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Phosphine-Free Ruthenium Complex-Catalyzed Synthesis of Mono- or Dialkylated Acyl Hydrazides via the Borrowing Hydrogen Strategy

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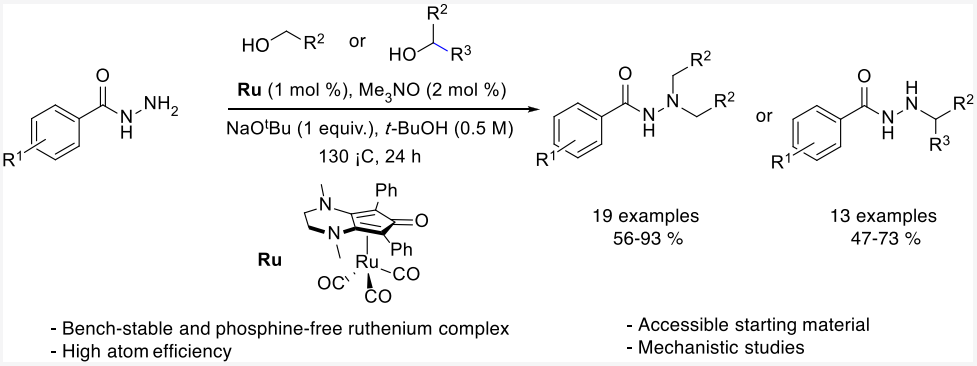

ABSTRACT: Herein, we report a diaminocyclopentadienone ruthenium tricarbonyl complex-catalyzed synthesis of mono- or dialkylated acyl hydrazide compounds using the borrowing hydrogen strategy in the presence of various substituted primary and secondary alcohols as alkylating reagents. Deuterium labeling experiments confirm that the alcohols were the hydride source in this cascade process. Density functional theory (DFT) calculations unveil the origin and the threshold between the mono- and dialkylation.

INTRODUCTION

The hydrogen autotransfer strategy is a blooming area of research.[1] This methodology is a formal alkylation reaction of a nucleophile with alcohols and allows the construction of new C−C and/or C−N bonds.[2] Such a strategy is a greener and safer route than the traditional alkylation with halides or pseudohalides as water is the only side product and as it shortens the synthesis. Since the pioneer work of Grigg,[3] a plethora of metal-based complexes, including both noble and earth-abundant ones, has been described in such bond-forming reactions.[1,2]

The *N*-alkylation of nitrogen-containing compounds via the borrowing hydrogen or hydrogen autotransfer methodology is now a well-established area of research and an alternative to the well-known alkylation chemistry with alkyl halides, hydrogenation of imines, or reductive amination.[2a,3,4] However, while alkylation of amines or amides following this concept has been well described in the literature, alkylation of hydrazine derivatives is still underestimated. Zhou reported the first alkylation of acyl hydrazides in acidic conditions in 2017. A set of benzyl alcohols reacted with hydrazides in the presence of a nickel/bis(dicyclohexylphosphine)propane (dcpp) or nickel/(*S*)-binapine complex and molecular sieves at 110 °C in a mixture of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and *tert*-amyl alcohol (Scheme 1).[5] Enantiomeric excesses, contained between 72 and 96%, were reached by combining Ni(II) and (*S*)-binapine.[5] More recently, Gunanathan described a Ru-Macho-catalyzed dialkylation of benzohydrazides mainly with primary alcohols in toluene at 135 °C (Scheme 1).[6]

In the last few years, the diaminocyclopentadienone iron tricarbonyl complexes demonstrated their efficiency not only as versatile precatalysts for the formation of C−C bonds in the alkylation of ketones,[7,8] indoles,[9] oxidoles,[10] and alcohols,[11−13] but also as active complexes for the methylation and ethylation of amines via the hydrogen autotransfer technology.[8,14] Based on these results and previous works by Zhou and Gunanathan, we initially envisioned the synthesis of substituted acyl hydrazides via the alkylation of an acyl hydrazide with a variety of primary and secondary alcohols in the presence of iron or ruthenium complexes (Scheme 2).

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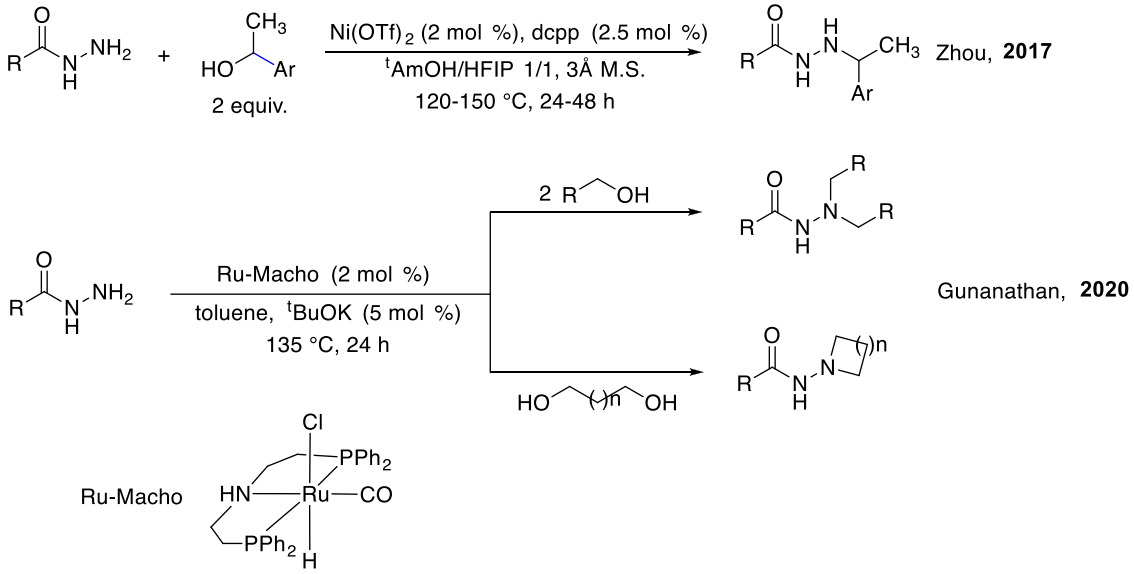
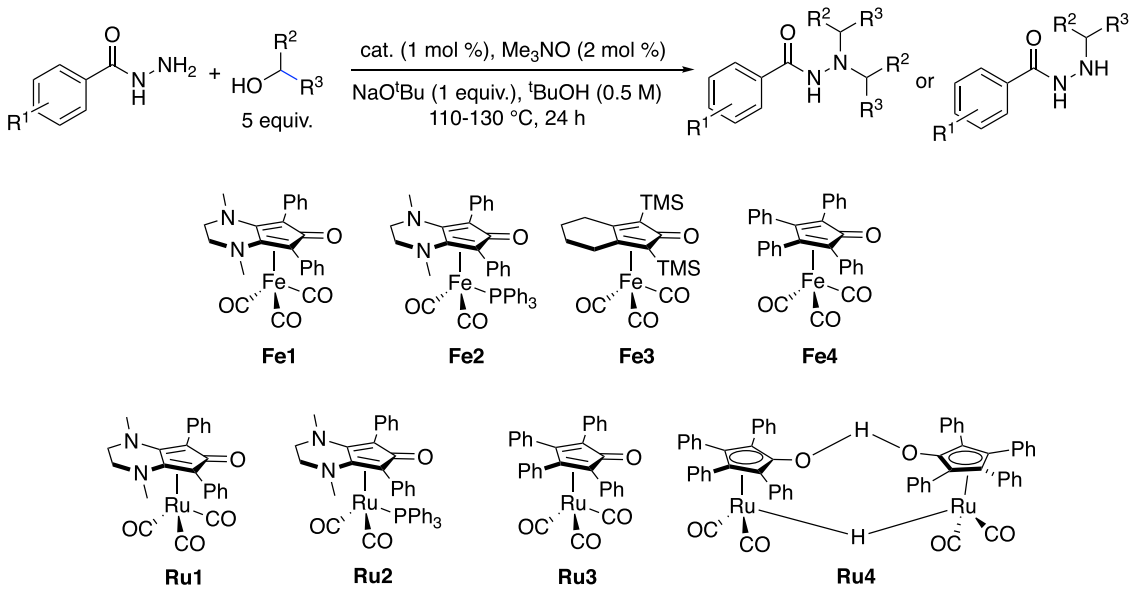
Scheme 1. Previous Syntheses of Alkylated Acyl Hydrazides via the Borrowing Hydrogen Strategy



Scheme 2. Outline of the Synthesis of Substituted Acyl Hydrazides



RESULTS AND DISCUSSION

Surprisingly, while cyclopentadienone iron complexes are known to catalyze the amine alkylation reaction,[8,14] the initial alkylation of phenyl hydrazide with iron complexes (**Fe1**−**Fe4**) failed and a mixture of compounds was observed by the ^{1}H NMR analysis. However, the introduction of ruthenium analogues in this hydrogen-borrowing strategy opened the way to the synthesis of alkylated hydrazide compounds. The complex **Ru1**, bearing the electron-rich cyclopentadienone ligand, has been initially developed and applied by Haak for the activation of propargyl alcohol.[15] The ruthenium complexes **Ru1**−**3** were activated either by addition of Me_3NO[16] (**Ru1** and **Ru3**) or thermally (**Ru2**), the Shvo's complex (**Ru4**) was used without any further activation. An intensive screening of the reaction conditions is performed and illustrated in Tables 1 and S1.

A screening of the temperature displayed that a minimum of 130 °C was necessary to obtain a full conversion of the benzoyl hydrazide **1a** into the *N*,*N*-dialkylated hydrazide **2a** in the presence of 1 mol % of ruthenium complex **Ru1** (entries 1−3, Table 1). At lower temperatures, the *N*-alkylated derivative **3a** was selectively obtained albeit in low conversions. An excess of hexanol (5 equiv) was required to reach a full conversion at 130 °C (entries 1−4, Table S1). When hexanol was introduced as a proelectrophile in a lower amount (1.5 or 3 equiv), either almost no reactivity or no selectivity was noticed at this temperature (entries 1 and 2, Table S1). One of the key parameters was the base. Inorganic bases, such as NaOH or Na_2CO_3, led to low conversion when KO^{t}Bu provided the dialkylated compound **2a** with complete conversion and high selectivity (entries 9−11, Table 1). Solvents other than ^{t}BuOH, such as cyclopentyl methyl ether (CPME) or toluene, led to lower selectivity and/or conversion (entries 10−11, Table S1). Deviation of the base loading impeded both the conversion and the selectivity (entries 4−8, Table 1). Low conversion, but complete selectivity in favor of **3a**, was

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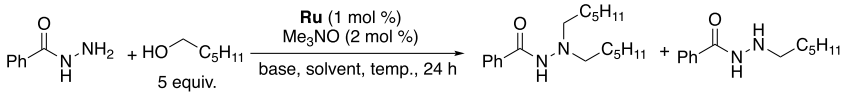
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	Ru	base (equiv)	temp. (°C)	conv.[b] (%)	2a/3a[b]
1	**Ru1**	NaO^{t}Bu (0.5)	90	23	−/100
2	**Ru1**	NaO^{t}Bu (0.5)	110	52	−/100
3	**Ru1**	NaO^{t}Bu (0.5)	130	100	98/2
4	**Ru1**	NaO^{t}Bu (0.1)	130	39	−/100
5	**Ru1**	NaO^{t}Bu (0.2)	130	64	34/66
6	**Ru1**	NaO^{t}Bu (0.3)	130	87	59/41
7	**Ru1**	NaO^{t}Bu (0.4)	130	100	71/29
8	**Ru1**	NaO^{t}Bu (1)	130	100	98/2
9	**Ru1**	NaOH (0.5)	130	23	−/100
10	**Ru1**	Na_2CO_3 (0.5)	130	59	83/17
11	**Ru1**	KO^{t}Bu (0.5)	130	100	91/9
12	**Ru2**	NaO^{t}Bu (0.5)	130	97	95/5
13	**Ru3**	NaO^{t}Bu (0.5)	130	38	60/40
14	**Ru4**	NaO^{t}Bu (0.5)	130	51	63/37

[a]General conditions: benzoyl hydrazide **1a** (0.5 mmol), hexanol (2.5 mmol), **Ru** (1 mol %), Me_3NO (2 mol %), base (equiv), and ^{t}BuOH (0.5 M) for 24 h. [b]Conversions and selectivity of **2a**/**3a** were determined by ^{1}H NMR analysis of the crude mixture.

obtained with 0.1 equiv of the base, when full conversion and high selectivity in favor of **2a** were reached with 0.5 equiv of NaO^{t}Bu (Table 1). The ruthenium complex **Ru2**, a thermally activated analogue of **Ru1**, also catalyzed the alkylation and provided the *N*,*N*-dihexyl phenyl hydrazide but in a somewhat lower conversion and selectivity (entries 3 and 12, Table 1). The other cyclopentadienone ruthenium complexes **Ru3** and **Ru4** (Shvo's complex) were less efficient in this process (entries 13 and 14, Table 1) and no conversion was observed in the absence of the ruthenium complex (entry 20, Table S1). These results, as noticed also in iron catalysis,[7−14] shed light on the importance of the diaminocyclopentadienone ligand, which enhanced the reactivity and/or the selectivity of the corresponding complex. Accordingly, the optimized conditions were as follows: 0.5 mmol of benzoyl hydrazide **1a** underwent a double alkylation in the presence of 5 equiv of hexanol, 1 mol % of complex **Ru1** and 50 mol % of NaO^{t}Bu at 130 °C in ^{t}BuOH (0.5 M) to yield 78% of the dialkylated compound **2a**. Having determined the optimized reaction conditions, the scope of the dialkylation of acyl hydrazides **1** was delineated (Scheme 3). A range of primary aliphatic alcohols were initially applied in this dialkylation process (Scheme 3). *N*,*N*-dialkylated benzoyl hydrazides **2a**−**h** were isolated in good yields (69−93%, Scheme 3). Methanol, whose dehydrogenation is known to be more energetically demanding than this of other alcohols,[17] reacted even better than ethanol or longer chain alcohols and the dimethylated benzoyl hydrazide **2f** was prepared in 93% yield (Scheme 3). In these reaction conditions, primary alcohols bearing a strained small ring, such as cyclopropyl methanol and cyclobutyl methanol, reacted smoothly and the corresponding alkylated hydrazides **2h**−**i** were synthesized in 69 and 81% yield, respectively (Scheme 3). Finally, pent-4-en-1-ol was introduced as the proelectrophile in this process without any reduction of the alkene moiety and **2j** was obtained in 77% yield (Scheme 3). Electron-donating (alkyl, methoxy) and electron-withdrawing groups (fluoride) on the aryl ring were accepted in these conditions and did not modify the reactivity. The corresponding alkylated acyl hydrazides **2n**−**r** were isolated in 56−90% yield (Scheme 3). In contrast to the results reported by Gunanathan with the Ru-Macho complex,[6] alkylation of the furanoyl hydrazide derivative furnished the dialkylated compound **2s** in 77% yield.

To showcase the synthetic applicability of this approach, a gram scale alkylation of the phenyl hydrazide with butanol was performed and **2c** was isolated in 78% yield.

When α-substituted primary alcohols were used as proelectrophiles, whatever the reaction conditions, no *N*,*N*-dialkylated hydrazide but only the monoalkylated product was obtained. Owing to the opportunity to access the monoalkylated hydrazides **3**, we extended this work to the alkylation with secondary alcohols and sterically hindered primary alcohols (Scheme 4).

Monoalkylated compounds **3b**−**e** were isolated in 48−71% yields from α- or β-substituted primary aliphatic alcohols (Scheme 4). As observed previously, isolated alkene was tolerated and not hydrogenated in these conditions. When cyclopentanol was used as the proelectrophile, compound **3f** was obtained in 47% yield (Scheme 4). Benzylic secondary alcohols can also be engaged in the monoalkylation of acyl hydrazide. The *N*-alkylated derivatives **3g**−**n** were prepared in good yields (63−73%, Scheme 4). Electron-donating or electron-withdrawing group on the aromatic ring have a minimum impact on the yield and compounds **3i**, **3k**−**n** were isolated in 63−73% yields (Scheme 4). Even a heteroaromatic ring such as a thiophene ring can be introduced without any depletion of the chemical yield (**3j**, 69%).

Under the optimized conditions, alkylation of benzoyl hydrazide with deuterated methanol and benzylic alcohol yielded **2f**-d_6 and **3g**-d_1 in 88 and 68% yield, respectively (Scheme 5). The chemical yields were comparable to the nondeuterated reaction (Schemes 3 and 4). The deuterium incorporation, in the α-position relative to the hydrazide function, suggested that the Ru−D complex reduced an acyl hydrazone intermediate.

To gain more insights on the selectivity (mono- versus dialkylation, Schemes 3 and 4), density functional theory (DFT) calculations were performed (Figure 1). In a simplified mechanism, the borrowing hydrogen strategy implies three

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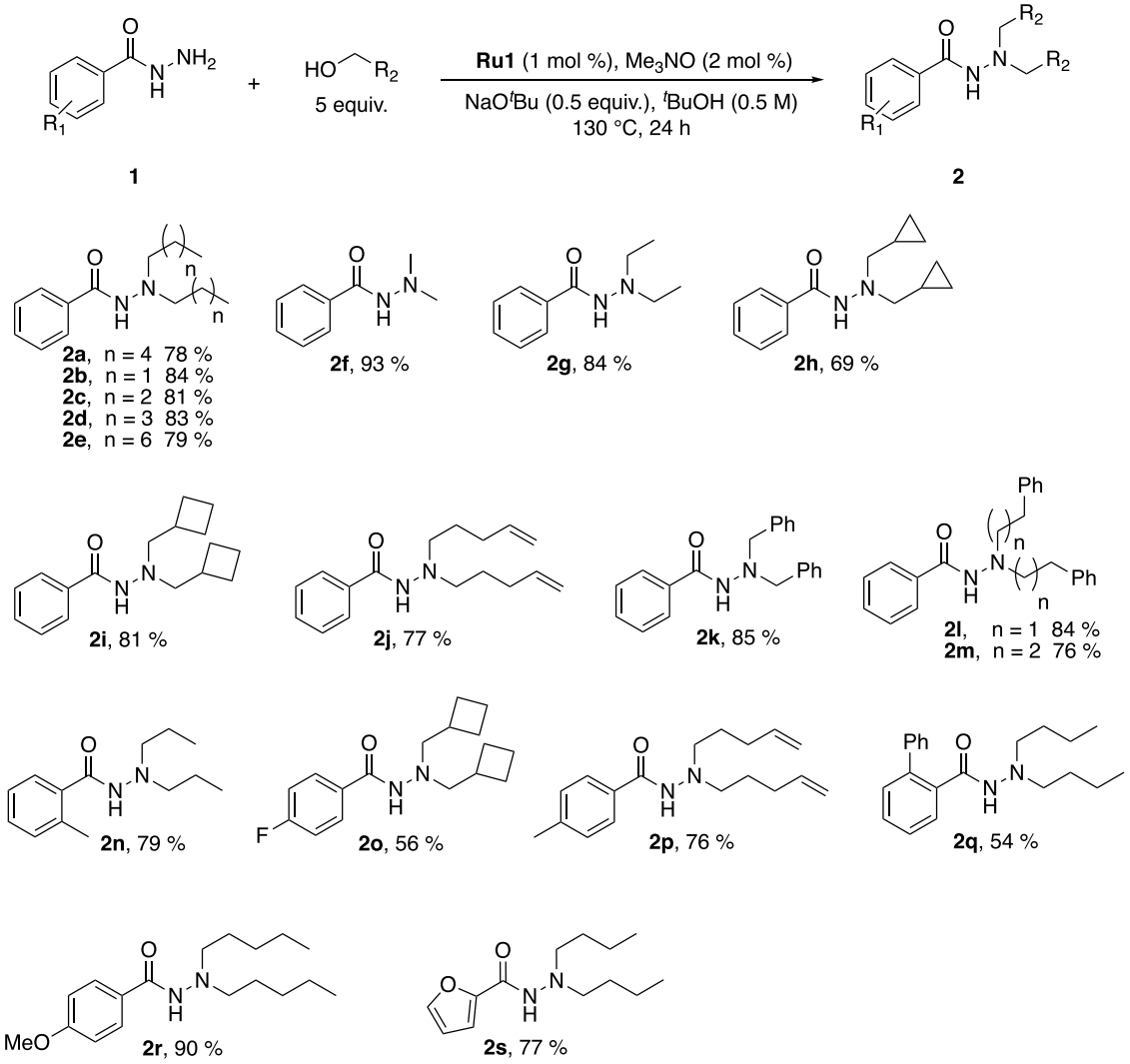
Scheme 3. Scope of the Ruthenium-Catalyzed Synthesis of Dialkylated Acyl Hydrazides[a,b]



[a]General conditions: benzoyl hydrazide **1** (0.5 mmol, 1 equiv), alcohol (2.5 mmol, 5 equiv), **Ru1** (1 mol %), Me_3NO (2 mol %), and NaO^tBu (0.25 mmol, 0.5 equiv) at 130 °C in *tert*-butanol (1 mL) for 24 h. [b]Isolated yields.

steps: a metal-based complex catalyzed the dehydrogenation of the alcohol into aldehyde or ketone and the reduction step (steps 1 and 3), and a condensation step (in this work, the formation of a hydrazone intermediate).[17] The noncatalyzed steps appeared to define the rate-limiting step (rds) in this process. Figure 1 shows some mechanistic evidence for the second alkylation of substituted benzoyl hydrazide with methanol (providing **2f**) or with the more sterically crowded alcohols leading to the monoalkylated products **3b** and **3d**.[18]

Monoalkylation of the acyl hydrazide is always feasible, whatever the starting alcohol, and, consequently, is not rate determining. The second condensation of the ketone or aldehyde on the substituted acyl hydrazide is a two-step process (addition followed by the release of water) assisted by the solvent (^{t}BuOH). Finally, a facile reduction of the unsaturated intermediate delivered the dialkylated product. The rate-determining step of the reaction is the formation of the iminium, the second unsaturated intermediate, with a barrier of 31.9 kcal/mol, which leads to the achievement of **2f**, while the dialkylation giving **3b** has an unbearable cost of 33.6 kcal/mol. This barrier was increased up to 37.6 kcal/mol when the 2,2-dimethyl-1-propanol was used as the proelectrophile for the dialkylation, thus concluding that the substitution of hydrogens in the β-carbon of the alcohol blocks dialkylation. On the other hand, the elongation of the alkyl chain does not imply any impediment to this dialkylation with a maximum kinetic cost of 31.6 and 31.8 kcal/mol for **2g** and **2s**, respectively.

To avoid the study of the overall pathway for all alcohols, calculations of the $\%V_{Bur}$ measurement index, introduced by Cavallo and co-workers,[19] allowed us to discern the threshold between mono- and dialkylation. The results, reported in Table S2, identify a $\%V_{Bur}$ of 47.7% for the alcohol above which the dialkylation is unlikely. This value was obtained for cyclohexyl methanol, an alcohol providing the monoalkylated compound **3c** (Scheme 4). Even more clear is the 2,2-dimethyl propanol that leads to the monoalkylated **3d** since its sterical hindrance is more pronounced with a $\%V_{Bur}$ of 53.1% and it shows a more hindered steric map (see Figure 2d). In other words, the substitution at the β-carbon of a primary alcohol is sufficient to prevent dialkylation. The length of the alcohol alkyl chain is also meaningless since it does not affect the environment around the carbonyl group. Comparison of the $\%V_{Bur}$ of 2,2-dimethyl propanol and 2-methylpentanol ($\%V_{Bur}$ of 47.9%,

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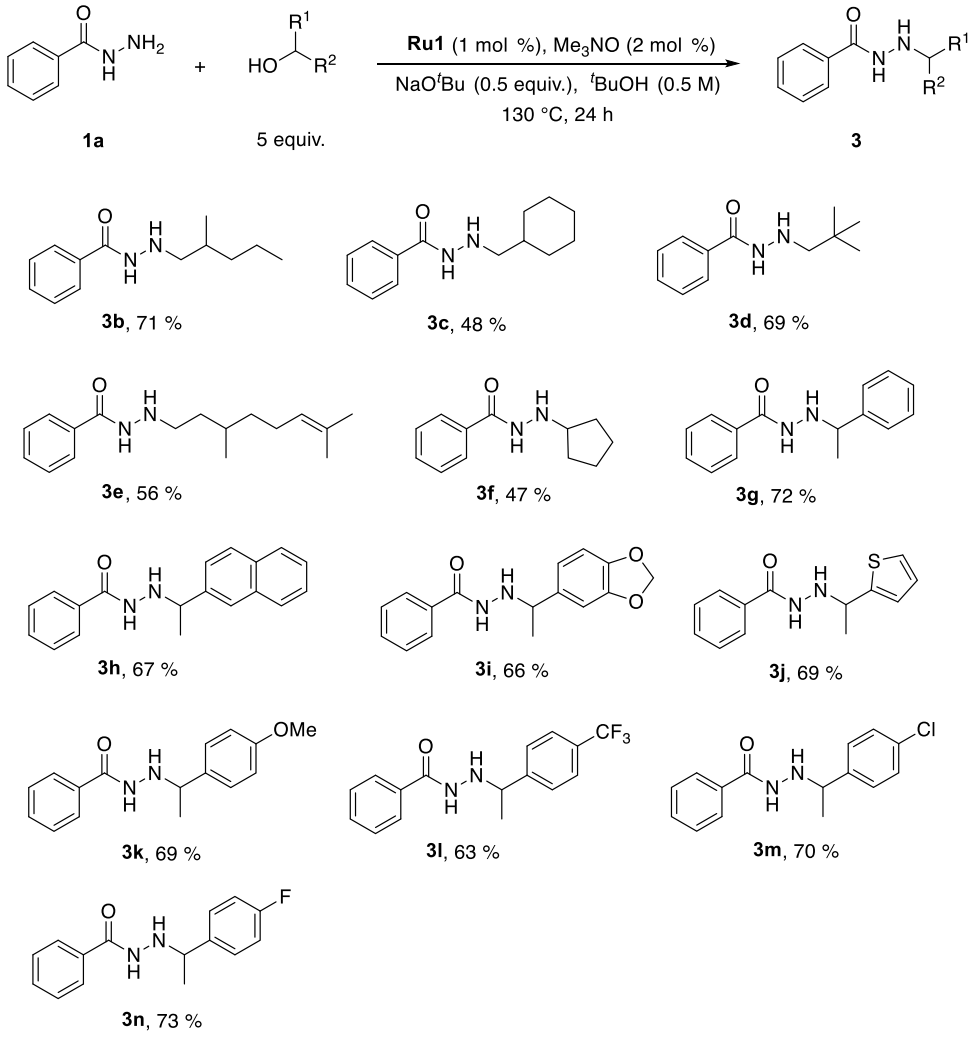
Scheme 4. Scope of the Ruthenium-Catalyzed Synthesis of Monoalkylated Acyl Hydrazones[a,b]



[a]General conditions: benzoyl hydrazide **1a** (0.5 mmol, 1 equiv), alcohol (2.5 mmol, 5 equiv), **Ru1** (1 mol %), Me_3NO (2 mol %), and NaO^{t}Bu (0.25 mmol, 0.5 equiv) at 130 °C in *tert*-butanol (1 mL) for 24 h. [b]Isolated yields.

Scheme 5. Deuterium Labeling Experiment

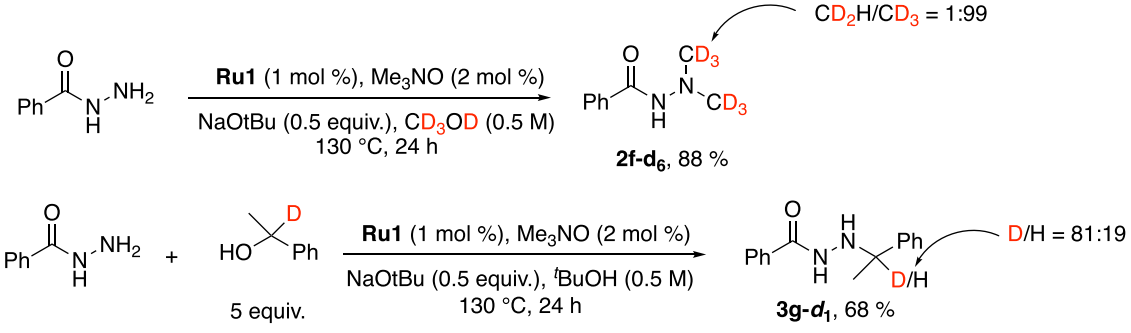


Figure 2c) also illustrated these calculations. However, it should be noted that to perfectly reproduce the separation between both families of substrates, it must be said that the boundary is very subtle. As an example, 2-phenyl ethanol furnished the dialkylated benzoyl hydrazide **2l**, and the value of its $\%V_{Bur}$ (45.2%, Figure 2b) is much higher than the value of 25.6% calculated for methanol (Figure 2a). Again, steric maps in Figure 2 unveil such a huge difference.

CONCLUSIONS

In conclusion, we have disclosed the first phosphine-free ruthenium complex-catalyzed alkylation of acyl hydrazides using alcohols via the hydrogen autotransfer strategy. A variety of primary as well as secondary alcohols were introduced in this alkylation and afforded mono- and dialkylated acyl hydrazides in moderate to good yields. These results again highlighted that bifunctional diaminocyclopentadienone complexes compete with phosphine-containing complexes in

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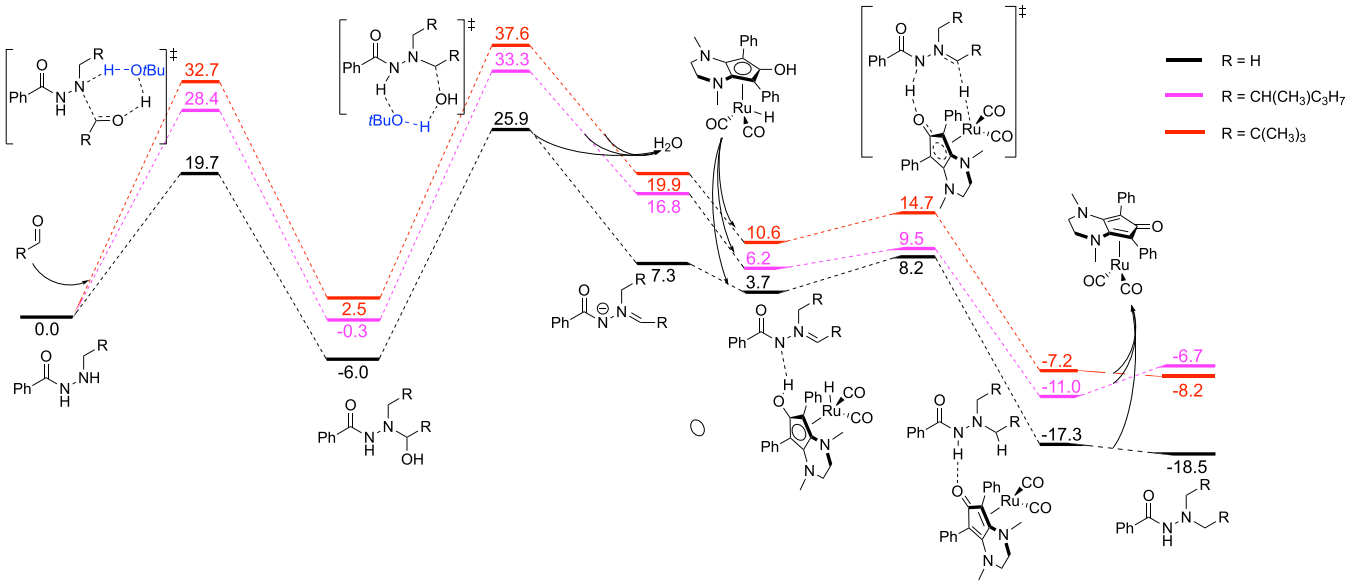

Figure 1. Energy profile for the dialkylation of the monoalkylated acyl hydrazides (relative Gibbs energies in kcal/mol). Alkylation of *N*-methyl benzoyl hydrazide (leading to **2f**, R = H in black) and alkylation of the monoalkylated compounds **3b** (R = $CH(CH_3)C_3H_7$ in violet) and **3d** (R = $C(CH_3)_3$, in red) using Ru1 as the catalyst.

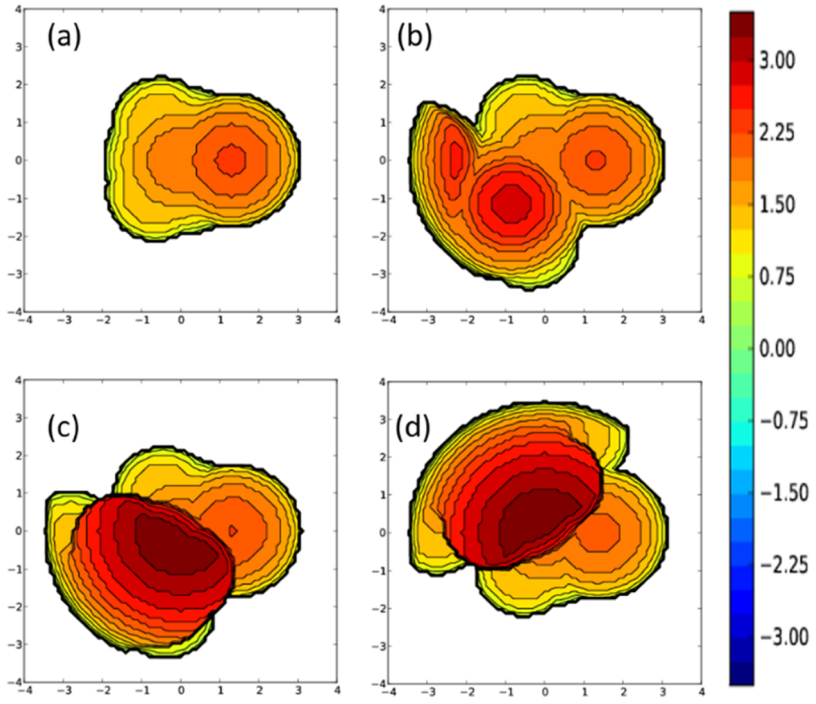

Figure 2. Topographic steric maps (plane *xy*) of the alcohols that lead to the aldehyde/ketone to generate (a) **2f**, (b) **2l**, (c) **3b**, and (d) **3d** with a radius of 3.5 Å.[20]

hydrogenation and dehydrogenation reactions and may open new research areas with such complexes. Moreover, DFT calculations and the buried volumes of the DFT-optimized alcohols provided insight into the mechanism and allowed us to explain the selectivity. The mono- versus dialkylation selectivity can now be anticipated with this catalytic system as it depends on the steric parameters of the alcohol.

Experimental Part. General considerations: All air- and moisture-sensitive manipulations were carried out using standard vacuum line Schlenk tube techniques. Dry toluene was dried using a solvent purification system from Innovative Technologies, by passage through towers containing activated alumina. Xylene was purchased from Carlo Erba and was distilled over sodium and stocked over 4 Å molecular sieves. Both were deglazed prior to use by bubbling argon gas directly in the solvent. Other solvents and chemicals were purchased from different suppliers and used as received. Neutral alumina was purchased from Alfa Aesar (Brockmann Grade I, 58 Å, −60 mesh powder, S.A. 150 m^2/g) and silica from Carlo Erba (60 Å, 40−63 μm). Deuterated solvents for NMR spectroscopy were purchased from Sigma-Aldrich and used as received. NMR spectra were recorded on a 500 MHz Brücker

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spectrometer. Proton (^{1}H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; and m, multiplet), coupling constant(s) (J) in Hertz (Hz), and number of protons. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and *br* indicates the signal in question broadened. Carbon ^{13}C{^{1}H} NMR spectra are reported in ppm (δ) relative to $CDCl_3$ unless noted otherwise. Infrared spectra were recorded over a PerkinElmer Spectrum 100 FT-IR spectrometer using neat conditions. Melting points were measured on noncrystalline solids using an Electrothermal IA 9100 apparatus. HRMS analyses were performed by Laboratoire de Chimie Moléculaire et Thioorganique analytical Facilities.

Synthesis of Ruthenium Complexes. *Synthesis of Ruthenium Complex (**Ru1**).* [15a]In a 50 mL dried Schlenk tube under an argon atmosphere, the cyclopentadienone ligand (2.53 mmol, 800 mg, 1 equiv) and Ru_3CO_{12} (1.26 mmol, 806 mg, 0.5 equiv) were introduced in a dry and free-O_2 toluene solution (12 mL). The reaction mixture was stirred under reflux in an oil bath overnight. After cooling down to room temperature, the resulting mixture was purified on neutral alumina oxide column chromatography (eluent: CH_2Cl_2 to CH_2Cl_2/MeOH [98:2]). Precipitation in a mixture of pentane/diethyl ether (1:1) followed by filtration under vacuum gave the pure complex **Ru1** as a yellow powder (973 mg, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48−7.47 (m, 4H), 7.38−7.35 (m, 4H), 7.32−7.29 (m, 2H), 3.42−3.38 (m, 2H), 2.64−2.60 (m, 2H), 2.17 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 199.1, 172.1, 132.9, 132.3, 128.5, 127.7, 116.7, 69.7, 50.1, 43.8. IR (neat) ν 2959, 2045, 2005, 1637, 1508, 1492, 1439, 1410, 1360, 1265, 1194, 1114, 1071, 1048, 1028, 1004, 946, 848, 785 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{24}H_{21}RuN_2O_4$ 503.0545; found 503.0556.

*Synthesis of Ruthenium Complex (**Ru2**).* In a 50 mL dried Schlenk tube under an argon atmosphere, tricarbonyl ruthenium complex **Ru1** (0.90 mmol, 1 equiv, 451 mg) and triphenylphosphine (2.7 mmol, 3 equiv, 708 mg) were solubilized in a O_2-free xylene solution (24 mL) and then refluxed in an oil bath at 140 °C overnight. Purification by flash column chromatography on neutral aluminum oxide (eluent: pentane/ethyl acetate [90:10] to [70:30]) afforded the pure triphenylphosphine ruthenium complex **Ru2** as a yellow powder (430 mg, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42−7.41 (m, 4H), 7.25−7.22 (m, 6H), 7.20−7.17 (m, 3H), 7.12−7.09 (m, 2H), 7.05−7.00 (m, 10H), 3.35−3.31 (m, 2H), 3.11−3.06 (m, 2H), 2.37 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 203.2, 166.9, 134.2, 133.9, 133.8, 133.3, 133.2, 132.0, 129.4, 128.0, 127.9, 127.6, 125.9, 111.5, 70.7, 48.7, 42.1. ^{31}P NMR ($CDCl_3$, 162 MHz): δ 29.1. IR (neat): ν 3047, 2952, 2860, 2038, 1982, 1923, 1609, 1538, 1517, 1480, 1432, 1409, 1362, 1261, 1198, 1179, 1090, 1045, 944, 755, 735, 696, 586, 520, 496 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{41}H_{36}RuN_2O_3P$ 737.1507; found 737.1522.

*Synthesis of Ruthenium Complex (**Ru3**).* Ruthenium complex **Ru3** was prepared according to a procedure described by Shvo.[21] In a 50 mL dried Schlenk tube under an argon atmosphere, 2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one (2 mmol, 768 mg, 1 equiv) and Ru_3CO_{12} (1 mmol, 639 mg, 0.5 equiv) were introduced in a dry and free-O_2 toluene solution (12 mL). The reaction mixture was stirred under reflux in an oil bath overnight. After cooling down to room temperature, the resulting mixture was purified by column chromatography on silica gel (eluent: dichloromethane to dichloromethane/methanol [98:2]) to afford the pure complex **Ru3** as a pale yellow powder (863 mg, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48−7.47 (m, 4H), 7.25−7.22 (m, 6H), 7.20−7.17 (m, 2H), 7.13−7.10 (m, 4H), 7.07−7.05 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 194.5, 174.0, 132.1, 131.6, 130.9, 129.9, 128.7, 128.2, 128.1, 127.5, 107.9, 82.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{32}H_{21}RuO_4$ 571.0483; found 571.0499.

*Synthesis of Ruthenium Complex (**Ru4**).* Ruthenium complex **Ru4** was prepared according to a procedure described by Shvo.[21] In a 50 mL dried Schlenk tube under an argon atmosphere, ruthenium complex **Ru3** (0.5 mmol, 285 mg) was dissolved in acetone (20 mL) and a saturated solution of sodium carbonate (10 mL) was added. The mixture was stirred at room temperature for 0.5 h. The reaction was neutralized with saturated ammonium chloride solution and acetone was evaporated under vacuum. The residue was extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using pentane−dichloromethane (1:1) as the eluent to afford the pure complex **Ru4** as an orange powder (195 mg, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12−7.06 (m, 15H), 7.01−6.99 (m, 25H), −18.37 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 200.9, 154.3, 132.2, 131.2, 130.7, 130.4, 128.0, 127.9, 127.7, 126.9, 103.6, 87.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{62}H_{43}Ru_2O_6$ 1087.1147; found 1087.1196.

SYNTHESIS OF ACYL HYDRAZIDES

General Procedure A. In a round-bottomed flask, the desired quantity of benzoic acid (10 mmol) was dissolved in methanol (10 mL). Ten drops of sulfuric acid (96%) were added to the solution. The mixture was refluxed for 12 h in an oil bath. The reaction was then dissolved in water and extracted three times with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was directly engaged to the next step. The ester was dissolved in methanol (5 mL); hydrazine monohydrate (5 equiv) was then added and the mixture was refluxed for 16 h. The solvent was then removed under reduced pressure. The residue was dissolved in water and extracted with dichloromethane. The organic layer was washed with water and dried over sodium sulfate. The solvent was then removed to afford the desired product **1** without further purification.

*4-Methoxybenzohydrazide (**1b**).*[22] According to the general procedure A, **1b** was obtained from 4-methoxybenzoic acid (10 mmol, 1.66 g) as a white solid (1.49 g, 90%) without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, 2H, J = 8.8 Hz), 7.43 (br. s, 1H), 6.92 (d, 2H, J = 8.8 Hz), 4.08 (br. s, 2H), 3.85 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 168.5, 162.6, 128.8, 125.0, 114.1, 55.5.

*4-Fluorobenzohydrazide (**1c**).*[22] According to the general procedure A, **1c** was obtained from methyl 4-fluorobenzoic acid (10 mmol, 1.54 g) as a white solid (1.42 g, 92%) without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78−7.75 (m, 2H), 7.42 (br. s, 1H), 7.14−7.11 (m, 2H), 3.02 (br. s, 2H). ^{19}F NMR (500 MHz, $CDCl_3$): −107.2. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 167.9, 165.1 (d, J = 250.9 Hz), 129.3 (d, J = 8.9 Hz), 128.9 (d, J = 3.2 Hz), 116.0 (d, J = 21.8 Hz).

*4-Methylbenzohydrazide (**1d**).*[22] According to the general procedure A, **1d** was obtained from 4-methylbenzoic acid (10

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mmol, 1.36 g) as a white solid (1.35 g, 90%) without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (d, 2H, J = 8.1 Hz), 7.37 (br. s, 1H), 7.24 (d, 2H, J = 8.0 Hz), 4.08 (br. s, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 168.8, 142.6, 129.9, 129.5, 127.0, 21.6.

*2-Phenylbenzohydrazide (**1e**).* According to the general procedure A, **1e** was obtained from 2-phenylbenzoic acid (10 mmol, 2.12 g) as a white solid (1.73 g, 82%) without further purification. Mp 102.3−102.7 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (dd, 1H, J = 1.1; 7.6 Hz), 7.49 (td, 1H, J = 1.3; 7.6 Hz), 7.44−7.36 (m, 7H), 6.53 (br. s, 1H), 3.84 (br. s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.6, 140.0, 140.0, 133.6, 130.7, 130.5, 129.0, 128.9, 128.6, 128.1, 127.8. IR (neat): ν 3248, 1649, 1541, 1446, 1292, 1162, 1072, 969, 909, 854, 749, 691, 664, 527 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{13}N_2O$ 213.1028; found 213.1030.

*2-Methylbenzohydrazide (**1f**).*[23] According to the general procedure A, **1f** was obtained from 2-methylbenzoic acid (10 mmol, 1.36 g) as a white solid (1.39 g, 93%) without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36−7.33 (m, 2H), 7.25−7.20 (m, 2H), 6.98 (br. s, 1H), 4.10 (br. s, 2H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.0, 136.8, 134.2, 131.3, 130.6, 127.1, 126.0, 19.9.

*Furan-2-carbohydrazide (**1g**).*[22] According to the general procedure A, product **1g** was obtained from furan-2-carboxylic acid (10 mmol, 1.12 g) as a white solid (1.12 g, 88%) without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (br. s, 1H), 7.45 (dd, 1H, J = 0.7; 1.7 Hz), 7.14 (dd, 1H, J = 0.7; 3.5 Hz), 6.51 (dd, 1H, J = 1.7; 3.5 Hz), 4.02 (br. s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 159.6, 146.8, 144.4, 115.0, 112.2.

■ ALKYLATION OF ACYL HYDRAZIDES

General Procedure B. In a 15 mL flame-dried Schlenk tube equipped with a stirring bar, hydrazide **1** (0.5 mmol), the alcohol (5 equiv), Me_3NO (1.1 mg, 2 mol %), ruthenium complex **Ru1** (2,51 mg, 1 mol %), and NaO^{t}Bu (24 mg, 0.5 equiv) were added to a solution of ^{t}BuOH (1.0 mL) under an argon atmosphere. The mixture was then placed into a preheated oil bath and stirred at 130 °C for 24 h. The mixture was cooled down to room temperature, filtered over a pad of Celite and eluted with diethyl ether, and concentrated under reduced pressure. The conversion was determined by ^{1}H NMR spectroscopy and the residue was purified by flash chromatography on silica gel using pentane−ethyl acetate as the eluent to afford the desired product. For some compounds, distillation using a glass oven Kugelrohr was necessary to remove the excess alcohol.

*N′,N′-Dihexylbenzohydrazide (**2a**).*[6] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with hexan-1-ol (5 equiv, 309 μL) afforded the pure product **2a** as a white solid (119 mg, 78%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74−7.72 (m, 2H), 7.52−7.49 (m, 1H), 7.45−7.42 (m, 2H), 6.52 (br. s, 1H), 2.83−2.80 (m, 4H), 1.58−1.54 (m, 4H), 1.34−1.24 (m, 12H), 0.85 (t, 6H, J = 6.9 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.9, 134.4, 131.7, 128.9, 127.2, 58.8, 32.0, 27.3, 27.2, 22.8, 14.3.

*N′,N′-Dipropylbenzohydrazide (**2b**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with propan-1-ol (5 equiv, 187 μL) afforded the pure product **2b** as a white solid (92 mg, 84%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). Mp 80.8−81.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, 2H, J = 7.0 Hz), 7.50 (t, 1H, J = 7.4 Hz), 7.43 (t, 2H, J = 7.5 Hz), 6.54 (br. s, 1H), 2.80 (t, 4H, J = 7.6 Hz), 1.65−1.55 (m, 4H), 0.94 (t, 6H, J = 7.4 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.8, 134.2, 131.7, 128.8, 127.1, 60.4, 20.5, 11.8. IR (neat): ν 3228, 2960, 1648, 1539, 1290, 1067, 946, 913, 695, 668, 604, 523 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{21}N_2O$ 221.1654; found 221.1658.

*N′,N′-Dibutylbenzohydrazide (**2c**).*[6] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with butan-1-ol (5 equiv, 229 μL) afforded the pure product **2c** as a white solid (101 mg, 81%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 2H, J = 7.3 Hz), 7.42 (t, 1H, J = 7.4 Hz), 7.33 (t, 2H, J = 7.5 Hz), 6.87 (br. s, 1H), 2.79−2.76 (m, 4H), 1.53−1.47 (m, 4H), 1.27 (sext, 4H, J = 7.3 Hz), 0.84 (t, 6H, J = 7.3 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.7, 134.1, 131.4, 128.5, 127.0, 58.1, 29.2, 20.4, 14.0.

Scale up for **2c**. In a 30 mL flame-dried Schlenk tube equipped with a stirring bar, benzohydrazide **1a** (5 mmol, 680 mg), butan-1-ol (5 equiv, 2.29 mL), ruthenium complex **Ru1** (25.1 mg, 1 mol %), Me_3NO (11.1 mg, 2 mol %), and NaO^{t}Bu (240 mg, 0.5 equiv) were added to a solution of ^{t}BuOH (10 mL, 0.5 M) under an argon atmosphere. The mixture was rapidly stirred at room temperature for 2 min and then placed into a preheated oil bath at 130 °C and stirred over 24 h. The mixture was cooled down to room temperature, filtered over a pad of Celite and eluted with diethyl ether. The conversion was determined by ^{1}H NMR spectroscopy and the residue was purified by flash chromatography on silica gel using pentane−ethyl acetate (9:1) as the eluent to afford the pure product **2c** as a white solid (968 mg, 78%). ^{1}H NMR data were comparable with the previous NMR data.

*N′,N′-Dipentylbenzohydrazide (**2d**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with pentan-1-ol (5 equiv, 271 μL) afforded the pure product **2d** as a white solid (114 mg, 83%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). Mp 80.8−82.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, 2H, J = 7.0 Hz), 7.50 (t, 1H, J = 7.4 Hz), 7.43 (t, 2H, J = 7.5 Hz), 6.53 (br. s, 1H), 2.84−2.79 (m, 4H), 1.61−1.54 (m, 4H), 1.33−1.29 (m, 8H), 0.88 (t, 6H, J = 7.1 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.8, 134.3, 131.6, 128.8, 127.1, 58.6, 29.6, 26.9, 22.7, 14.2. IR (neat): ν 3229, 2943, 2929, 1651, 1541, 1470, 1314, 1080, 937, 695, 680, 669, 604, 527, 506, 444 cm^{-1}. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{29}N_2O$ 277.2280; found 277.2284.

*N′,N′-Dioctylbenzohydrazide (**2e**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with octan-1-ol (5 equiv, 392 μL) afforded the pure product **2e** as a white solid (142 mg, 79%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). The excess of octan-1-ol was then removed by distillation (T = 120 °C, P = 110 mbar). Mp 82.1−84.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, 2H, J = 7.0 Hz), 7.47 (t, 1H, J = 7.4 Hz), 7.40 (t, 2H, J = 7.5 Hz), 6.61 (br. s, 1H), 2.82−2.79 (m, 4H), 1.53 (app t, 4H, J = 7.3 Hz), 1.32−1.24 (m, 20H), 0.84 (t, 6H, J = 7.0 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.8, 134.3, 131.6, 128.72,

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127.1, 58.6, 31.9, 29.6, 29.4, 27.4, 27.2, 22.8, 14.2. IR (neat): ν 32232, 2941, 1650, 1542, 1472, 1316, 1081, 932, 680, 672, 604, 527, 506, 482 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{41}N_2O$ 361.3219; found 361.3219.

N′,N′-Dimethylbenzohydrazide (2f).[6] According to a modified general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with methanol, used as the solvent (0.5 M), afforded the pure product **2f** as a white solid (76 mg, 93%) after purification by flash column chromatography on silica gel (pure ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 2H, J = 7.0 Hz), 7.42 (t, 1H, J = 7.4 Hz), 7.33 (t, 2H, J = 7.5 Hz), 7.24 (br. s, 1H), 2.64 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.8, 133.8, 131.6, 128.5, 127.1, 47.6.

N′,N′-Diethylbenzohydrazide (2g).[6] According to a modified general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with ethanol (10 equiv, 292 μL) afforded the pure product **2g** as a white solid (81 mg, 84%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 2:8). ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, 2H, J = 7.2 Hz), 7.49 (t, 1H, J = 7.4 Hz), 7.32 (t, 2H, J = 7.5 Hz), 6.41 (br. s, 1H), 2.86 (q, 4H, J = 7.1 Hz), 1.16 (t, 6H, J = 7.1 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.1, 134.2, 131.7, 128.8, 127.1, 52.5, 12.2.

N′,N′-Bis(cyclopropylmethyl)benzohydrazide (2h). According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with cyclopropyl methanol (5 equiv, 202 μL) afforded the pure product **2h** as a white solid (84 mg, 69%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 73.9−75.8 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, 2H, J = 7.0 Hz), 7.51 (t, 1H, J = 7.4 Hz), 7.44 (t, 2H, J = 7.4 Hz), 6.98 (br. s, 1H), 2.86 (d, 4H, J = 6.7 Hz), 1.06−0.98 (m, 2H), 0.55−0.50 (m, 4H), 0.16 (q, 4H, J = 4.7 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.7, 134.5, 131.6, 128.8, 127.0, 61.9, 8.4, 3.6. IR (neat): ν 3232, 3070, 2995, 1649, 1543, 1313, 1177, 1017, 935, 892, 698, 670, 597, 520, 448, 409 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{21}N_2O$ 245.1654; found 245.1651.

N′,N′-Bis(cyclobutylmethyl)benzohydrazide (2i). According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with pent-4-en-1-ol (5 equiv, 256 μL) afforded the pure product **2i** as a white solid (105 mg, 77%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 75.6−77.7 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 2H, J = 7.1 Hz), 7.43 (t, 1H, J = 7.4 Hz), 7.34 (t, 2H, J = 7.6 Hz), 7.00 (br. s, 1H), 5.74 (td, 2H, J = 6.7; 16.9 Hz), 4.98−4.95 (m, 2H), 4.92−4.88 (m, 2H), 2.83−2.78 (m, 4H), 2.12−2.08 (m, 4H), 1.65−1.57 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.8, 138.3, 134.0, 131.6, 128.5, 127.0, 114.9, 57.6, 31.3, 26.4. IR (neat): ν 3231, 3062, 2951, 2841, 1645, 1536, 1302, 1288, 1073, 991, 909, 801, 694, 669 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{25}N_2O$ 273.1967; found: 273.1968.

N′,N′-Di(pent-4-en-1-yl)benzohydrazide (2j). According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with pent-4-en-1-ol (5 equiv, 256 μL) afforded the pure product **2j** as a white solid (105 mg, 77%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 70.7−71.3 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 2H, J = 7.1 Hz), 7.43 (t, 1H, J = 7.4 Hz), 7.34 (t, 2H, J = 7.6 Hz), 7.00 (br. s, 1H), 5.74 (td, 2H, J = 6.7; 16.9 Hz), 4.98−4.95 (m, 2H), 4.92−4.88 (m, 2H), 2.83−2.78 (m, 4H), 2.12−2.08 (m, 4H), 1.65−1.57 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.8, 138.3, 134.0, 131.6, 128.5, 127.0, 114.9, 57.6, 31.3, 26.4. IR (neat): ν 3231, 3062, 2951, 2841, 1645, 1536, 1302, 1288, 1073, 991, 909, 801, 694, 669 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{25}N_2O$ 273.1967; found: 273.1968.

N′,N′-Dibenzylbenzohydrazide (2k).[24] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with benzyl alcohol (5 equiv, 265 μL) afforded the pure product **2k** as a white solid (134 mg, 85%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). The excess of benzyl alcohol was then removed by distillation (T = 105 °C, P = 110 mbar). ^1H NMR (500 MHz, $CDCl_3$): δ 7.42 (t, 7H, J = 7.7 Hz), 7.36−7.27 (m, 8H), 7.00 (br. s, 1H), 4.33 (s, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.5, 137.5, 134.1, 131.5, 129.4, 128.6, 128.5, 127.6, 126.9, 59.4.

N′,N′-Diphenethylbenzohydrazide (2l). According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 2-phenylethan-1-ol (5 equiv, 299 μL) afforded the pure product **2l** as a white solid (145 mg, 84%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). The excess of 2-phenylethan-1-ol was then removed by distillation (T = 120 °C, P = 110 mbar). Mp 87.3−88.4 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, 2H, J = 7.4 Hz), 7.40 (t, 1H, J = 7.4 Hz), 7.30 (t, 2H, J = 7.5 Hz), 7.20−7.17 (m, 5H), 7.12−7.09 (m, 5H), 6.75 (br. s, 1H), 3.15−3.12 (m, 4H), 2.85−2.81 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.9, 139.9, 133.7, 131.8, 128.8, 128.7, 128.6, 127.1, 126.3, 59.4, 34.0. IR (neat): ν 3223, 3059, 3026, 2961, 2839, 1643, 1547, 1494, 1453, 1293, 1124, 1027, 934, 752, 727, 694, 671, 613, 498, 471 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{25}N_2O$ 345.1967; found 345.1967.

N′,N′-Bis(3-phenylpropyl)benzohydrazide (2m). According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 3-phenylpropan-1-ol (5 equiv, 327 μL) afforded the pure product **2m** as a white solid (141 mg, 76%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). The excess of 3-phenylpropan-1-ol was then removed by distillation (T = 130 °C, P = 110 mbar). Mp 85.5−88.9 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, 2H, J = 7.4 Hz), 7.38 (t, 1H, J = 7.5 Hz), 7.29 (t, 2H, J = 7.5 Hz), 7.18−7.15 (m, 5H), 7.10−7.07 (m, 5H), 6.52 (br. s, 1H), 2.74 (t, 4H, J = 7.2 Hz), 2.61 (t, 4H, J = 7.3 Hz), 1.76 (quint, 4H, J = 7.3 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.8, 142.1, 134.0, 131.7, 128.7, 128.6, 128.4, 128.4, 127.0, 125.9, 57.7, 33.4, 28.9. IR (neat): ν 3245, 3026, 2946, 2851, 1650, 1533, 1312, 1286, 1107, 1028, 938, 800, 751, 694, 669, 607, 596, 503, 489, 460 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{29}N_2O$ 373.2280; found 373.2284.

2-Methyl-N′,N′-dipropylbenzohydrazide (2n). According to the general procedure B, alkylation of 2-methylbenzohydrazide **1f** (0.5 mmol, 75 mg) with propan-1-ol (5 equiv, 187 μL) afforded the pure product **2n** as a white solid (92 mg, 79%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). Mp 74.0−78.9 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32−7.29 (m, 2H), 7.23−7.17 (m, 2H), 6.15 (br. s, 1H), 2.76 (t, 4H, J = 7.7 Hz), 2.45 (s, 3H), 1.60 (sext, 4H, J = 7.6 Hz), 0.95 (t, 6H, J = 7.4 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 169.0, 136.5, 135.6, 131.1, 130.1, 126.7, 125.8, 60.4, 20.5, 19.8, 11.9. IR (neat): ν 3214, 3056, 2961, 2937, 2857, 2833, 1653, 1538, 1466, 1375, 1314, 1281, 1165, 1067, 948, 914, 867, 750, 723, 691, 660,

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466, 455 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{23}N_2O$ 221.1654; found 221.1658.

***N′,N′*-Bis(cyclobutylmethyl)-4-fluorobenzohydrazide (2o).** According to the general procedure B, alkylation of 4-fluorobenzohydrazide **1c** (0.5 mmol, 77 mg) with cyclobutyl methanol (5 equiv, 242 μL) afforded the pure product **2o** as a white solid (81 mg, 56%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 77.9−79.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72−7.69 (m, 2H), 7.07 (t, 2H, *J* = 8.6 Hz), 6.59 (br. s, 1H), 2.87 (d, 4H, *J* = 6.9 Hz), 2.61−2.55 (m, 2H), 2.06−12.00 (m, 4H), 1.91−1.83 (m, 2H), 1.81−1.68 (m, 6H). ^{19}F NMR (500 MHz, $CDCl_3$): −108.1. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.4, 132.4, 129.2 (d, *J* = 8.8 Hz), 115.7 (d, *J* = 22.5 Hz), 114.6, 64.0, 34.1, 27.6, 19.2. IR (neat): ν 3280, 3048, 2957, 2933, 2855, 1650, 1603, 1553, 1500, 1454, 1322, 1292, 1277, 1236, 1225, 1159, 1097, 930, 855, 765, 654, 625, 603 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{24}N_2OF$ 291.1873; found 291.1879.

*4-Methyl-N′,N′-di(pent-4-en-1-yl)benzohydrazide (**2p**).* According to the general procedure B, alkylation of 4-methylbenzohydrazide **1d** (0.5 mmol, 75 mg) with pent-4-en-1-ol (5 equiv, 256 μL) afforded the pure product **2p** as a white solid (109 mg, 76%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 71.2−72.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, 2H, *J* = 8.1 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 6.59 (br. s, 1H), 5.75 (td, 2H, *J* = 6.7; 16.9 Hz), 5.03−4.98 (m, 2H), 4.95−4.93 (m, 2H), 2.86−2.83 (m, 4H), 2.39 (s, 3H), 2.14−2.10 (m, 4H), 1.69−1.63 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.7, 142.2, 138.4, 131.2, 129.4, 127.1, 115.0, 57.8, 31.4, 26.5, 21.6. IR (neat): ν 3230, 2949, 1646, 1492, 1312, 1288, 1071, 909, 774, 694, 669 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{27}N_2O$ 287.2123; found 287.2127.

*N′,N′-Dibutyl-[1,1′-biphenyl]-2-carbohydrazide (**2q**).* According to the general procedure B, alkylation of [1,1′-biphenyl]-2-carbohydrazide **1e** (0.5 mmol, 106 mg) with butan-1-ol (5 equiv, 229 μL) afforded the pure product **2q** as a white solid (88 mg, 54%) by silica flash column chromatography (pentane/ethyl acetate 9:1). Mp 77.5−80.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (dd, 1H, *J* = 1.3; 7.6 Hz), 7.49−7.45 (m, 3H), 7.43−7.37 (m, 5H), 5.76 (br. s, 1H), 2.43 (t, 4H, *J* = 7.3 Hz), 1.20−1.18 (m, 8H), 0.82 (t, 6H, *J* = 7.1 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.3, 140.4, 139.6, 135.1, 130.3, 130.1, 129.0, 128.9, 128.8, 128.0, 127.7, 57.5, 28.4, 20.5, 14.0. IR (neat): ν 3215, 3058, 2955, 2861, 1651, 1543, 1466, 1317, 1304, 1073, 919, 760, 741, 696, 660, 565, 521 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{29}N_2O$ 325.2280; found 325.2286.

*4-Methoxy-N′,N′-dipentylbenzohydrazide (**2r**).* According to the general procedure B, alkylation of 4-methoxybenzohydrazide **1b** (0.5 mmol, 83 mg) with pentan-1-ol (5 equiv, 271 μL) afforded the pure product **2r** as a white solid (138 mg, 90%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 9:1). Mp 77.2−78.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 2H, *J* = 8.8 Hz), 6.91 (d, 2H, *J* = 8.8 Hz), 6.46 (br. s, 1H), 3.85 (s, 3H), 2.82−2.79 (m, 4H), 1.57−1.53 (m, 4H), 1.31−1.29 (m, 8H), 0.86 (t, 6H, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 166.3, 162.3, 128.9, 126.5, 114.0, 58.7, 55.6, 29.6, 26.9, 22.7, 14.2. IR (neat): ν 3243, 2932, 2858, 1647, 1607, 1537, 1508, 1459, 1289, 1253, 1182, 1082, 1026, 942, 929, 848, 771, 668, 631, 609, 534, 515 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{31}N_2O_2$ 307.2386; found 307.2383.

*N′,N′-Dibutylfuran-2-carbohydrazide (**2s**).* According to the general procedure B, alkylation of furan-2-carbohydrazide **1g** (0.5 mmol, 63 mg) with butan-1-ol (5 equiv, 229 μL) afforded the pure product **2s** as a white solid (92 mg, 77%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 68.9−71.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.41 (dd, 1H, *J* = 0.7; 1.7 Hz), 7.14 (dd, 1H, *J* = 0.7; 3.5 Hz), 6.78 (br. s, 1H), 6.49 (dd, 1H, *J* = 1.7; 3.5 Hz), 2.79−2.76 (m, 4H), 1.55−1.49 (m, 4H), 1.30 (sext, 4H, *J* = 7.4 Hz), 0.87 (t, 6H, *J* = 7.4 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 157.5, 147.4, 143.9, 115.0, 112.2, 58.6, 29.1, 20.5, 14.1. IR (neat): ν 3238, 2956, 2865, 1655, 1591, 1470, 1293, 1082, 1008, 885, 748, 596 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{23}N_2O_2$ 239.1760; found 239.1763.

*N′-(2-Methylpentyl)benzohydrazide (**3b**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 2-methylpentan-1-ol (5 equiv, 309 μL) afforded the pure product **3b** as a white solid (78 mg, 71%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). Mp 96.7−97.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (br. s, 1H), 7.76−7.73 (m, 2H), 7.51−7.48 (m, 1H), 7.40 (t, 2H, *J* = 7.5 Hz), 4.93 (br. s, 1H), 2.84 (dd, 1H, *J* = 5.8; 11.2 Hz), 2.69 (dd, 1H, *J* = 7.5; 11.2 Hz), 1.69−1.63 (m, 1H), 1.42−1.33 (m, 2H), 1.31−1.24 (m, 1H), 1.17−1.11 (m, 1H), 0.96 (d, 3H, *J* = 6.7 Hz), 0.85 (t, 3H, J = 7.0 Hz). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.3, 133.1, 131.8, 128.7, 127.0, 58.8, 37.2, 31.9, 20.1, 18.1, 14.4. IR (neat): ν 2988, 2901, 1648, 1493, 1392, 1232, 1067, 895, 694, 615, 432 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{21}N_2O$ 221.1654; found: 221.1658.

*N′-(Cyclohexylmethyl)benzohydrazide (**3c**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with cyclohexyl methanol (5 equiv, 307 μL) afforded the pure product **3c** as a white solid (56 mg, 48%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). Mp 98.2−99.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 7.3 Hz), 7.50 (t, 1H, *J* = 7.4 Hz), 7.43 (t, 2H, *J* = 7.5 Hz), 2.78 (d, 2H, *J* = 6.7), 1.83−1.81 (m, 2H), 1.74−1.67 (m, 2H), 1.54−1.49 (m, 1H), 1.29−1.14 (m, 4H), 1.02−0.95 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.3, 133.1, 131.9, 128.8, 126.9, 59.1, 36.8, 31.4, 26.7, 26.1. IR (neat): ν 3243, 2972, 2941, 1648, 1532, 1492, 1376, 1218, 1082, 896, 679, 652, 414 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}N_2O$ 233.1654; found 233.1651.

*N′-Neopentylbenzohydrazide (**3d**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 2,2-dimethylpropan-1-ol (5 equiv, 220 mg) afforded the pure product **3d** as a white solid (71 mg, 69%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). Mp 95.8−96.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (br. s, 1H), 7.73 (d, 2H, *J* = 7.3 Hz), 7.47 (t, 1H, *J* = 7.4 Hz), 7.39 (t, 2H, *J* = 7.5 Hz), 4.88 (br. s, 1H), 2.72 (s, 2H), 0.98 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 167.3, 133.1, 131.8, 128.8, 126.9, 64.4, 31.3, 27.8. IR (neat): ν 3231, 2954, 2843, 1628, 1460, 1364, 1328, 1160, 888, 695, 550 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{19}N_2O$ 207.1497; found 207.1499.

*N′-(3,7-Dimethyloct-6-en-1-yl)benzohydrazide (**3e**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 3,7-dimethyloct-6-en-1-ol

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(5 equiv, 456 μL) afforded the pure product **3e** as a light yellow solid (77 mg, 56%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). Mp 98.7−99.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (br. s, 1H), 7.74 (d, 2H, *J* = 7.3 Hz), 7.50 (t, 1H, *J* = 7.4 Hz), 7.42 (t, 2H, *J* = 7.6 Hz), 5.09−5.06 (m, 1H), 3.00−2.90 (m, 2H), 2.02−1.91 (m, 2H), 1.73−1.62 (m, 5H), 1.59−1.49 (m, 5H), 1.83−1.81 (m, 2H), 0.89 (d, 3H, *J* = 6.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.4, 133.0, 131.9, 131.4, 128.8, 127.0, 124.8, 50.5, 37.3, 35.2, 30.6, 25.8, 25.6, 19.7, 17.8. IR (neat): ν 3243, 2985, 2905, 1649, 1497, 1421, 1364, 1292, 1068, 982, 926, 692, 617, 418 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{17}H_{27}N_2O$ 275.2123; found 275.2119.

*N′-Cyclopentylbenzohydrazide (**3f**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with cyclopentanol (5 equiv, 218 μL) afforded the pure product **3f** as a white solid (48 mg, 47%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). Mp 94.5−96.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76−7.74 (m, 2H), 7.68 (br. s, 1H), 7.53−7.50 (m, 1H), 7.46−7.43 (m, 2H), 4.87 (br. s, 1H), 3.59−3.58 (m, 1H), 1.79−1.70 (m, 4H), 1.61−1.51 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.4, 133.2, 131.9, 128.9, 127.0, 61.9, 31.4, 24.3. IR (neat): ν 3062, 2956, 1634, 1578, 1536, 1455, 1075, 989, 798, 693 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{12}H_{17}N_2O$ 205.1341; found 205.1342.

*N′-(1-Phenylethyl)benzohydrazide (**3g**).*[5] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 1-phenylethan-1-ol (5 equiv, 299 μL) afforded the pure product **3g** as a white solid (86 mg, 72%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (br. s, 1H), 7.64−7.63 (m, 2H), 7.49−7.46 (m, 2H), 7.40−7.33 (m, 5H), 7.30−7.27 (m, 1H), 5.12 (br. s, 1H), 4.23 (q,1H, *J* = 6.6 Hz), 1.42 (d, 3H, *J* = 6.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.4, 143.1, 132.9, 131.9, 128.7, 128.7, 127.7, 127.3, 127.0, 60.1, 21.2.

*N′-(1-(Naphthalen-2-yl)ethyl)benzohydrazide (**3h**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 1-(naphthalen-2-yl)ethan-1-ol (5 equiv, 430 mg) afforded the pure product **3h** as a white solid (97 mg, 67%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 100.1−100.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87−7.81 (m, 4H), 7.61−7.57 (m, 3H), 7.51−7.44 (m, 4H), 7.37−7.34 (m, 2H), 5.19 (br. s, 1H), 4.41 (q, 1H, *J* = 6.6 Hz), 1.51 (d, 3H, *J* = 6.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.5, 140.8, 133.6, 133.2, 133.0, 132.0, 128.8, 128.6, 128.0, 127.8, 127.0, 126.3, 126.0, 125.3, 60.4, 21.5. IR (neat): ν 3266, 2962, 1648, 1519, 1392, 1285, 912, 893, 751, 693, 486 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{19}H_{19}N_2O$ 291.1422; found 291.1426.

*N′-(1-(Benzo[d][1,3]dioxol-5-yl)ethyl)benzohydrazide (**3i**).* According to the general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(benzo[*d*][1,3]-dioxol-5-yl)ethan-1-ol (5 equiv, 415 mg) afforded the pure product **3i** as a light yellow solid (94 mg, 66%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 99.2−99.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65−7.63 (m, 3H), 7.47 (t, 1H, *J* = 7.5 Hz), 7.37 (t, 2H, *J* = 7.5 Hz), 6.93 (d, 1H, *J* = 1.4 Hz), 6.80 (dd, 1H, *J* = 1.4; 7.9 Hz), 6.74 (d, 1H, *J* = 7.9 Hz), 5.93 (s, 2H), 5.04 (br. s, 1H), 4.15 (q, 1H, *J* = 6.5 Hz), 1.36 (d, 3H, *J* = 6.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.5, 148.0, 147.0, 137.2, 133.0, 131.9, 128.8, 127.0, 120.8, 108.3, 107.4, 101.1, 59.9, 21.4. IR (neat): ν 3061, 2970, 2888, 1634, 1485, 1438, 1239, 1037, 934, 806, 692, 638, 442 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1239; found 285.1245.

*N′-(1-(Thiophen-2-yl)ethyl)benzohydrazide (**3j**).*[5] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with (thiophen-2-yl)ethan-1-ol (5 equiv, 320 mg) afforded the pure product **3j** as a light yellow solid (85 mg, 69%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (br. s, 1H), 7.67 (d, 2H, *J* = 7.2 Hz), 7.48 (t, 1H, *J* = 7.3 Hz), 7.39 (t, 2H, *J* = 7.5 Hz), 7.26−7.24 (m, 1H), 6.98−6.95 (m, 2H), 5.13 (br. s, 1H), 4.54 (q, 1H, *J* = 6.5 Hz), 1.50 (d, 3H, *J* = 6.5 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.6, 147.1, 132.9, 132.0, 128.8, 127.0, 126.8, 124.9, 124.7, 55.8, 22.0.

*N′-(1-(4-Methoxyphenyl)ethyl)benzohydrazide (**3k**).*[5] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 1-(4-methoxyphenyl)-ethan-1-ol (5 equiv, 380 mg) afforded the pure product **3k** as a white solid (93 mg, 69%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56−7.55 (m, 2H), 7.43−7.40 (m, 1H), 7.34−7.31 (m, 3H), 7.25 (d, 2H, *J* = 8.5 Hz), 6.81 (d, 2H, *J* = 8.5 Hz), 4.12 (q, 1H, *J* = 6.6 Hz), 3.73 (s, 3H), 1.34 (d, 3H, *J* = 6.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.4, 159.2, 135.2, 133.1, 131.9, 128.8, 128.5, 127.0, 114.1, 59.5, 55.4, 21.3.

*N′-(1-(4-(Trifluoromethyl)phenyl)ethyl)benzohydrazide (**3l**).*[5] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 1-(4-(trifluoromethyl)phenyl)ethan-1-ol (5 equiv, 475 mg) afforded the pure product **3l** as a white solid (97 mg, 63%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63−7.61 (m, 4H), 7.53 (d, 2H, *J* = 8.1 Hz), 7.52−7.49 (m, 1H), 7.42−7.37 (m, 3H), 5.07 (br. s, 1H), 4.33 (q, 1H, *J* = 6.6 Hz), 1.43 (d, 3H, *J* = 6.6 Hz). ^{19}F NMR (500 MHz, $CDCl_3$): −62.4. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.8, 147.6, 132.8, 132.2, 128.9, 128.7 (d, *J* = 139 Hz), 127.7, 127.0, 125.7 (q, *J* = 3.7 Hz), 59.9, 21.6.

*N′-(1-(4-Chlorophenyl)ethyl)benzohydrazide (**3m**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 1-(4-chlorophenyl)ethan-1-ol (5 equiv, 390 mg) afforded the pure product **3m** as a white solid (96 mg, 70%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Mp 98.3−99.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63−7.61 (m, 2H), 7.51−7.48 (m, 1H), 7.45 (br. s, 1H), 7.41−7.38 (m, 2H), 7.35−7.31 (m, 4H), 5.05 (br. s, 1H), 4.22 (q, 1H, *J* = 6.6 Hz), 1.39 (d, 3H, *J* = 6.6 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.6, 141.9, 133.4, 132.9, 132.1, 128.9, 128.8, 128.7, 127.0, 59.6, 21.4. IR (neat): ν 2968, 1636, 1462, 1312, 1129, 1075, 1017, 867, 805, 716, 692, 483, 413 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{15}H_{16}N_2OCl$ 275.1602; found 275.1608.

*N′-(1-(4-Fluorophenyl)ethyl)benzohydrazide (**3n**).*[5] According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 1-(4-fluorophenyl)ethan-1-ol (5 equiv, 350 mg) afforded the pure product **3n** as a white solid (94 mg, 73%) after purification by flash column

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chromatography on silica gel (pentane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (br. s, 1H), 7.63 (d, 2H, J = 7.2 Hz), 7.50−7.47 (m, 1H), 7.40−7.34 (m, 4H), 7.06−6.99 (m, 2H), 5.00 (br. s, 1H), 4.24 (q, 1H, J = 6.6 Hz), 1.38 (d, 3H, J = 6.6 Hz). ^{19}F NMR (500 MHz, $CDCl_3$): −115.1. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.5, 161.3 (d, J = 243.8 Hz), 138.9 (d, J = 3.1 Hz), 132.9, 132.0, 128.9 (d, J = 7.9 Hz), 128.8, 127.0, 115.4 (d, J = 21.1 Hz), 59.4, 21.3.

Deuterium Labeling. *N′,N′-Dimethylbenzohydrazide (**2f-d$_6$**).* According to a modified general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with methanol-d_4 used as the solvent (0.5 M) afforded the pure product **2f-d$_6$** as a white solid (75 mg, 88%) after purification by flash column chromatography on silica gel (pure ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (br. s, 1H), 7.76−7.74 (m, 2H), 7.52−7.49 (m, 1H), 7.41 (t, 2H, J = 7.5 Hz).

*N′-(1-Phenylethyl)benzohydrazide (**3g-d$_1$**).* According to the general procedure B, alkylation of benzohydrazide **1a** (0.5 mmol, 68 mg) with 1-phenylethan-1-d_1-ol (5 equiv, 308 mg) afforded the pure product **3g-d$_1$** as a white solid (82 mg, 68%) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63−7.61 (m, 2H), 7.50−7.47 (m, 1H), 7.43−7.34 (m, 7H), 7.31−7.28 (m, 1H), 5.09 (br. s, 1H), 1.43 (br. s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00654.

Spectroscopic details of the catalytic reactions and DFT calculations; optimization of benzohydrazide dialkylation; mechanistic studies; NMR spectra of ruthenium complexes; NMR spectra of starting materials; NMR spectra of products (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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