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Ruthenium-Catalyzed α-Alkylation of Ketones Using Secondary Alcohols to β-Disubstituted Ketones

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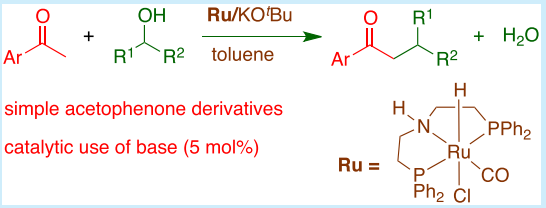
ABSTRACT: An assortment of aromatic ketones was successfully functionalized with a variety of unactivated secondary alcohols that serve as alkylating agents, providing β-disubstituted ketone products in good to excellent yields. Remarkably, challenging substrates such as simple acetophenone derivatives are effectively alkylated under this ruthenium catalysis. The substituted cyclohexanol compounds displayed product-induced diastereoselectivity. Mechanistic studies indicate the involvement of the hydrogen-borrowing pathway in these alkylation reactions. Notably, this selective and catalytic C−C bond-forming reaction requires only a minimal load of catalyst and base and produces H_2O as the only byproduct, making this protocol attractive and environmentally benign.



The hydrogen-borrowing strategy is an attractive method for C−C and C−N bond formations, and these transformations are fundamentally important in chemical synthesis.[1] This strategy becomes acceptable and well-recognized as it enhances the importance of low waste transformations. In these processes, the catalyst borrows the hydrogen from alcohols via oxidation reactions to provide corresponding carbonyl compounds and further concomitant condensation, with nucleophilic enolates forming C═C bonds. Finally, the "borrowed hydrogen" by the catalyst is added to the unsaturated intermediate (C═C bonds) to deliver the hydrogenated/alkylated product. Conventionally, α-alkylated ketones are prepared from the reaction of ketone enolate species with alkyl halides.[2] The involvement of alkyl halides and a stoichiometric excess of base produces copious hazardous salt waste and undesired aldol side products (Scheme 1c) and, thus, decreases the atom economy. Therefore, the development of a simple, selective, and atom-economical alkylation reaction for the construction of C−C bonds is strongly desired. Notably, alcohols are cheap, readily available, and can be produced from lignocellulosic biomass.[3] Thus, alcohols are considered as potential alkylating agents that produce water as the only byproduct.[1,4]

Ketones are of great importance in biology and industries, where they are produced on a large scale as solvents, polymer precursors, and pharmaceuticals.[5] The use of primary alcohols for α-alkylation of ketones and β-alkylation of secondary alcohols has been well-established, which generates linear chain α-alkylated ketones.[1,4,6] A ruthenium-catalyzed hydrogen-borrowing strategy using primary alcohols with ketone enolates is well-known (Scheme 1a).[1,4] However, the use of secondary alcohols for alkylation reactions is poorly documented. In contrast to α-branched ketones, formation of β-disubstituted branched products is more challenging and relatively underdeveloped. In 2017, the Donohoe group reported the synthesis of β-branched ketones via α-alkylation of ketones using secondary alcohols.[7] Very recently Co,[8] Fe,[9] and Mn[10]-catalyzed α-alkylation of ketones using secondary alcohols was developed (Scheme 1b). All of these enticing developments can be summarized as follows: (i) Stoichiometric excess base is required, which results in aldol side reactions. (ii) To avoid base-promoted self-condensation, highly hindered aryl ketones are employed. In general, these methods work only for pentamethylphenyl (Ph*) ketone or trisubstituted aryl ketones. (iii) Unsubstituted or other aryl ketones are less successful and, thus, suffer from a limited substrate scope. Importantly, the Ph* group averts ketone self-condensation reactions, which can also be detached to prepare a range of carbonyl derivatives such as esters and amides through a retro-Friedel−Crafts acylation reaction.[7−10] To circumvent these drawbacks, an efficient catalytic system is essential for the success of this process and its broad application, which also should preclude the self-condensation of the nonsubstituted ketone substrates. Recently, selective cross-coupling of secondary alcohols to β-disubstituted ketones was reported by our group.[11] However, as far as we know, there is no general method for α-alkylation of ketones (especially for acetophenone with no or less substitution) using secondary alcohols. Thus, a simple catalytic method with a broad substrate scope is urgently required.

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Scheme 1. Selective Catalytic α-Alkylation of Ketones Using Primary and Secondary Alcohols

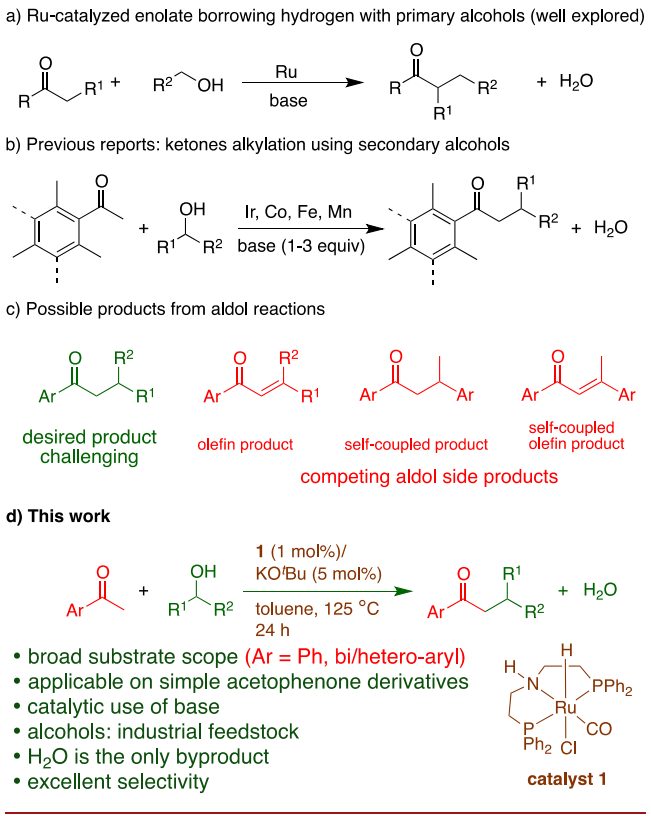
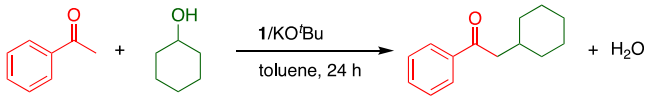


Table 1. Optimization for the α-Alkylation of Ketones Using Secondary Alcohols Catalyzed by 1[a]



entry	catalyst (mol %)	base (mol %)	alcohol (equiv)	temperature (°C)	conversion (%)[b]	yield (%)[c]
1	1	200	2	135	>99	59
2	1	200	2	125	>99	68
3	1	100	1.2	125	>99	70
4	1	20	1.2	125	>99	73
5	**1**	**5**	**1.2**	**125**	**>99**	**80**
6	1	2	1.2	125	40	35
7	1	5	1.5	125	>99	79
8	1	5	1.2	120	97	74
9	1	5	1.2	100	5	
10	0.5	2.5	1.2	125	95	75
11[d]	1	5	1.2	125	85	65
12[e]	1	5	1.2	125	5	
13[f]	1	5	1.2	125	>99	79
14[g]		5	1.2	125	55	
15[g]			1.2	125		
16[h]	1	5	1.2	125	>99	75

[a]Reaction conditions: acetophenone (0.5 mmol), cyclohexanol (0.6 mmol), catalyst **1**, KO^{t}Bu, and toluene (1.5 mL) were heated at 125 °C under open conditions with an argon flow. [b]Conversion of acetophenone was determined by GC using mesitylene as an internal standard. [c]Isolated yields after column chromatography. [d]1,4-Dioxane used as a solvent. [e]5 mol % of Cs_2CO_3 used as a base. [f]5 mol % of NaO^{t}Bu used as a base. [g]Reaction performed twice. [h]Reaction performed on a 1 mmol scale.

Modern transition metal catalysis is keen on development of sustainable, one-step, and atom-economical strategies for the preparation of valuable building blocks from readily available starting materials. In this regard, we have developed ruthenium pincer catalyzed selective hydrogenation of epoxides,[12] ketazine synthesis,[13] α-alkylation, and α-olefination of nitriles and *N*,*N*-dialkylation of acylhydrazides using alcohols.[14] Remarkably, liberated H_2 and H_2O are the only byproducts from these green catalytic methods.

Initially, the reaction of acetophenone (0.5 mmol) and cyclohexanol (1 mmol) was investigated as a model system in the presence of a ruthenium pincer catalyst **1** (1 mol %, Ru-MACHO) and 2 equiv of a base (KO^{t}Bu) in toluene at 135 °C. Surprisingly, catalyst **1** was found to exhibit distinctively high activity in forming the alkylated product **2a** along with a trace amount of aldol side products. The undesired aldol side products (Scheme 1c) were inseparable from column chromatography, and thus, we were unable to isolate and identify them. The complete conversion of acetophenone was observed in 24 h, and the desired α-alkylated product **2a** was isolated in 59% yield (entry 1, Table 1). When temperature and the amount of base (KO^{t}Bu) and secondary alcohol were decreased, the product formation was slightly increased (entries 2 and 3). Use of a stoichiometric amount of base resulted in a considerable amount of aldol side reactions (Scheme 1c and Table 1,entries 1−3). Thus, decreasing the amount of KO^{t}Bu to 20 and 5 mol % resulted in improved product yields of 73 and 80%, respectively (entries 4 and 5). However, use of 2 mol % of base provided only 40% conversion (entry 6). The product yield was not improved upon using a slight excess of cyclohexanol (entry 7). Further, decreasing the temperature and catalyst load provided considerably lower yields (entries 8−10). The solvent effect on the reaction was noticeable. When 1,4-dioxane was used as a solvent, product yield was diminished (entry 11). Whereas use of Cs_2CO_3 as a base provided no product formation, NaO^{t}Bu produced results comparable to those of KO^{t}Bu (entries 12 and 13). Control experiments confirmed that no product was formed in the absence of catalyst **1** and base, implying their requirement in the α-alkylation of ketones (entries 14 and 15).

The reactivity of acetophenone with different secondary alcohols was explored (Scheme 2). Substituted cyclohexanol derivatives afforded the corresponding alkylated products **2b**−**2e** in good to moderate yields. The substitution on the cyclohexyl ring resulted in products as a mixture of diastereoisomers. Reaction of cycloheptanol and *exo*-norborenol with acetophenone afforded the α-alkylated products **2f** and **2g** in 60 and 75% yields, respectively. Highly hindered 2-adamantanol provided product **2h** in 40% yield. Decahydronaphthalen-2-ol is well-tolerated in this catalytic protocol and converted into α-alkylated product **2i** in 74% yield (Scheme 2). Diphenylmethanol provided product **2j** in 68% yield. Finally, 5 equiv of 3-pentanol and 4-heptanol reacted with acetophenone with increased catalyst load (5 mol %) and KO^{t}Bu (10 mol %), and the corresponding alkylated products **2k** and **2l** were isolated in moderate yields (Scheme 2).

Next, application of the α-alkylation reaction was extended to diverse ketones with different secondary alcohols, which delivered the β-branched ketone products in good to excellent yields (Scheme 3). Both electron-donating and electron-withdrawing groups on aryl ketones were well-tolerated in this catalytic protocol. Reaction of cyclohexanol with a variety of

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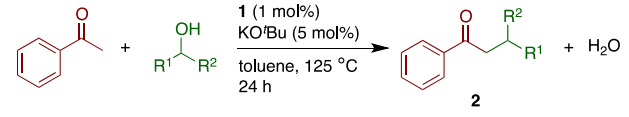
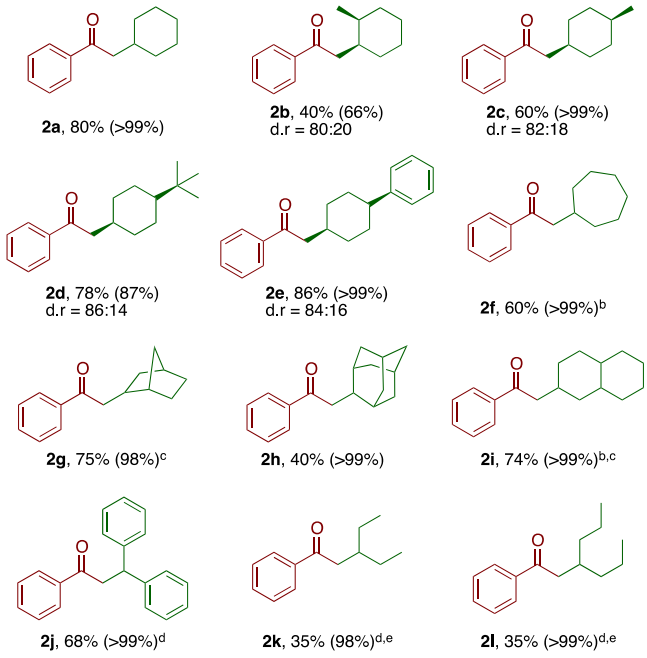
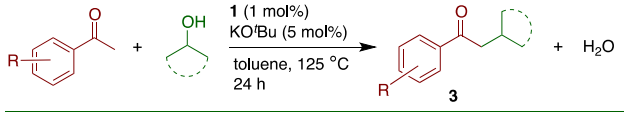
Scheme 2. Ruthenium-Catalyzed α-Alkylation of Acetophenone Using Secondary Alcohols[a]

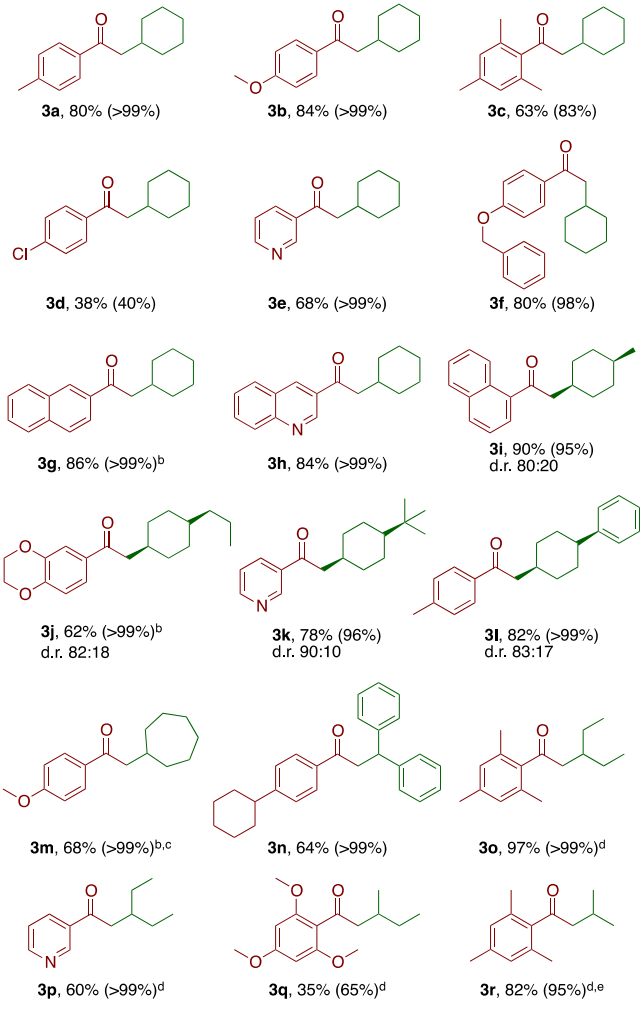




[a]Reaction conditions: acetophenone (0.5 mmol), secondary alcohol (0.6 mmol), toluene (1.5 mL), catalyst **1** (1 mol %), and KO^{t}Bu (5 mol %) were heated at 125 °C under open conditions with a nitrogen flow. Conversion of acetophenone was determined by GC analysis using mesitylene as an internal standard and given within parentheses. Diastereomeric ratios (dr) were determined from ^{1}H NMR analysis of the crude reaction mixture; only the major isomer is shown. Yields refer to isolated pure products after column chromatography. [b]3 mol % of catalyst **1** and 10 mol % of base were used. [c]Diastereomeric mixture and dr ratio not determined. [d]Reaction performed using 5 mol % of catalyst **1** and 10 mol % of base. [e]5 equiv of alcohol was used.

Scheme 3. Ruthenium-Catalyzed α-Alkylation of Ketones Using Secondary Alcohols[a]





[a]Reaction conditions: same as those in the footnote of Scheme 1 except that instead of acetophenone, ketone (0.5 mmol) was used. [b]3 mol % of catalyst **1** and 15 mol % of KO^{t}Bu were used. [c]3 equiv of cycloheptanol was used. [d]Reaction performed using 5 equiv of alcohol, 5 mol % of catalyst **1**, and 20 mol % of base. [e]10 equiv of isopropyl alcohol was used.

ketones provided α-alkylated ketone products **3a**−**3h**. 4-Methyl, 4-propyl, 4-*tert*-butyl, and 4-phenyl-substituted cyclohexanol derivatives provided products **3i**−**3l** as a mixture of diastereoisomers. Cycloheptanol reacted with 4-methoxyacetophenone and resulted in product **3m** (68% yield). Diphenylmethanol reacted with 4-cyclohexylacetophenone, and the desired ketone product **3n** was isolated in 64% yield. Interestingly, unactivated acyclic secondary alcohols are well-tolerated, enabling the synthesis of β-disubstituted ketones **3o**−**3r** in very good yields. Remarkably, heteroarene-embedded ketones successfully participated in α-alkylation with secondary alcohols and provided products **3e**, **3h**, **3k**, and **3p** in moderate to good yields (Scheme 3). However, reaction of heteroaromatic ketones such as 2-acetylpyridine, 2-acetylfuran, and 2-acetylthiophene with cyclohexanol failed to provide the desired α-alkylation products. Catalytic alkylation of aliphatic ketones such as cyclopropyl methyl ketone and 2-heptanone with cyclohexanol were performed, which resulted in an incomplete reaction and provided complex mixtures, indicating the importance of the aryl group in ketones.

Experiments to decipher the reaction pathways and kinetic analysis were further carried out. Under standard conditions, the reaction of acetophenone and cyclohexanol catalyzed by **1** was monitored using GC, which revealed that the consumption of acetophenone follows first-order kinetics (Figure 1).

Reaction of 1-mesitylethan-1-one with 2-adamantanol reacted under standard reaction conditions to provide selective formation of α,β-unsaturated ketone product **4a**, which was isolated in 90% yield (Scheme 4a). Due to the high steric hindrance on enone **4a**, further hydrogenation by the catalyst was prevented, and this observation confirms the involvement of enone intermediacy in the reaction. Cyclohexanone reacted with 1-phenylethanol and afforded the α-alkylated ketone product **2a** in 83% yield (Scheme 4b). Use of a catalytic amount of base minimizes the self-dimerization of in situ formed acetophenone

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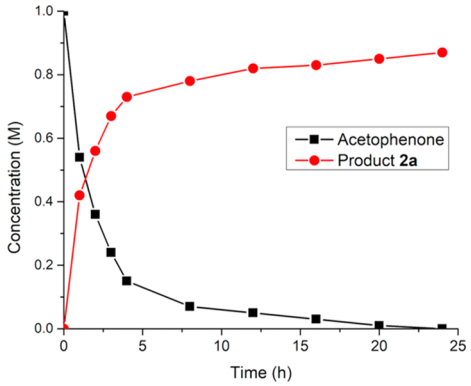
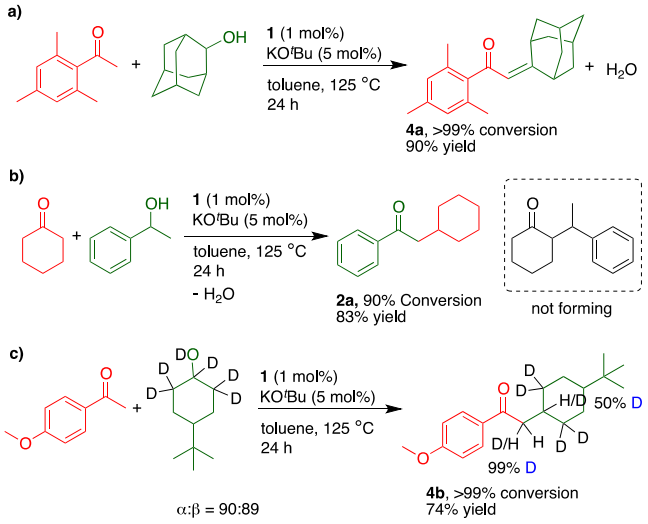


Figure 1. Monitoring of the reaction progress by GC. Concentration of acetophenone (black line) and product **2a** (red line) in the catalytic α-alkylation using cyclohexanol.

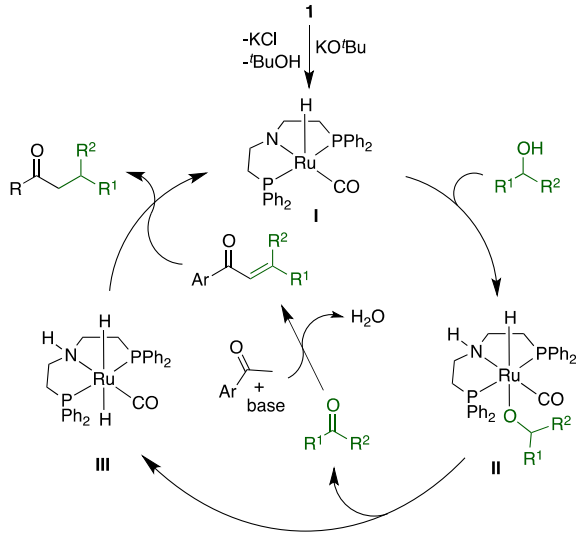
Scheme 4. Mechanistic Studies for the α-Alkylation of Ketones Using Secondary Alcohols



and other aldol side products (see Scheme 1c and Table 1, entries 1−5), which are observed only in minor amounts. Notably, cyclohexanone failed to undergo α-alkylation with 1-phenylethanol. This observation clearly indicates that the aryl group in ketones is important for the α-alkylation reaction. A deuterium-labeling experiment was performed with 4-methoxyacetophenone and deuterated 4-*tert*-butylcyclohexanol, and the outcome revealed that the reactions proceeded through the hydrogen-borrowing pathway. Product **4b** was isolated in 74% yield, which exhibited 99 and 50% deuterium incorporation at the α- and β-positions, respectively (Scheme 4c). The H/D scrambling at the β-position may be the result of H/D exchange between the in situ formed Ru−D intermediate and H_2O, and the preferential deuteration at the α-position is perhaps due to the selective reaction of catalyst with an α,β-unsaturated intermediate through the hydrogen-borrowing methodology.

The plausible mechanism for α-alkylation of ketones using secondary alcohols catalyzed by **1** is delineated in Scheme 5. Facile O−H, N−H, and sp-C−H bond activation reactions were established with catalyst **1** in our previous reports.[11−15] An unsaturated reactive intermediate **I** is formed in situ upon reaction of **1** with base,[15b,16] which further reacts with the secondary alcohol to result in an alkoxy-ligated intermediate **II**.[15d] Further, the β-hydride elimination reaction leads to

Scheme 5. Proposed Reaction Mechanism for the Ruthenium-Catalyzed α-Alkylation of Ketones Using Secondary Alcohols



dehydrogenation, which releases the ketone and generates a ruthenium dihydride intermediate **III**. An in situ formed ketone undergoes condensation with aromatic ketone under basic conditions, leading to the formation of an α,β-unsaturated carbonyl compound. Finally, an α,β-unsaturated carbonyl compound intermediate is hydrogenated by ruthenium dihydride complex **III**, resulting in the alkylated product, which regenerates the catalytically active intermediate **I**. The amine−amide metal−ligand cooperation in the catalytic system allows the same oxidation state (+2) in all intermediates involved in the catalytic cycle.

In conclusion, a ruthenium pincer catalyzed efficient and convenient method was developed for the α-alkylation of ketones using secondary alcohols to β-branched ketones. Contrary to previously reported procedures, this strategy explored the utility of unsubstituted and nonhindered acetophenone compounds with a variety of secondary alcohols, which are used as alkylating agents. Interestingly, this catalytic method has widespread substrate scope and produces water as the only byproduct, making it highly atom-economical and environmentally friendly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02787.

Experimental procedures, graphical and tabular characterization information (PDF)

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Notes

The authors declare no competing financial interest.

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