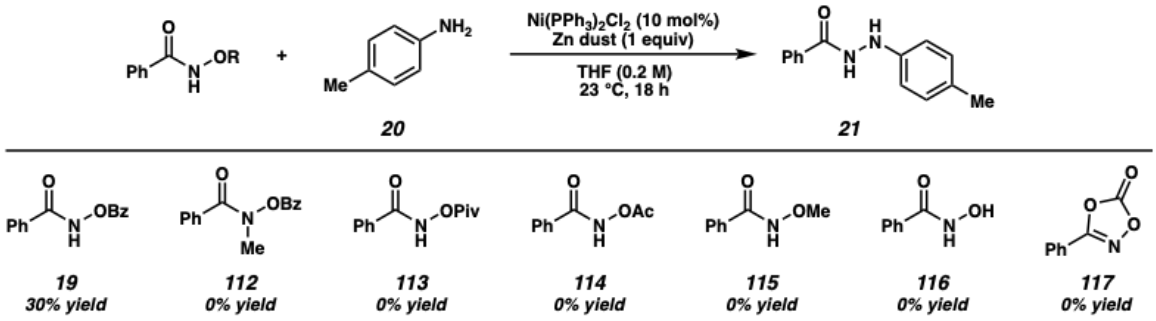
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.1, 118.5, 91.8, 53.7, 23.9, 23.6.

IR (neat film): 3088, 2974, 2933, 2875, 1424, 1213, 777, 728, 694 cm^{-1}.

HRMS (FD): m/z calc'd for $C_{14}H_{21}N_2ClNi$ $[M]^{+\bullet}$: 310.07467, found 310.07478.

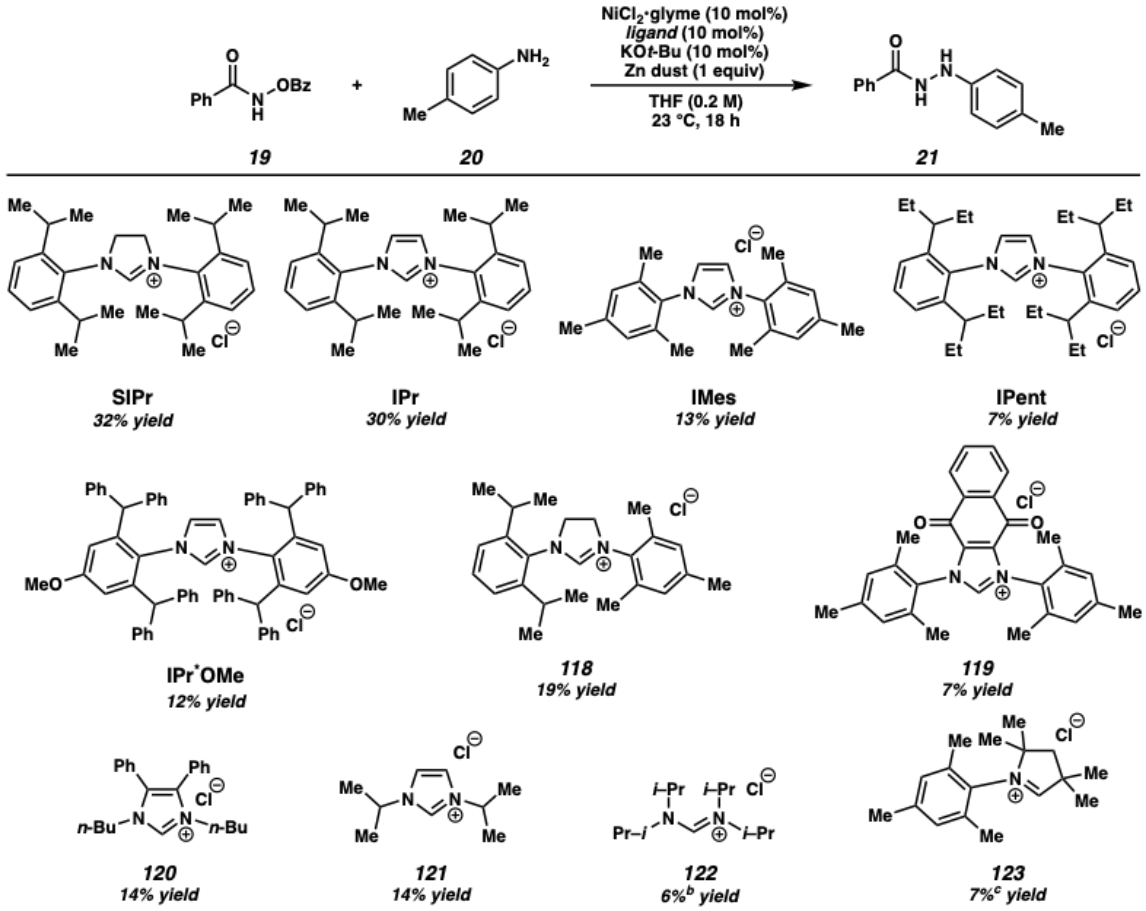
1.7.3 ADDITIONAL OPTIMIZATION DATA

Table 1.3. *Initial evaluation of alternative electrophiles.*[a].



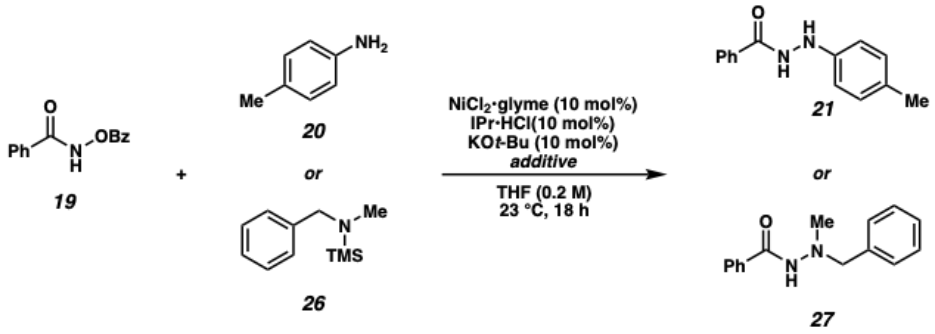
[a] Yields determined by LC/MS integration against internal standard.

Table 1.4. *Initial evaluation of NHC ligands.*[a]



[a] Yields determined by LC/MS integration against internal standard. [b] KHMDS used instead of KO*t*-Bu.[c] LDA used instead of KO*t*Bu.

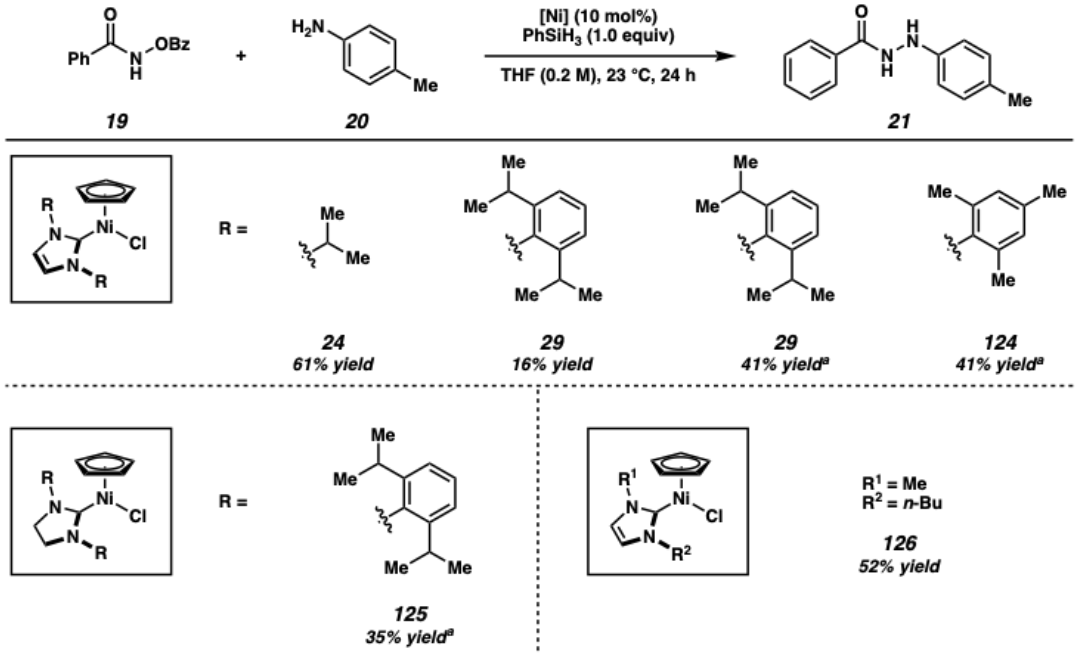
Table 1.5. *Evaluation of additives.*[a]



Entry	Additive	Equiv	Nucleophile	Deviation	Yield (%)[a]
1	Zn dust	1 equiv	2	–	30
2	Mn dust	1 equiv	2	–	7
3	B_2Pin_2	1 equiv	2	–	54
4	B_2Pin_2	1 equiv	8b	–	0
5	Et_3SiH	1 equiv	2	–	37
6	Et_3SiH	1 equiv	8b	–	36
7	$Me(OEt)_2SiH$	1 equiv	2	–	33
8	PMHS	5 equiv	2	SIPr instead of IPr	53
9	$PhSiH_3$	1 equiv	2	–	68
10	$PhSiH_3$	1 equiv	8b	–	65

[a] Yields determined by LC/MS integration against internal standard.

Table 1.6. *Evaluation of half-sandwich complexes with aryl amines.*



[a] Reaction time 72 h.

Table 1.7 *Evaluation of half-sandwich complexes with aliphatic amines.*

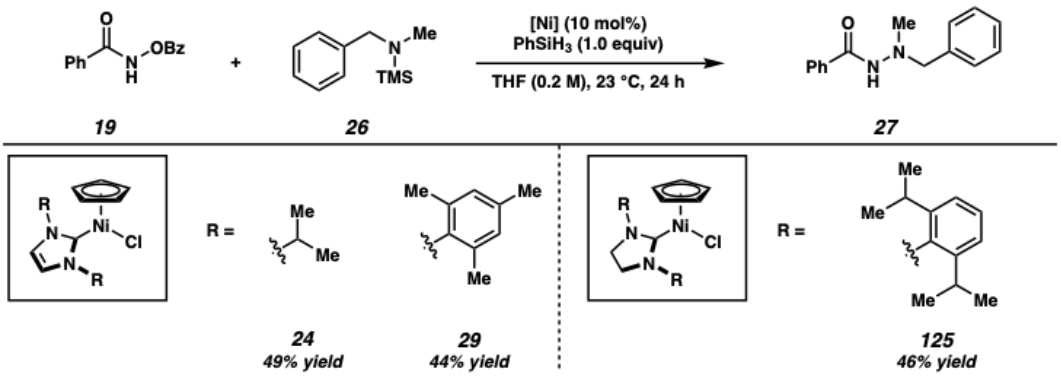
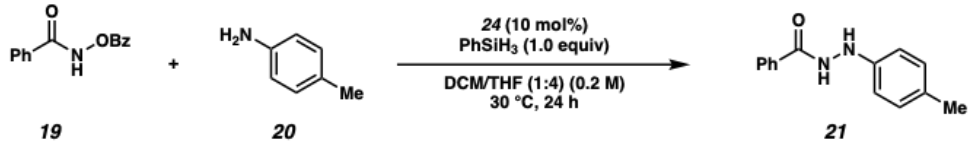
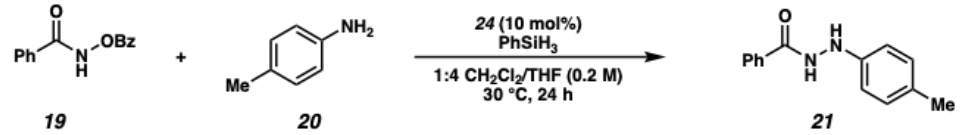


Table 1.8 *Control studies.*



Entry	Devation	Yield (%)
1	No [Ni]	0
2	No $PhSiH_3$	24
3	No [Ni] or $PhSiH_3$	0
4	under air	54

Table 1.9 *Examination of reduced silane loadings.*



entry	$PhSiH_3$ (mol%)	yield (%)
1	10	49[a]
2	20	71
3	50	81

[a] Yield determined by ^1H NMR integration against internal standard.

1.8 REFERENCES AND NOTES

(1) For a general overview of N–N bonds in nature, see: (a) Blair, L. M.; Sperry, J. *J. Nat. Prod.* **2013**, *76*, 794–812. (b) Chen, L.; Deng, Z.; Zhao, C. *ACS Chem. Biol.* **2021**, *16*, 559–570. (c) He, H. -Y.; Niikura, H.; Du, Y. -L.; Ryan, K. S. *Chem. Soc. Rev.* **2022**, *51*, 2991–3046. (d) Narang, R.; Narasimhan, B.; Sharma, S. *Curr. Med. Chem*. **2012**, *19*, 569–612.

(2) For general reviews of oxidative N–N coupling, see (a) Guo, Q.; Lu, Z. *Synthesis* **2017**, *49*, 3835–3847. (b) Tabey, A.; Y. Vemuri, P.; Patureau, F. *Chem. Sci.* **2021**, *12*, 14343–14352.

(3) Pereira, M. M.; Alcântara, A. F. de C.; Piló-Veloso, D.; Raslan, D. S. *J. Braz. Chem. Soc.* **2006**, *17*, 1274–1280.

(4) Ahmed, F. S.; Helmy, Y. S.; Helmy, W. S. *Sci. Rep.* **2022**, 12, 6974–6983.

(5) Bentué-Ferrer, D.; Arvieux, C.; Tribut, O.; Ruffault, A.; Bellissant, E. *Expert Opin. Drug Metab. Toxicol.* **2009**, 5, 1455–1468.

(6) Majumdar, P.; Pati, A.; Patra, M.; Behera, R. K.; Behera, A. K. *Chem. Rev.* **2014**, *114*, 2942–2977.

(7) Selected non-catalyzed oxidative N–N homodimerizations: (a) Branch, G. E. K.; Smith, J. F. *J. Am. Chem. Soc.* **1920**, *42*, 2405. (b) Perkin, W. H., Tucker, S. H. *J. Chem. Soc., Trans*. **1921**, *119*, 216. (c) McLintock, J.; Tucker, S. H. *J. Chem. Soc.* **1927**, 1214.

(8) Selected Cu-catalyzed homodimerizations: (a) Yan, X. M.; Chen, Z.-M.; Yang, F.; Huang, Z. -Z. *Synlett* **2011**, 569. (b) Zhu, Y.; Shi, Y. *Org. Lett*. **2013**, *15*, 1942. (c) C. B. R. Reddy et. al., *Catal. Commun.* **2014**, *56*, 50–54.

(9) Selected electrochemical N–N homodimerizations: (a) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5571. (b) Feng, E.; Hou, Z.; Xu, H. *Chin. J. Org. Chem.* **2019**, *39*, 1424. (c) Shrestha, M. L.; Dunn, A. L.; Sanford, M.S. *Org. Lett.* **2018**, *20*, 204.

(10) Selected oxidative N–N cross-couplings: (a) Ryan, M.C.; Martinelli, J. R.; Stahl, S. S. *J. Am. Chem. Soc.*, **2018**, *140*, 9074. (b) Yin, D.; Jin, J. *Eur. J. Org. Chem.*, **2019**, 5646. (c) Lv, S.; Han, X.; Wang, J. Y.; Zhou, M.; Wu, Y.; Ma, L.; Niu, L.; Gao, W.; Zhou, J.; Hu, W.; Cui, Y.; Chen, J. *Angew. Chem., Int. Ed.* **2020**, *59*, 11583.

(11) Vemuri, P. Y.; Patureau, F. W. *Org. Lett.* **2020**, *11*, 1170.

(12) (a) Baeyer, A. *Chem. Ber.* **1874**, *7*, 1638–1640. (b) Mills, C. *J. Chem. Soc.* **1895**, *67*, 925933.

(13) Huynh, U.; Uddin, M. N.; Wengryniuk, S. E.; McDonald, S. L.; Coltart, D. M. *Tetrahedron Lett.* **2016**, *57*, 4799–4802.

(14) Selected works discussing acyl nitrene precursors: (a) Wang, Y. -C.; Lai, X. -J.; Huang, K.; Yadav, S.; Qiu, G.; Zhang, L.; Zhou, H. *Org. Chem. Front.* **2021**, *8* (7), 1677–1693. (b) Shimbayashi, T.; Sasakura, K.; Eguchi, A.; Okamoto, K.; Ohe, K. *Chemistry* **2019**, *25* (13), 3156–3180. (c) van Vliet, K. M.; de Bruin, B. *ACS Catal.* **2020**, *10* (8), 4751–4769. (d) Jung, H.; Keum, H.; Kweon, J.; Chang, S. *J. Am. Chem. Soc.* **2020**, *142* (12), 5811–5818.

(15) Wang, H.; Jung, H.; Song, F.; Zhu, S.; Bai, Z.; Chen, D.; He, G.; Chen, G.; Chang, S. *Nat. Chem.* **2021**, *13*, 379–385.

(16) Zhou, Z.; Chen, S.; Hong, Y.; Winterling, E.; Tan, Y.; Hemming, M.; Harms, K.; Houk, K. N.; Meggers, E. *J. Am. Chem. Soc.* **2019**, *141*, 19048–19057.

(17) (a) Hong, S. Y.; Park, Y.; Hwang, Y. B.; Kim, M. -H.; Chang, S. *Science* **2018**, *359*, 1016–1021. (b) Franklin, E. C. *Chem. Rev.* **1934**, *14* (2), 219–250.

(18) (a) Dible, Benjamin R.; Sigman, Matthew S.; Arif, Atta M. *Inorg. Chem.* **2005**, *44*, 3774–3776. (b) Laskowski, C. A.; Hillhouse, G. L. *Organometallics* **2009**, *28*, 6114–6120.

(19) Laskowski, C. A.; Miller, A. J. M.; Hillhouse, G. L.; Cundari, T. R. *J. Am. Chem. Soc.* **2011**, *133*, 771–773.

(20) Banach, Ł.; Guńka, P. A.; Zachara, J.; Buchowicz, W. *Coord. Chem. Rev.* **2019**, *389*, 19–58.

(21) Ulm, F.; Cornaton, Y.; Djukic, J.; Chetcuti, M. J.; Ritleng, V. *Chem. – Eur. J.* **2020**, *26*, 8916–8925.

(22) (a) Wu, J.; Nova, A.; Balcells, D.; Brudvig, G. W.; Dai, W.; Guard, L. M.; Hazari, N.; Lin, P. -H.; Pokhrel, R.; Takase, M. K. *Chem. Eur. J.* **2014**, *20*, 5327–5337. (b) Abernethy, C. D.; Clyburne, J. A. C.; Cowley, A. H.; Jones, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 2329–2330.

(23) Stephens, D. N.; Szilagyi, R. K.; Roehling, P. N.; Arulsamy, N.; Mock, M. T. *Angew. Chem. Int. Ed.* **2023**, *62*, e202213462.

(24) (a) Malapit, C. A.; Borrell, M.; Milbauer, M. W.; Brigham, C. E.; Sanford, M. S. *J. Am. Chem. Soc.* **2020**, *142*, 5918–5923. (b) Smith, C. J.; Early, T. R.; Holmes, A. B.; Shute, R. E. *Chem Commun.* **2004**, *17*, 1976–1977. (c) Verma, V.; Koperniku, A.; M. Edwards, P.; L. Schafer, L. N. *Chem. Commun.* **2022**, *58*, 9174–9189.

(25) Thorén, M.; Adamson, U.; Sjöberg, H. E. *Acta Endocrinol. (Copenh.)* **1985**, *109*, 451–457.

(26) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679–3688.

(27) (a) Lyu, X.; Zhang, J.; Kim, D.; Seo, S.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 5867–5877. (b) Choi, H.; Lyu, X.; Kim, D.; Seo, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 10064–10074.

(28) (a) Hossain, I.; Schmidt, J. A. R. *Organometallics* **2020**, *39*, 3441–3451. (b) Ulm, F.; Poblador-Bahamonde, A. I.; Choppin, S.; Bellemin-Laponnaz, S.; Chetcuti, M. J.; Achard, T.; Ritleng, V. *Dalton Trans.* **2018**, *47*, 17134–17145.

(29) Ma, Z.; Zhou, Z.; Kürti, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 9886–9890.

(30) Tse, E. G.; Houston, S. D.; Williams, C. M.; Savage, G. P.; Rendina, L. M.; Hallyburton, I.; Anderson, M.; Sharma, R.; Walker, G.S.; Obach, R.S.; Todd, M. H.; *J. Med. Chem.* **2020**, *63*, 11585–11601.

(31) Rojas, J. J.; Croft, R. A.; Sterling, A. J.; Briggs, E. L.; Antermite, D.; Schmitt, D. C.; Blagojevic, L.; Haycock, P.; White, A. J. P.; Duarte, F.; Choi, C.; Mousseau, J. J.; Bull, J. A. *Nat. Chem.* **2022**, *14*, 160–169.

(32) Goldstein, D. J. *Neuropsychiatr. Dis. Treat*. **2007**, *3*, 193–209.

(33) Walker, N.; Howe, C.; Glover, M.; McRobbie, H.; Barnes, J.; Nosa, V.; Parag, V.; Bassett, B.; Bullen, C. *N. Engl. J. Med.* **2014**, *371*, 2353–2362.

(34) For examples of bimetallic H_2 reductive elimination, see: (a) Jeon, J.; Lee, C.; Seo, H.; Hong, S. *J. Am. Chem. Soc.* **2020**, *142*, 20470–20480. (b) Schaefer, B. A.; Margulieux, G. W.; Small, B. L.; Chirik, P. J. *Organometallics* **2015**, *34*, 1307–1320. (c) Gu, N. X.; Oyala, P. H.; Peters, J. C. *J. Am. Chem. Soc.* **2018**, *140*, 6374–6382.

(35) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *J. Organometallics* **1996**, *15*, 1518–1520.

(36) Rosenau, C. P., Jelier, B. J., Gossert, A. D., & Togni, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 9528–9533.

(37) Oliveira, R. A., Silva, R. O., Molander, G. A., & Menezes, P. H. *Magn. Reson. Chem* **2009**, *47*, 873–878.

(38) Mattingly, P. G.; Miller, M. *J. Org. Chem.* **1980**, *45*, 410–415.

(39) Webb, N. J.; Marsden, S. P.; Raw, S. A. *Org. Lett.* **2014**, *16*, 4718–4721.

(40) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457.

(41) Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893–3914.

(42) Jiang, H.; Studer, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 12273–12276.

(43) Bizet, V.; Buglioni, L.; Bolm, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5639–5642.

(44) D. Žerovnik, U. Grošelj, D. Kralj, Č. Malavašič, J. Bezenšek, G. Dahmann, K. Stare, A. Meden, B. Stanovnik, J. Svete, *Synthesis* **2010**, 3363–3373.

(45) Kelly, R. A.; Scott, N. M.; Díez-González, S.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 3442–3447.

(46) Wu, J.; Nova, A.; Balcells, D.; Brudvig, G. W.; Dai, W.; Guard, L. M.; Hazari, N.; Lin, P.-H.; Pokhrel, R.; Takase, M. K. *Chemistry* **2014**, *20*, 5327–5337.

(47) Oertel, A. M.; Ritleng, V.; Chetcuti, M. *Organometallics* **2012**, *31*, 2829–2840.

(48) Luca, O. R.; Thompson, B. A.; Takase, M. K.; Crabtree, R. H. *J. Organomet. Chem.* **2013**, *730*, 79–83.

(49) Jeon, J.; Lee, C.; Seo, H.; Hong, S. *J. Am. Chem. Soc.* **2020**, *142*, 20470–20480.

(50) Wang, H.; Jung, H.; Song, F.; Zhu, S.; Bai, Z.; Chen, D.; He, G.; Chang, S.; Chen, G. *Nat. Chem.* **2021**, *13*, 378–385.