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Nickel-Catalyzed Guerbet Type Reaction: C-Alkylation of Secondary Alcohols *via* Double (de)Hydrogenation

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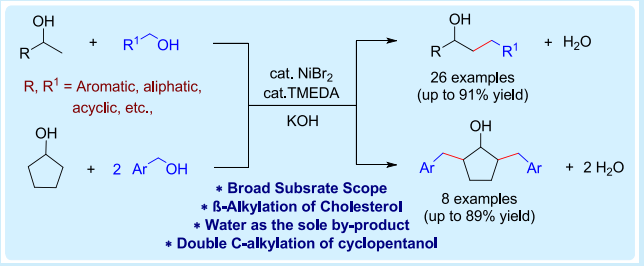
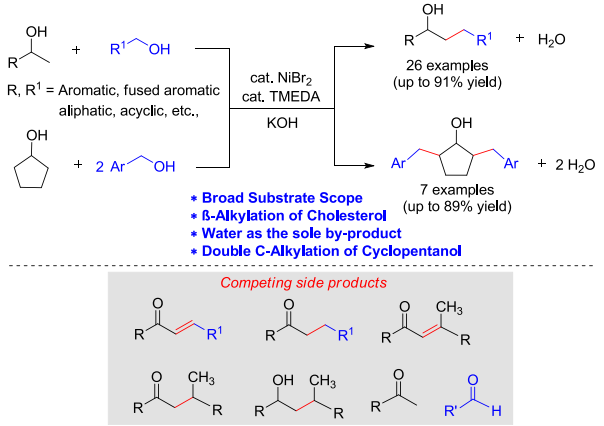
ABSTRACT: Acceptorless double dehydrogenative cross-coupling of secondary and primary alcohols under nickel catalysis is reported. This Guerbet type reaction provides an atom- and a step-economical method for the C-alkylation of secondary alcohols under mild, benign conditions. A broad range of substrates including aromatic, cyclic, acyclic, and aliphatic alcohols was well tolerated. Interestingly, the C-alkylation of cholesterol derivatives and the double C-alkylation of cyclopentanol with various alcohols were also demonstrated.



The construction of functionalized diverse molecules from simple abundant chemicals by C−C bond-forming reactions is one of the fundamental reactions in organic synthesis.[1] Traditionally, the C−C bond formation of carbonyl compounds (*i.e.*, C(α)-alkylation) has been achieved by nucleophilic substitution reactions with alkyl halides or other activated derivatives.[2] Thus, classical methods require highly reactive, toxic, and expensive reagents, which generate stoichiometric amounts of hazardous waste.[3] In this regard, the development of a green and sustainable method by utilizing abundantly available feedstock alcohols for selective C−C bond formation is highly desirable.[4] Recently, transition metal-catalyzed alcohol activation through a borrowing hydrogen strategy (BH) has been seen to play a significant role in the direct C−C and C−N bond forming reactions, which often overcome limitations of classical methods and produce water as the byproduct.[5] The BH reaction relies on catalytic dehydrogenation of alcohols to carbonyl compounds, condensation reaction with a suitable C-, or N-nucleophile to form an α,β-unsaturated compound and an imine intermediate, respectively, and finally, selective hydrogenation of the α, β-unsaturated or imine intermediate leads to the saturated product by utilizing the hydrogen gas liberated in the initial dehydrogenation step.[6] Thus, the net reaction eliminates water as a sole byproduct.

Of late, C−C bond formation *via* the acceptorless dehydrogenative cross-coupling reaction of different alcohols is very interesting. This Guerbet type reaction provides an atom- and a step-economical method for the C-alkylation of secondary alcohols under mild, benign conditions (Scheme 1). Notably, the β-alkylation of secondary alcohols with primary alcohols has been widely investigated under precious metal (Ru, Rh, Ir, and Pd) catalysis.[7−10] In addition to this, seminal examples based on heterogeneous catalytic systems have been established for the β-alkylation of secondary alcohols.[11] In recent times, judiciously designed earth-abundant 3d-transition metal catalysts for sustainable chemical synthesis *via* the C−C cross-coupling of alcohols has gained much interest due to economic and environmental benefits.[12]

Scheme 1. Guerbet Type C-Alkylation of Secondary Alcohols with Primary Alcohols



In 2017, a seminal work on the PNP-cobalt pincer complex catalyzed C−C cross-coupling of secondary alcohols using primary alcohols has been reported by Kempe and co-workers.[13] Of late, the research group of Yu has reported the manganese-catalyzed cross-coupling of secondary alcohols with

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primary alcohols to access β-alkylated secondary alcohol products under dehydrogenative conditions.[14] Recently, notable progress has been made in the development of homogeneous catalysts used for the Guerbet-type reactions.[15] Notably, the first enantioselective Guerbet reaction at room temperature has been achieved using a commercially available chiral ruthenium complex developed by Zhao and co-workers.[15f]

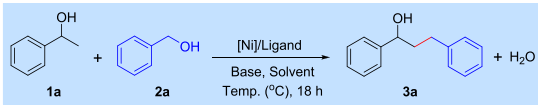
Lang and co-workers have studied the homogeneous Ni(II) *N*-heterocycle thiolate cluster mediated coupling of secondary and primary alcohols to yield α,β-unsaturated ketones, α-alkylated ketones, and β-alkylated secondary alcohols by tuning the reaction conditions.[16] However, this hexanuclear nickel thiolate cluster catalyzed cross-coupling reaction of alcohols requires high catalyst loading, multistep synthesis of $[Ni(dmpymt)_2]_6$ cluster, and limited substrate scope. Thus, the development of a simple, elegant catalytic system for C−C bond formation *via* the Guerbet type strategy is highly desirable and demanding in contemporary science. Herein, we have reported the selective β-alkylation of secondary alcohols with primary alcohols, using a commercially available, inexpensive $NiBr_2$/TMEDA as an efficient catalytic system. Interestingly, more challenging substrate conversions were achieved under benign conditions using primary alcohols as potential alkylating agents with various secondary alcohols. A broad range of substrates including aromatic, cyclic, acyclic, and aliphatic alcohols was well tolerated. Gratifyingly, the double C-alkylation of cyclopentanol with various alcohols was also demonstrated.

For the nickel-catalyzed dehydrogenative C-alkylation of secondary alcohols with primary alcohols, we have chosen 1-phenyl ethanol (**1a**) and benzyl alcohol (**2a**) as the benchmark substrates. Initially, a model reaction was performed using $NiBr_2$ (5 mol %) as nickel source, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 5 mol %) as a ligand, and KO^{t}Bu (1 equiv) as a base in toluene solvent at 130 °C for 18 h (Table 1, entry1). To our delight, the β-alkylated product **3a** was obtained in 72% of isolated yield. It was found that *n*-octane could be the optimal solvent achieving the desired product **3a** in excellent yield with selectivity (Table 1, entry 2). Under identical conditions, the effect of various bases such as KOH, LiO^{t}Bu, NaO^{t}Bu, NaOH, LiOH·H_2O, and K_2CO_3 was examined (Table 1, entries 3−8). Notably, KOH was found to be efficient and gave the desired product **3a** in excellent yield (Table 1, entry 3). The variation of solvent indicated that the reaction proceeded efficiently in *n*-octane (Table 1, entries 1,3 and 9−11).

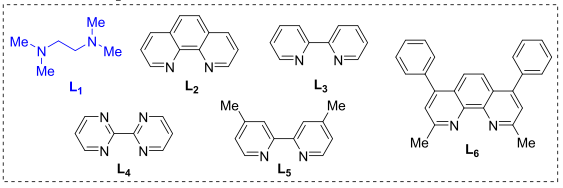
Other nickel catalysts were not effective for the present catalytic transformation and yielded the product **3a** in moderate yields (Table1, entries 3 and 12−15). Also, attempts to decrease the mole percentage of base ended with low yields of the desired product **3a**. Next, we have examined the effect of various commercially available nitrogen-based bidentate ligands (**L1**−**L6**) (Table 1, entries 19−23). Gratifyingly, the ligand **L1** was found to be more effective for this reaction (Table1, entry 3).

A control experiment in the absence of a base, ligand, as well as nickel catalyst led to no product formation (Table 1, entries 16−18). These results confirmed that the combination of the base, ligand, and nickel catalyst is necessary to access the desired β-alkylated alcohols. By lowering the reaction temperature from 130 to 100 °C, the yield of the product **3a** was reduced to 70% (Table 1, entries 3 and 24−25).

Table 1. Optimization Studies[c]



Entry	[Ni] source	Base	Solvent	Ligand	Temp. (°C)	Yield(%)[a]
1	$NiBr_2$	KO^{t}Bu	Toluene	L1	130	72
2	$NiBr_2$	KO^{t}Bu	n-Octane	L1	130	75
3	$NiBr_2$	KOH	n-Octane	L1	130	91(83)[b]
4	$NiBr_2$	LiO^{t}Bu	n-Octane	L1	130	19
5	$NiBr_2$	NaO^{t}Bu	n-Octane	L1	130	47
6	$NiBr_2$	NaOH	n-Octane	L1	130	65
7	$NiBr_2$	LiOH.H_2O	n-Octane	L1	130	NR
8	$NiBr_2$	K_2CO_3	n-Octane	L1	130	25
9	$NiBr_2$	KOH	*m*-Xylene	L1	130	44
10	$NiBr_2$	KOH	1,4-dioxane	L1	130	58
11	$NiBr_2$	KOH	DMF	L1	130	10
12	$NiCl_2$	KOH	n-Octane	L1	130	68
13	$Ni(acac)_2$	KOH	n-Octane	L1	130	69
14	$Ni(OTf)_2$	KOH	n-Octane	L1	130	NR
15	$NiCl_2(PMe_3)_2$	KOH	n-Octane	L1	130	68
16	----	KOH	n-Octane	L1	130	NR
17	$NiBr_2$	----	n-Octane	L1	130	NR
18	$NiBr_2$	KOH	n-Octane	----	130	NR
19	$NiBr_2$	KOH	n-Octane	L2	130	75
20	$NiBr_2$	KOH	n-Octane	L3	130	72
21	$NiBr_2$	KOH	n-Octane	L4	130	55
22	$NiBr_2$	KOH	n-Octane	L5	130	78
23	$NiBr_2$	KOH	n-Octane	L6	130	NR
24	$NiBr_2$	KOH	n-Octane	L1	110	81
25	$NiBr_2$	KOH	n-Octane	L1	100	70



[a]Yield calculated by ^{1}H NMR using dibromomethane as an internal standard. [b]Isolated yield. [c]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [Ni] source (5 mol %), Ligand ($\mathbf{L_1}$−$\mathbf{L_6}$) (5 mol %), base (0.5 mmol), and 1 mL of solvent heated in an oil-bath for 18 h.

With the optimized reaction conditions in hand, we next explored the applicability of the present nickel catalysis for the β-alkylation of secondary alcohols using diverse primary alcohols as an alkylating agent. At first, the scope of primary alcohols with secondary alcohols under standard reaction conditions was investigated (Table 2). As shown in Table 2, the electron-donating substituents such as methyl, ethyl, isopropyl, *t*-butyl, methoxy, and thioether groups containing benzyl alcohols afforded good to excellent yields of the β-alkylated product (products **3b**−**3l** in 74−87% isolated yields). Notably, halide substituted benzyl alcohols resulted in the products **3m**−**3o** in 66−79% of isolated yields. In particular, a fused aromatic compound, 1-naphthyl methanol, produced the corresponding product **3p** in 71% yield under the optimized reaction conditions. Moreover, aliphatic alcohols such as 1-hexanol and 1-pentanol resulted in the corresponding products **3q** in 75%, and **3r** in 72% of isolated yields, respectively.

Subsequently, we have explored the scope of secondary alcohol for the selective β-alkylation reaction using 4-methoxy benzyl alcohol (**2e**) as the benchmark substrate (Table 3). Pleasingly, the dehydrogenative C−C coupling reactions proceeded smoothly for a variety of secondary alcohols with electron-neutral, electron-deficient, and electron-rich substituents led to the corresponding β-alkylated product in good to excellent yields. Under the optimized reaction conditions, the

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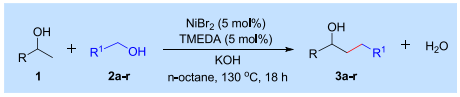
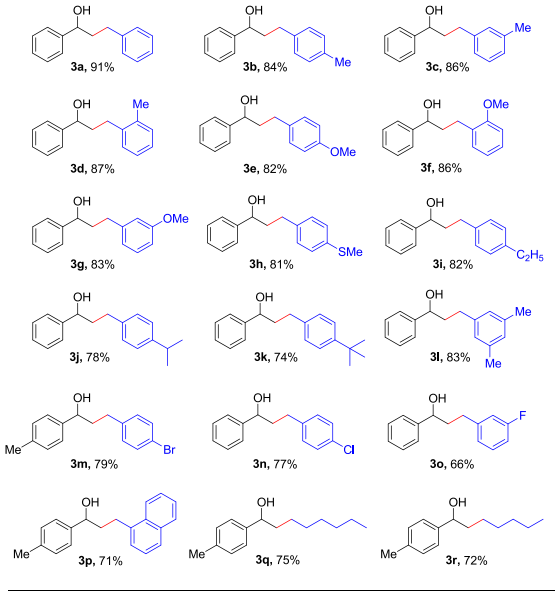
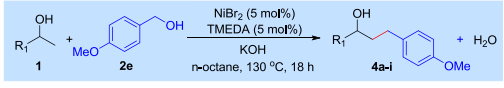
Table 2. Scope of Primary Alcohols[a,b]

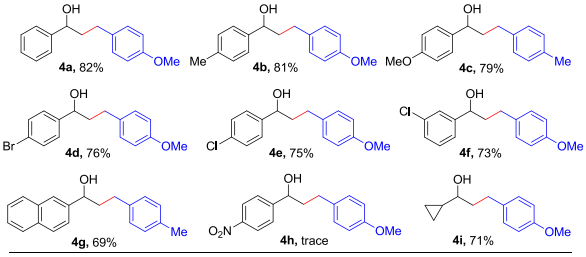




[a]Reaction conditions: **1** (0.5 mmol, **2** (0.5 mmol), $NiBr_2$ (5 mol %), TMEDA (5 mol %), and KOH (0.5 mmol) in 1 mL of *n*-octane heated at 130 °C (oil-bath temperature) for 18 h. [b]Isolated yields.

Table 3. Scope of Secondary Alcohols[a,b]





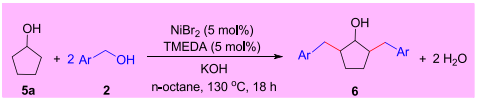
[a]Reaction conditions: **1** (0.5 mmol, **2e** (0.5 mmol), $NiBr_2$ (5 mol %), TMEDA (5 mol %), and KO^{t}Bu (0.5 mmol) in 1 mL of *n*-octane heated at 130 °C (oil-bath temperature) for 18 h. [b]Isolated yields.

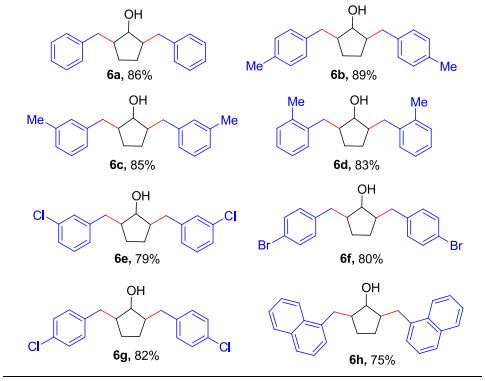
electron-donating substituents such as -Me, and -OMe groups on secondary alcohols afforded the β-alkylated products in good yields (products **4b**−**4c**, 79−84%). In particular, the halide (−Cl, and −Br) group containing secondary alcohols successfully underwent β-alkylation reaction and gave the products **4d** to **4f** in 76−75% of isolated yields under the optimized reaction conditions.

Interestingly, fused-aromatic secondary alcohol such as 1-(2-naphthyl)ethanol was efficiently C(β)-alkylated with 4-methyl benzyl alcohol under the present nickel-catalyzed conditions and produced the product **4g** in 69% yield. Unfortunately, secondary alcohols bearing a strong electron-withdrawing group (*e.g.*, $-NO_2$) failed to yield the desired product under our reaction conditions. Furthermore, 1-cyclopropylethanol resulted in the expected product **4i** in 71% of isolated yield under the present nickel-catalyzed conditions.

Interestingly, we extended our present catalytic system for tandem double alkylation of cyclopentanol **5a** with primary alcohols to access di(β-alkylated) secondary alcohol **6** products (Table 4). Thus, the benzyl alcohol bearing electron-donating

Table 4. Substrate Scope of Double C-Alkylation of Cyclopentanol[a,b]





[a]Reaction conditions: **5a** (0.5 mmol, **2** (1 mmol), $NiBr_2$ (5 mol %), TMEDA (5 mol %), and KOH (0.5 mmol) in 1 mL of *n*-octane heated at 130 °C (oil-bath temperature) for 18 h. [b]Isolated yields.

group, for example, methyl group at the *ortho*, *meta*, and *para* positions, and halide substituted benzyl alcohols (−Cl, and −Br) underwent β-alkylation reaction and gave the di(β-alkylated) products **6b**−**6g** in 79−89% of isolated yields under the optimized reaction conditions. Notably, other cyclic secondary alcohols such as cyclohexanol and cycloheptanol did not afford the desired products under standard reaction conditions.

The present nickel-catalyzed Guerbet type C(β)-alkylation strategy was successfully applied for the derivatization of cholesterol derivatives. As a result, the reaction of cholesterol derivative **7a** with 2.5 equiv of benzyl alcohol under standard reaction conditions yielded the corresponding C(β)-alkylated product **8a** in 78% isolated yield, wherein hydrogenation of C═C bond was observed (Scheme 2). Similarly, with an excess of benzyl alcohol compound **7b** yielded bis-β-alkylated product **8b** in 87% yield with the hydrogenation of olefinic and carbonyl moieties of **7b.**

To gain preliminary insights into the present nickel-catalyzed β-alkylation of secondary alcohols with primary alcohols, various control experiments were performed. Evaluation of H_2 gas from the benchmark reaction was detected by gas chromatography (GC) analysis (Scheme 3a). Next, two independent reactions of acetophenone **1a′** with benzyl alcohol **2a** and 1-phenyl ethanol **1a** with benzaldehyde **2a′** gave a mixture of C−C bonded products such as 1,3-diphenylpropan-1-one (**3a′**, major), (*E*)-chalcone (**3a″**, minor), and trace amounts of 1,3-diphenylpropan-1-ol (**3a**) (Scheme 3b). Then, the reaction of (*E*)-chalcone **3a″** in the presence of 1-phenyl ethanol **1a** or benzyl alcohol **2a** resulted in 1,3-diphenylpropan-1-one **3a′** as a major product and 1,3-diphenylpropan-1-ol **3a** as a minor product (Scheme 3c). From

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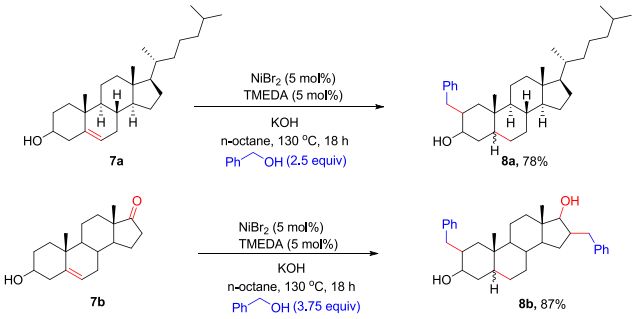
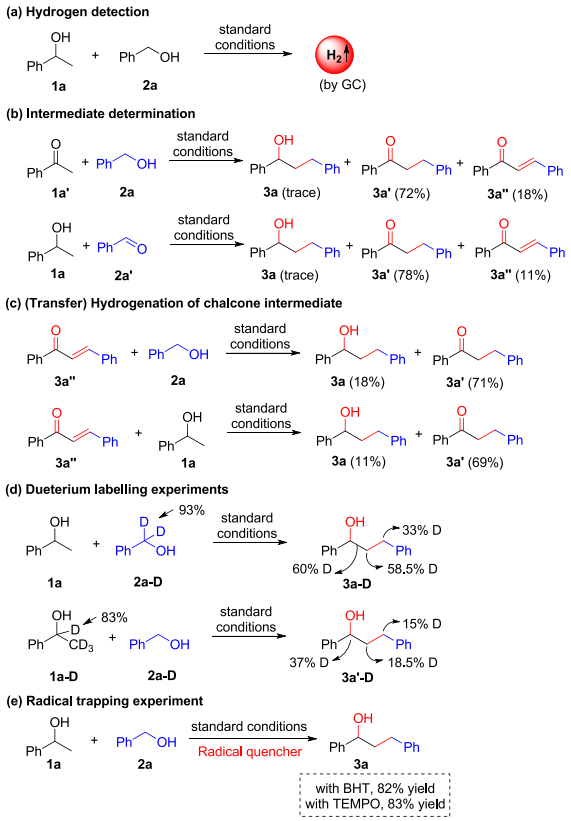
Scheme 2. β-Alkylation of Cholesterol Derivatives



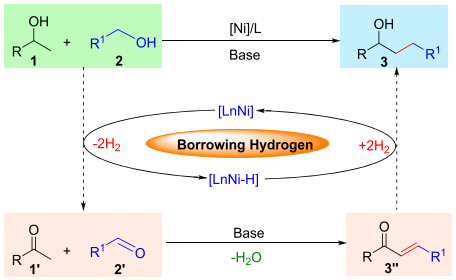
Scheme 3. Control Experiments



these results, it was observed that the reaction proceeds *via* the initial acceptorless dehydrogenation of alcohols followed by condensation and subsequent transfer hydrogenation of intermediate chalcone **3a″**. Moreover, the deuterium labeling experiments were performed using deuterated benzyl alcohol **2a-D** and deuterated 1-phenyl ethanol **1a-D** under the present nickel-catalyzed conditions and yielded the deuterium-incorporated β-alkylated secondary alcohols **3a-D** and **3a′-D**. The presence of deuterium atom at α, β, and γ positions of **3a-D** and **3a′-D** has further confirmed the dehydrogenation of an alcohol followed by (transfer) hydrogenation of intermediate **3a″** (Scheme 3d). Notably, in the presence of radical scavengers, such as BHT and TEMPO, the product formation was not affected, and indeed, the product **3a** was obtained in excellent yield (Scheme 3e). This result illustrates that the present nickel catalysis does not follow the SET (single electron transfer) mechanism.

On the basis of the control experiments and previous reports,[17−20] a plausible mechanism for the nickel-catalyzed cross dehydrogenative coupling of secondary alcohols with primary alcohols is proposed in Scheme 4. Initially, both the

Scheme 4. Plausible Mechanistic for the Nickel-Catalyzed β-Alkylation of Secondary Alcohols



primary and secondary alcohols undergo dehydrogenation under nickel catalysis leads to the corresponding carbonyls derivatives (ketone (**1′**) and aldehyde (**2′**), respectively) with the generation of hydrogen gas. Subsequently, a base-mediated cross-aldol type condensation of **1′** and **2′** generates an intermediate α,β-unsaturated ketone (**3″**). Finally, in the presence of a nickel catalyst transfer hydrogenation of α,β-unsaturated ketone (by the liberated hydrogen from the foremost dehydrogenation step) to access the desired β-alkylated secondary alcohol product (**3a**). Overall, the process is redox neutral and produces water as a sole byproduct.

In summary, we have reported an efficient β-alkylation of secondary alcohols with primary alcohols under benign conditions. This elegant approach exhibits a broad substrate scope providing the C−C coupled products of secondary alcohols and the double alkylation of cyclopentanol using aryl, fused aryl, and aliphatic primary alcohols. This Guerbet type protocol extended for the functionalization of cholesterol derivatives. Preliminary mechanistic studies and isotopic labeling experiments suggest that the C−C coupling reaction proceeds *via* the borrowing hydrogenation with the formation of water as a byproduct.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00782.

Experimental section; ^{1}H and ^{13}C NMR (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a−3r**; **3a′**; **3a′′**; **3a−D**; **3b−D**; **4a−4i**; **6a−6h**; **8a**; **8b** (ZIP)

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Notes

The authors declare no competing financial interest.

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