Nickel Catalyzed C–O Bond-Cleaving Alkylation of Esters: Direct Replacement of the Ester Moiety by Functionalized Alkyl Chains

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ABSTRACT: Two efficient protocols for the nickel-catalyzed aryl-alkyl cross-coupling reactions using esters as coupling components have been established. The methods enable the selective oxidative addition of nickel to acyl C–O and aryl C–O bonds and allow the aryl-alkyl cross-coupling via decarbonylative bond cleavage or through cleavage of C–O bond with high efficiency and good functional group compatibility. The protocols allow the streamlined, unconventional utilization of widespread ester groups and their precursors, carboxylic acids and phenols in synthetic organic chemistry.

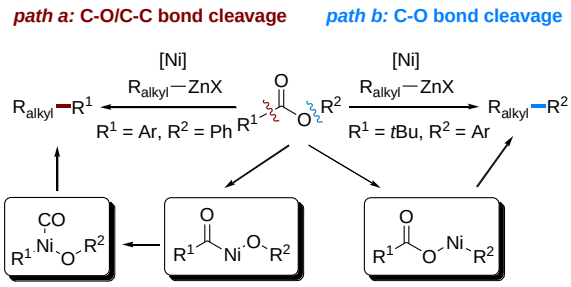
■ INTRODUCTION

Transition-metal catalyzed cross-coupling of organic halides with organic and organometallic substrates has emerged as a powerful method for the construction of carbon-carbon and carbon-heteroatom bonds in modern chemical science.[1] Moreover, the development of unconventional transformations through cross-coupling reactions via activation of unreactive bonds/groups led to the accomplishment of many valuable yet challenging organic syntheses in recent years. Esters, as fundamental synthetic materials, are generally employed as protecting groups in synthetic chemistry owing to their inertness to many reaction conditions. The development of new methodologies, utilizing esters as coupling components, will not only provide halogen-free synthetic processes but also open access to the unconventional, streamlined functionalization of a vast number of cheap and readily available esters and their precursors carboxylic acids and phenols. However, the employment of esters as electrophiles in cross-coupling arena still poses formidable challenges. The main challenge is the site-selectivity issue due to the presence of multiple C−O reactive sites (Scheme 1). On one hand, the oxidative addition of ester to the metal catalyst through acyl C−O bond cleavage generates acyl-metal species and the subsequent extrusion of carbon monoxide forms metal-carbon monoxide complexes and leads to decarbonylative couplings (Scheme 1, path a). On the other hand, overcoming the high activation barrier for the scission of aryl C–O bond of esters produces aryl-metal species directly and enables aryl C–O bond-cleaving reactions. The oxidative addition of the metal catalyst to acyl C–O or to aryl C–O bond leads to different reaction pathways. The ability to control the site-selectivity of the oxidative addition and selectively functionalize specific coupling components would not only dramatically expand the utility of esters, but would also broaden the synthetic repertoire.

In addition to the palladium-copper catalyzed decarboxylative biaryl coupling of aromatic carboxylic acids and haloarenes,[2a] a number of decarboxylative/decarbonylative cross-coupling reactions have been reported.[2-8]

Regarding the use of nickel for the decarbonylation of esters, despite early reports by Yamamoto et al. on the stoichiometric Ni(0)-mediated decarbonylation of aryl carboxylates via acyl metal species in the late '70s,[9,10] nickel-catalyzed decarbonylative C-C coupling reactions have been reported only recently by Itami and Yamaguchi through the reaction of phenolic esters with 1,3-azoles[6a,b] and arylboronic acids.[6c] Despite the advances realized, a highly general protocol for the decarbonylative aryl-alkyl cross-coupling reaction is still highly demanded. Regarding the application of phenol derivatives in the cross-coupling arena, a rather limited number of reactions have been reported through the activation of aryl C–O bond of ester derivatives.[11,12] The nickel-catalyzed cross-coupling of alkenyl/aryl pivalates with aryl zinc reagents has been reported by Shi.[11b] Furthermore, iron-mediated alkenyl/aryl-alkyl cross-coupling reactions of alkenyl/aryl carboxylates with Grignard reagents have been reported by Shi and Jacobi von Wangelin.[13] However, the use of Grignard reagents can sometimes be limited with regard to functional group tolerance.

Scheme 1. Nickel-catalyzed decarbonylative C–C and C–O bond-cleavage alkylation of esters.



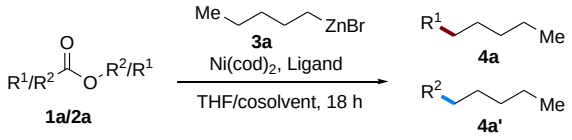
Therefore, the development of new protocols which enable the selective alkylation of the two potential coupling components

of esters is highly desirable. Herein, we describe the first nickel-catalyzed alkylation of esters in which a selective alkylation of either the carboxylic acid component via decarbonylative bond cleavage or the phenol component via cleavage of C–O bond[14] occurs.

■ RESULTS AND DISCUSSION

To achieve our goal in developing a successful decarbonylative alkylation of esters, we began to search for viable catalytic systems and nucleophiles and our attention was drawn on organozinc reagents as alkyl source. Beside their straight-forward preparation, high reactivity/selectivity, and high functional group tolerance, organozinc reagents proved to be excellent transmetalation reagents in aryl-alkyl and alkyl-alkyl cross-coupling reactions.[15] Phenyl esters of aryl carboxylic acids were selected as electrophiles and the initial investigation focused on the nickel-catalyzed decarbonylative coupling of phenyl 2-naphthoate (**1a**) with *n*-pentylzinc bromide (**3a**).

Table 1. Optimization of the reaction conditions.[a]

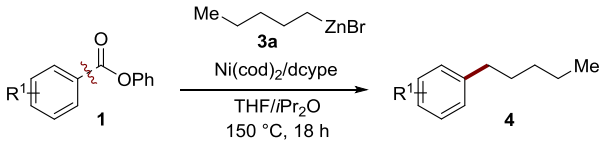


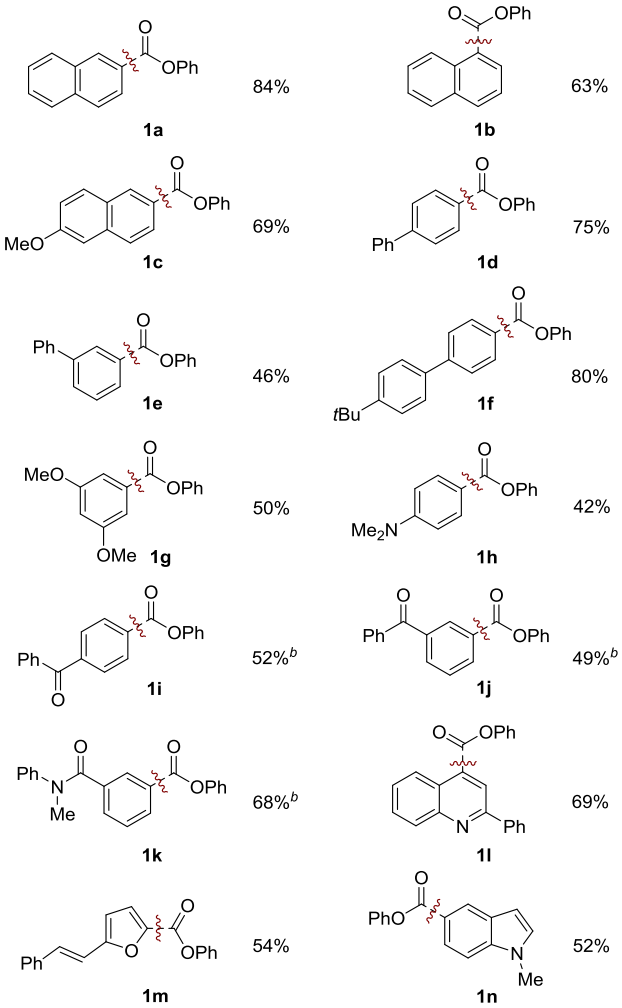
Entry	**1a**/**2a**	Ligand (mol%)	Temp (°C)	Yield (%)	
				4a	**4a'**
1	**1a**	IPr·HCl (20)	150	-	-
2	**1a**	SIPr·HCl (20)	150	-	-
3	**1a**	PCy_3 (20)	150	17	-
4	**1a**	$PnBu_3$ (20)	150	5	-
5	**1a**	dcype (10)	150	84	-
6[b]	**1a**	dcype (10)	150	45	-
7[c]	**1a**	dcype (10)	150	43	-
8[d]	**1a**	dcype (10)	150	71	-
9[d]	**1a**	dcype•2HBF_4 (10)	150	28	-
10[e]	**1a**	dcype (5)	150	-	-
11[f]	**2a**	dcype (5)	70	99	-
12[f]	**2a**	dcype (5)	60	73	-
13[g]	**2a**	dcype (5)	70	83	-
14[h]	**2a**	dcype (5)	70	93	-
15[h]	**2a**	dcype•2HBF_4 (5)	70	87	-
16[e]	**2a**	dcype (5)	70	-	-

1a = phenyl 2-naphthoate, **2a** = 2-naphthyl pivalate. [a]Reaction conditions: **1a**/**2a** (0.25 mmol), **3a** (0.5 mmol), $Ni(cod)_2$ (0.025 mmol), THF / *i*Pr2O (1.5 mL), sealed tube, 18h, yield of the isolated product. [b]in THF (1.5 mL). [c]THF / Toluene (1.5 mL). [d]$NiCl_2$ (0.025 mmol) was used. [e]Without $Ni(cod)_2$. [f]$Ni(cod)_2$ (0.0125 mmol) was used. [g]**3a** (0.275 mmol) was used. [h]$NiCl_2$ (0.0125 mmol) was used.

Ligands play a vital role in the activation of unreactive bonds and, therefore, various ligands were evaluated in our transformation. Firstly, *N*-heterocyclic carbene (NHC) ligands have been examined, however they did not promote the transformation (Table 1, entries 1 and 2). Further screening showed that the use of monodentate phosphine ligands PCy_3 and $P(nBu)_3$ gave promising results (Table 1, entries 3 and 4). Gratifyingly, when the bidentate phosphine ligand dcype was employed, the yield of the decarbonylative product **4a** increased to 84% (Table 1, entry 5). The solvent plays also an important role for our coupling reaction, since replacement of iPr_2O with THF or toluene as co-solvent dramatically decreased the yield (Table 1, entries 6 and 7). The yield decreased if $NiCl_2$ as catalyst and dcype·2HBF_4 as ligand were used (Table 1, entry 9). The robust pivaloyl group proved to be less prone to undergo acyl C–O bond scission in recent C–O bond activation reactions. Interestingly, when we switched to 2-naphthly pivalate as substrate, the aryl C–O bond-cleavage coupling product **4a** was isolated in quantitative yield (99%) when the reaction was performed with 5 mol% $Ni(cod)_2$ and 5 mol% dcype at 70 °C (Table 1, entry 11). A lower temperature was found to be detrimental to the yield (Table 1, entry 12). Decreasing the amount of *n*-pentylzinc bromide led also to a slightly lower yield (Table 1, entry 13). The use of $NiCl_2$ as catalyst and dcype·2HBF_4 as ligand led to a lower yield (Table 1, entry 15). However, this means that less sensitive Ni(II) salts can effectively be applied. Control experiments showed that, no alkylation reaction proceeded in the absence of the nickel catalyst (Table 1, entries 10 and 16).

Table 2. Substrate scope of phenyl esters for the decarbonylative alkylation.[a]



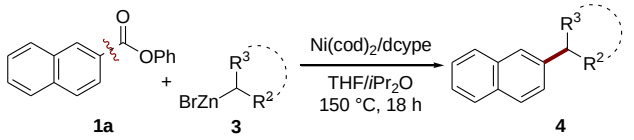


R = *n*-pentyl. [a]Reaction conditions: **1** (0.25 mmol), **3a** (0.5 mmol), $Ni(cod)_2$ (0.025 mmol, 10 mol%), dcype (0.025 mmol, 10 mol%), THF/iPr_2O (1.5 mL), sealed reaction tube, 150 °C, 18 h. [b]**3a** (0.25 mmol) was used.

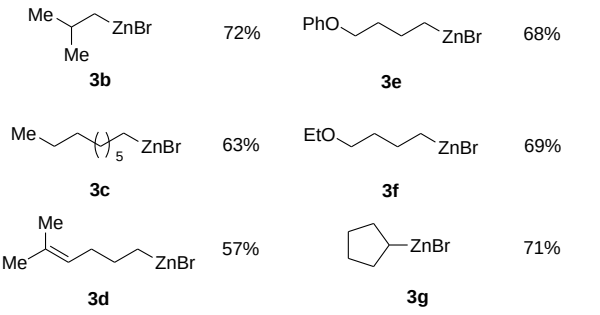
Encouraged by our initial studies, we next examined a series of phenyl esters of aryl carboxylic acids to determine the scope of the new decarbonylative alkylation. As shown in Table 2, a range of electronically and sterically diverse phenyl esters were found to be cross-coupled with *n*-pentylzinc bromide in good to excellent yields. Both naphthoic acid esters and simple benzoic acid esters (**1a-h**) underwent the decarbonylative coupling smoothly. Ketone groups, which are typically sensitive to organometallic reagents, were also tolerated in the transformation (**1i**, **1j**). Although nickel catalysts facilitate the functionalization of anisoles and amides, we found that under our conditions, the methoxy (**1c**, **1g**) and amide (**1k**) groups did not compete with the decarbonylative reaction. Furthermore, esters of heterocycles (**1l-n**) were also compatible with the reaction conditions and yielded the products in moderate to good yields.

Subsequently we performed the decarbonylative cross-coupling with various alkylzinc bromides **3** (Table 3). The scope of this cross-coupling includes alkylzinc bromides ranging from the short chain *iso*-butylzinc bromide (**3b**) to those bearing long alkyl chains (**3c-f**). Furthermore, alkylzinc bromides with alkenyl (**3d**) and ether moieties (**3e**, **3f**) as well as a cyclopentyl derivative (**3g**) underwent the decarbonylative alkylation reaction smoothly and produced the desired products in good yields.

Table 3. Substrate scope of alkylzinc bromides for the decarbonylative alkylation.[a]



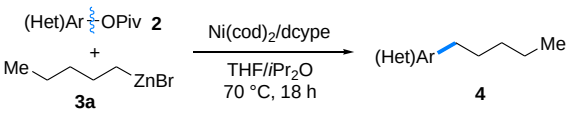
1a **3** **4**

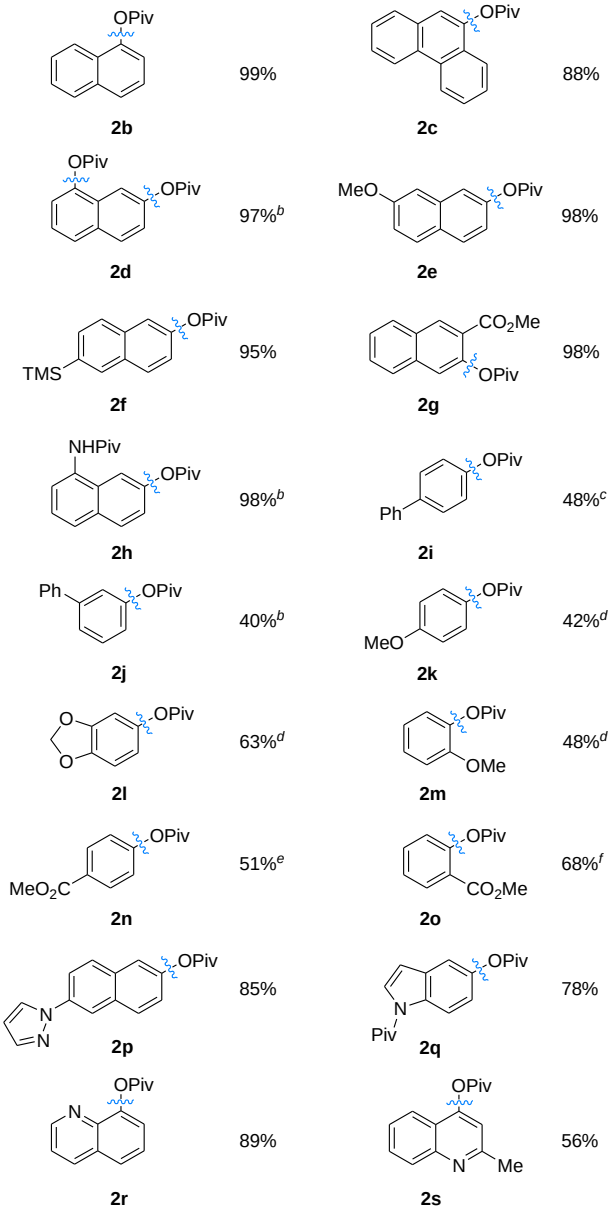


[a]Reaction conditions: **1a** (0.25 mmol), **3** (0.5 mmol), $Ni(cod)_2$ (0.025 mmol, 10 mol%), dcype (0.025 mmol, 10 mol%)), iPr_2O/THF (1.5 mL), sealed reaction tube, 150 °C, 18 h.

Following the successful establishment of the decarbonylative alkylation of phenyl esters, we turned our attention to examine the reactivity and functional group tolerance of the C–O bond-cleaving alkylation of pivaloyl esters (Table 4). A wide range of pivaloyl esters **2b-s** bearing electron-neutral, electron-donating, and electron-withdrawing substituents were smoothly converted into the desired products. Phenyl derivatives **2i-o** with *para*-, *meta*- and *ortho*-substitutions were evaluated and underwent the reaction smoothly. Interestingly, substrates bearing methoxy (**2e**, **2k**, **2m**), TMS (**2f**), amide (**2h**), and dioxole (**2l**) groups were tolerated, providing the corresponding products in good to excellent yields. Significantly, ester groups were also tolerated under our conditions, showing their orthogonal reactivity to pivaloyl groups (**2g**, **2n**, **2o**). Heterocyclic derivatives **2p-s** could also undergo the alkylation process, providing alkyl heterocyclic products in good to excellent yields.

Table 4. Substrate scope of aryl pivalates for the C–O bond-cleavage alkylation.[a]



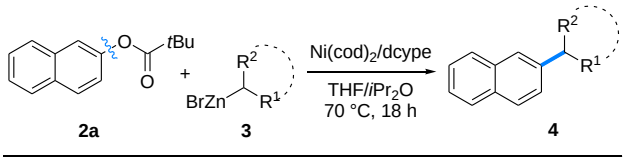


[a]Reaction conditions: **2** (0.25 mmol), **3a** (0.5 mmol), $Ni(cod)_2$ (0.0125 mmol, 5 mol%), dcype (0.0125 mmol, 5 mol%), iPr_2O/THF (1.5 mL), sealed reaction tube, 70 °C, 18 h. [b]**3a** (0.75 mmol) was used. [c]**3a** (0.75 mmol), $Ni(cod)_2$ (0.025 mmol), dcype (0.025 mmol), 130 °C, 72 h. [d]**3a** (1.0 mmol), $Ni(cod)_2$ (0.05 mmol), dcype (0.05 mmol), 130 °C, 72 h.

[e]$Ni(cod)_2$ (0.025 mmol), dcype (0.025 mmol), 110 °C. [f]$Ni(cod)_2$ (0.025 mmol), dcype (0.025 mmol) was used.

At the same time, the scope and generality of alkylzinc reagents were examined under our cross-coupling conditions (Table 5). The scope of this C–O bond cleavage cross-coupling includes alkylzinc reagents ranging from the short ethylzinc bromide (**3h**) to those bearing long alkyl chains (**3j**–**o**). The chemoselectivity profile of this reaction was nicely illustrated by the fact that functional substituents such as *i*Bu (**3b**), phenyl (**3i**), alkenyl (**3d**, **3j**), ether (**3e**), silyl ether (**3k**), ester (**3l**, **3m**), and amide (**3n**) moieties were tolerated under our conditions. It is worth to mention, that the cross-coupling reaction with **3o** underwent efficiently, with the potential reactive C–Cl bond untouched, yielding the chlorine-containing product in 88%. Furthermore, the protocol could also be applied to secondary alkylzinc bromides such as cyclopentyl, cyclohexyl, and cyclopropyl derivatives (**2g**, **3p**, **3q**) and proceeded smoothly with high efficiency. However, the use of *iso*-propylzinc bromide (**2p**) led to the linear product, most probably due to an isomerisation side reaction during the cross-coupling process.[16]

Table 5. Substrate scope of alkylzinc bromides for the C–O bond-cleavage alkylation.[a]



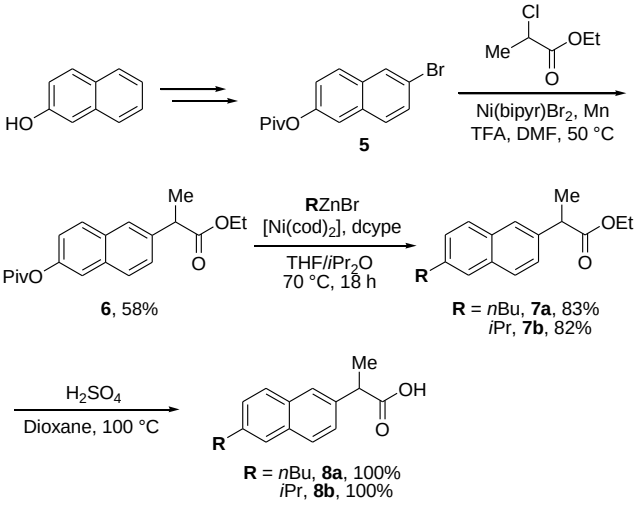
2a **3** **4**

Me–ZnBr **3a**	99%	ZnBr **3j**	44%
Me, Me–ZnBr **3b**	87%	TBSO–ZnBr **3k**	83%
Me, Me–ZnBr **3d**	95%	PivO–ZnBr **3l**	80%
PhO–ZnBr **3e**	87%	EtOOC–ZnBr **3m**	83%
Me–ZnBr **3h**	99%	Et_2NOC–ZnBr **3n**	82%
Ph–ZnBr **3i**	93%	Cl–ZnBr **3o**	88%
ZnBr **3g**	82%	ZnBr **3q**	57%
ZnBr **3p**	85%	Me, Me–ZnBr **3r**	99%[b]

[a]Reaction conditions: **2a** (0.25 mmol), **3** (0.5 mmol), $Ni(cod)_2$ (0.0125 mmol, 5 mol%), dcype (0.0125 mmol, 5 mol%), iPr_2O/THF (1.5 mL), sealed reaction tube, 70 °C, 18 h. [b]2-propylnaphthalene was formed.

The (+)-naproxen is a non-steroidal anti-inflammatory drug usually employed for the alleviation of pain, fever, and inflammation.[17] The modification of naproxen could produce potential drug candidates.[18] By employing our alkylation methodology, we succeeded in synthesizing two naproxen analogous **8a** and **8b**, otherwise not easily accessible (Scheme 2). Starting from 2-naphthol, bromide **5** was readily prepared according to a previous report.[19] The active/directing ability of phenols was illustrated by the bromination at C1 and C6 of 2-naphthol. Due to the orthogonal reactivity of aryl bromides and pivalates, a site-selective alkylation was performed to replace the bromide with the propionate side chain.[20] The alkylation took place with high efficiency at the pivalate position when pivalate **6** was employed in our nickel-catalyzed alkylation process. Exposing dialkylated naphthalene **7** to acid conditions overnight, the corresponding naproxen analogous **8a** and **8b** were obtained in quantitative yields.

Scheme 2. **The synthesis of naproxen analogous (8).**



■ CONCLUSIONS

In conclusion, we have developed two nickel-catalyzed aryl-alkyl cross-coupling reactions using esters as electrophilic coupling partners. The right choice of ester and catalyst allows controlling the selective oxidative addition of nickel to acyl C–O or aryl C–O bond, thus allowing the selective introduction of alkyl groups to the carboxylic acid component via decarbonylative bond cleavage or phenol component via C–O bond cleavage. The protocols are characterized by their efficiency and functional group tolerance with regard to both coupling partners. The newly developed aryl-alkyl cross-coupling reactions described herein may not only become a good alternative to the standard halide-based cross-couplings, but may also lead to late-stage synthetic strategies and unconventional utilization of esters and their carboxylic acid and phenol precursors in synthetic chemistry. Moreover, the synthetic utility has been demonstrated by the application of the method to the synthesis of naproxen analogous. Although further mechanistic and computational studies need to be part of our future research, we believe that the direct replacement, in particular, the first example of a direct exchange of the ester moiety by a long chain functionalized alkyl chain will be of use in retrosynthesis, late stage functionalizations and synthesis in general.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, spectral data for all compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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