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Interception of Nickel Hydride Species and Its Application in Multicomponent Reactions

Venkadesh Balakrishnan, Anirban Ganguly, and Ramesh Rasappan*

Cite This: *Org. Lett.* 2022, 24, 4804–4809 Read Online

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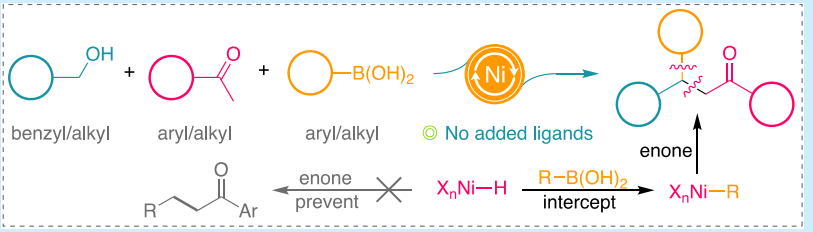
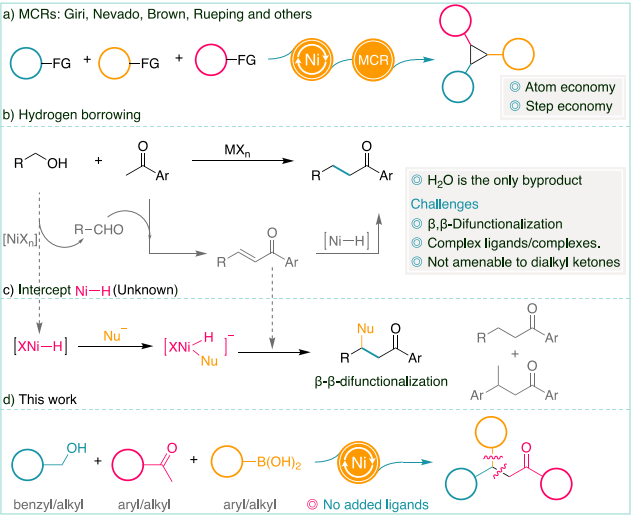


ABSTRACT: The hydrogen borrowing strategy is an economical method for the α-functionalization of ketones. While this strategy is extremely advantageous, it does not lend itself to the synthesis of β,β-disubstituted ketones. This can be achieved, if the in situ generated metal hydride can be intercepted with a nucleophilic coupling partner. We present a multicomponent strategy for the coupling of alcohols, ketones, and boronic acids using only 1 mol % nickel catalyst and without the need for added ligands.

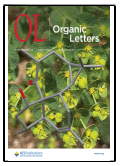
In organic synthesis, multicomponent reactions (MCRs) enable the rapid construction of diverse molecules.[1] The atom and step economies make it extremely desirable for the synthesis of natural and bioactive compounds.[2] MCRs have also been actively used in recent years in nickel-mediated cross-coupling reactions that produce complex molecules in a single step.[3] However, it is mostly the alkyl or aryl halides employed as coupling partners. Given the widespread availability, economics, and environmental friendliness of alkyl alcohols,[4] strategies utilizing them as a coupling partner in MCRs are yet to be developed. On the other hand, hydrogen borrowing strategies incorporating alkyl alcohols have been successful in synthesizing carbonyl compounds, which are ubiquitous in natural and bioactive molecules.[5]

For the α-functionalization of ketones, the hydrogen borrowing strategy has been exponentially developed (Scheme 1b).[6] Although primary alcohols were mostly employed in these processes, secondary alkyl alcohols have been employed recently to produce β,β-disubstituted products. Due to the high energy barrier associated with the oxidation of secondary alkyl alcohols, self-condensation of aryl ketones was observed as the predominant product. To suppress the formation of a self-condensed byproduct, Donohoe et al. employed a highly substituted aryl ketone in the presence of $[Cp^*Ir(III)Cl_2]_2$,[7] to obtain β,β-disubstituted ketones. Subsequently, [Cp*Co(III)-(N,O)I],[8] iron carbonyl,[9] and manganese carbonyl complexes[10] were employed in a similar manner. Gunanathan et al. recently reported on the use of ruthenium pincer complexes, which does not require highly substituted aryl ketones.[11] However, the strategy necessitates the handling of a complex ligand and a moisture-sensitive metal hydride in a glovebox. Additionally, all of these methods require acyl arenes and are incompatible with dialkyl ketones. It is worth noting that nickel nanoparticles[12] and $NiBr_2$[13] have also been used in hydrogen borrowing reactions, although their application is limited to the use of primary alcohols.

Scheme 1. Multicomponent Reactions



Received: June 4, 2022
Published: June 27, 2022

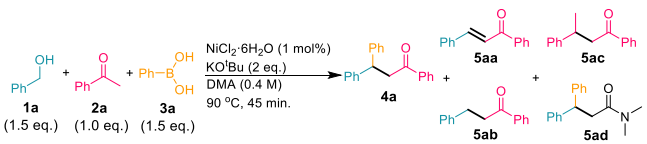


https://doi.org/10.1021/acs.orglett.2c01862
Org. Lett. 2022, 24, 4804–4809

We wondered whether it would be possible to intercept the nickel hydride species, produced by the reaction of NiX_2 and alkyl alcohol (Scheme 1) prior to 1,4-addition, a daunting task that requires accelerated transmetalation prior to 1,4-addition. If established, this will enable the synthetic application of hydrogen borrowing to MCRs, a strategy that has not been developed earlier. As a part of our ongoing studies in nickel-mediated cross-coupling reactions,[14] herein we report a multicomponent reaction (MCR) in which the intermediate nickel hydride formed by the reaction of alcohol and NiX_n was successfully intercepted with arylboronic acids, thereby extending the hydrogen borrowing strategy for the delivery of β,β-disubstituted ketones without the use of added ligands.

We commenced our study with benzyl alcohol **1a**, acetophenone **2a**, and phenyl boronic acid **3a**. Preliminary experiments were focused to mitigate the formation of byproducts such as the intermediate enone **5aa**, reduced product **5ab**, homocoupled product **5ac**, and DMA adduct **5ad**. The optimal condition necessitates the use of $NiCl_2\cdot 6H_2O$ and KO^{t}Bu at a temperature of 90 °C. We obtained the cross-coupled product **4a** in 78% isolated yield under these conditions (Table 1, entry 1). Of the several nickel catalysts

Table 1. Screening Table[a]



entry	deviation from above	5aa, 5ab, 2a[b]	4a (%)[b]
1	no deviation	3, 10, ND	80 (78)[c]
2	$NiBr_2\cdot 3H_2O$	45, 5, ND	40
3	$NiBr_2$·glyme	30, 8, ND	50
4	$Ni(NO_3)_2\cdot 6H_2O$	30, 5, ND	50
5	$NiBr_2$	10, 30, ND	40
6	NiI_2	20, 20, ND	40
7	$NiCl_2$	20, 15, ND	53
8	$NiCl_2$·glyme	20, 10, ND	55
9	5 mol % of $NiCl_2\cdot 6H_2O$	3, 30, ND	50
10	10 mol % of $NiCl_2\cdot 6H_2O$	5, 20, ND	60
11	$FeCl_2$	ND, ND, 78	ND
12	$CoCl_2$	ND, ND, 85	ND
13	LiO^{t}Bu instead of KO^{t}Bu	ND, ND, 20	30
14	NaO^{t}Bu instead of KO^{t}Bu	10, 30, 9	50
15	rt instead of 90 °C	2, 2, 80	10
16	60 °C instead of 90 °C	ND, 5, 25	66
17	toluene instead of DMA	20, 40, ND	25
18	THF instead of DMA	6, 5, 56	20
19	DMF instead of DMA	5, 4, 77	5
20	ACN instead of DMA	ND, ND, 20	ND
21	8.3 mmol scale of **2a**	4, 12, ND	75

[a]Reaction conditions: 1.86 mmol of **1a**, 1.24 mmol of **2a**, 1.86 mmol of **3a**, 1 mol % $NiCl_2\cdot 6H_2O$, 2.47 mmol of KO^{t}Bu, DMA (0.4 M), 90 °C, 45 min. [b]GC yield. [c]Isolated yield. ND: not detected.

screened (entries 1–8, Table 1), only $NiCl_2\cdot 6H_2O$ offered the cross-coupled product **4a** in 78% isolated yield with the minimal formation of byproducts **5aa**–**5ad**. To our surprise, the reaction is extremely sensitive to the amount of nickel catalyst used; we discovered that the reaction can be carried out at a concentration of 1 mol % of $NiCl_2\cdot 6H_2O$ (entry 1). By increasing the catalyst loading to 5 or 10 mol %, the yield of **4a** was decreased (entries 9–10), while increasing the amount of byproduct **5ab**, indicating that the nickel hydride addition to **5aa** was enhanced. Strikingly, the use of KO^{t}Bu is required to obtain **4a** in high yield; using LiO^{t}Bu or NaO^{t}Bu significantly reduced the amount of cross-coupled product **4a**. A comparison of entry 1 vs entries 13 and 14 showcases the importance of KO^{t}Bu. Notably, when LiO^{t}Bu or NaO^{t}Bu was used, we observed a clumsy solid (see SI-47). A remarkable improvement in yield was observed by increasing the reaction temperature from rt to 60 °C (entries 15–16), despite the fact that the reaction stalled at 75% conversion of **2a**, demonstrating the necessity of elevated temperature to accelerate the reaction.

Another point worth noting is the role of solvents. While solvents with a high dielectric constant (polarity) may favor the reaction, solvents such as DMF, THF, and CH_3CN with relatively more coordinating ability were equally unsuitable (entries 18–20), leaving ketone **2a** largely unreacted. When the premade nickel–hydride complex **6** (Figure S9 in SI-38) is dissolved in relatively less coordinating DMA, it retains its color (yellow), but the color deteriorates dramatically in DMF/THF/CH_3CN, demonstrating that a subtle balance of coordinating ability and polarity of the solvent is required. Notably, because the reaction does not require added ligands, employing additional ligands was inconsequential (SI-4). To expand the synthetic utility, we also carried out the reaction on an 8.3 mmol scale (**2a**) using 1 mol % of $NiCl_2\cdot 6H_2O$ (entry 21).

We screened a broad spectrum of alcohols, ketones, and boronic acids under optimized conditions. Initially, a variety of benzylic and unactivated alkyl alcohols **1** were employed (Table 2). Benzylic alcohols **1b**–**d** with halide substituents afforded the corresponding ketones **4b**–**d** in 77%, 74%, and 70% isolated yields. The π-extended 1- and 2-naphthyl derivatives **4e**–**f** were efficiently synthesized in 75% and 78% yields. Pleasingly, ethers **1g** and **1h** were also tolerated under the optimized conditions, affording the cross-coupled products **4g** and **4h** in high yields. The efficiency of the reaction was not impeded by the amine in **1i**. Given the importance of heteroarenes in pharmaceuticals and agrochemicals, we subjected π-deficient quinoline **1j** and pyridine **1k** to this, and they all reacted smoothly to provide corresponding ketones **4j** and **4k** in very good yields.

Despite the difficulties inherent in using unactivated alkyl alcohols as coupling partners, the long alkyl chain alcohols **1l**–**n** underwent cross-coupling reactions to provide ketones **4l**–**n** in 58%, 55%, and 58% yields, respectively, with the homocoupled product being formed in a significant amount. Cyclohexylmethanol **1o**, which is sterically demanding, also yielded the coupled product **4o** in 57%. We further extended the scope to include a variety of acyl arenes. As expected, ketone substrates (Table 2) containing OMe (**2q**) and OBn (**2r**) groups gave very good yields of the ketones **4q** and **4r**. The pharmaceutically significant CF_3 group **2s** was also compatible, resulting in a 68% isolated yield of ketone **4s**. The 2-naphthyl derivative **4t** and the 3-pyridyl ketone **4u** were isolated in 79% and 40% yields, respectively. Under the optimized condition, the more challenging α-branched dialkyl ketones **4v**–**ab** were also employed, yielding ketones **4v** and **4w** in 51% and 52% yields, respectively. The drug derivatives **4x** (naproxen) and **4y** (ibuprofen) were also isolated in 42% and 40% yields, respectively. Sterically hindered cyclic ketones **2z**–**ab** also underwent cross-coupling to afford the corre-

https://doi.org/10.1021/acs.orglett.2c01862
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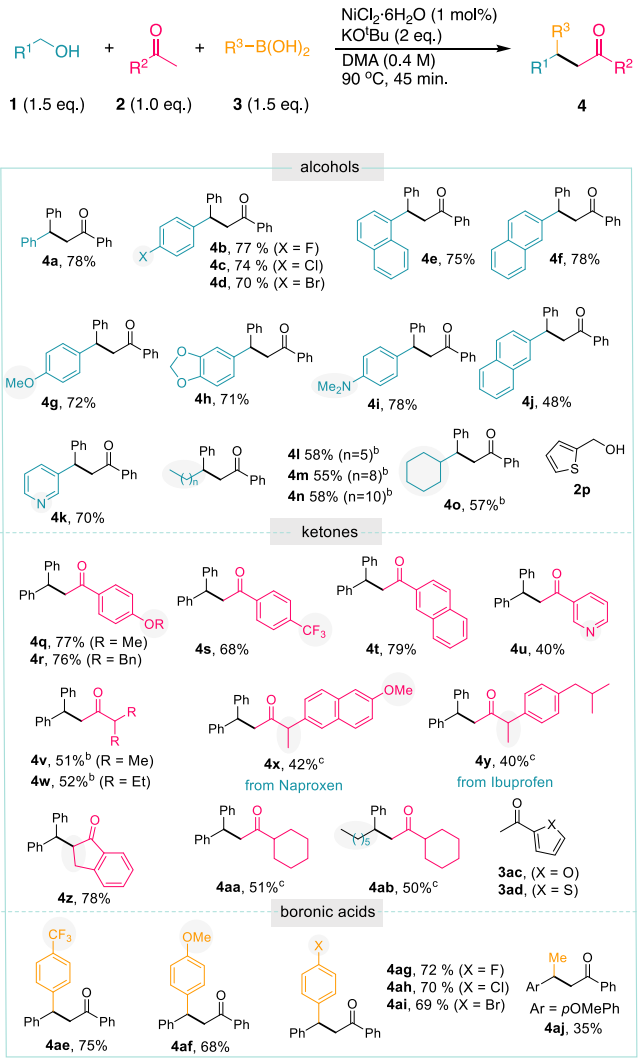
Table 2. Substrate Scope[a]

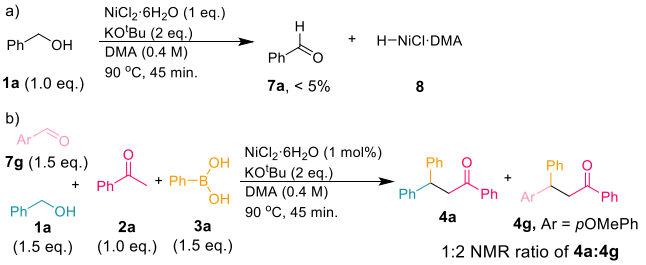


[a]Reaction conditions: 3.12 mmol of **1a**, 2.08 mmol of **2a**, 3.12 mmol of **3a**, 0.020 mmol of $NiCl_2{\cdot}6H_2O$ (1 mol %), 4.16 mmol of KO^{t}Bu, DMA (0.4 M), 90 °C, 45 min. [b]0.52 mmol of $NiCl_2{\cdot}6H_2O$ (2.5 mol %), 4.16 mmol of LiO^{t}Bu, 145 °C, 12 h. [c]0.052 mmol of $NiCl_2{\cdot}6H_2O$ (2.5 mol %), 4.16 mmol of NaO^{t}Bu, 90 °C, 12 h.

sponding ketones **4z**–**ab** in good yields. It is worth mentioning that the methodology can accommodate unactivated alkyl alcohol and the dialkyl ketones as coupling partners; n-heptanol and cyclohexyl methyl ketone **2ab** afforded ketone **4ab** in 50% isolated yield. Despite the success of the current method, alcohol **2p**, ketone **3ac**, and **3ad** derived from thiophene or furan were found to be completely unreactive; coordination of a sulfur or oxygen atom to the nickel center may be responsible for deactivating the catalyst. Additionally, a variety of aryl boronic acids were employed, and substrates containing CF_3, OMe, and halide groups **3ae**–**ai** were well-tolerated affording the corresponding ketones **4ae**–**ai** in very good yields. As expected, methyl boronic acid exhibited decreased reactivity and yielded the corresponding ketone **4aj** only in 35% isolated yield; the lower yield is due to byproducts such as the reduced product **5ab** and DMA adduct **5ad**. The other alkyl boronic acids were not amenable to this strategy.

We anticipated the in situ generation of intermediate aldehyde **7a** and subsequent reactions.[13,15] Thus, alcohol **1a** was subjected to the optimized condition in the absence of ketone **2a** and boronic acid **3a** (Scheme 2a); surprisingly, we

Scheme 2. (a) Oxidation of Alcohol and (b) Crossover Experiment



observed only a trace of aldehyde **7a** in GC–MS. Employing stoichiometric $NiCl_2{\cdot}6H_2O$ was not beneficial. This prompted us to conduct a crossover experiment in which we used stoichiometric aldehyde **7g** (Ar = *p*OMe) under optimized conditions (Scheme 2b). As expected, we observed the product **4a** along with crossover product **4g** in a 1:2 NMR ratio. These findings strongly suggest the presence of an intermediate in the form of aldehyde **7**.

Although the formation of transient nickel hydride species **8** (Scheme 2a) is expected in conjunction with the formation of aldehyde **7**, additional experiments were designed to gain support for the presence of transient nickel hydride species **8**. Consequently, we prepared the nickel hydride complex $Ni(II)HCl(PCy_3)_2$ **6** via the reduction of $Ni(II)Cl_2(PCy_3)_2$ with $NaBH_4$ (SI-36).[16] ^{31}P NMR analysis of $Ni(II)HCl(PCy_3)_2$ complex **6** revealed that the ligated PCy_3 resonates at 33.42 ppm, consistent with previous reports.[16] Fortunately, we observed the same resonance peak in ^{31}P NMR analysis of aliquots of the standard reaction mixture, albeit in a lower intensity (Figure 1).

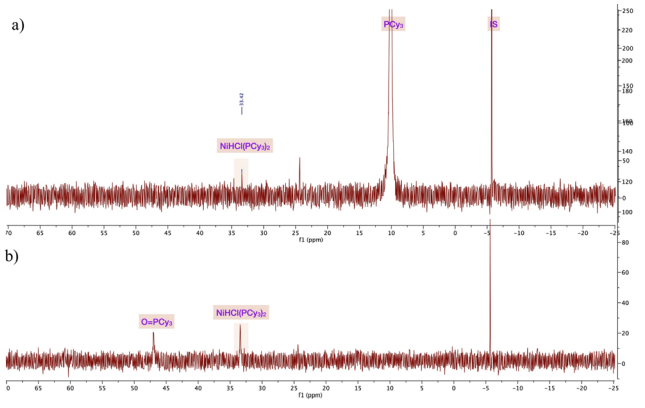


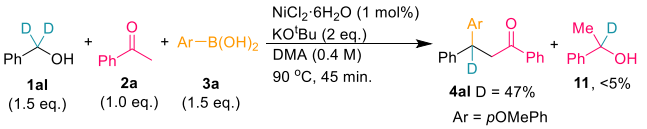
Figure 1. ^{31}P NMR of $Ni(II)HCl(PCy_3)_2$ complex. (a) In situ nickel hydride. (b) Preprepared nickel hydride complex **6**.

The premade complex **6** can also promote the standard reaction, and we observed the formation of the expected product **4a** in 43% (SI-37). Taken together, these experiments demonstrate the presence of a transient nickel hydride species in the reaction medium. According to the results that we obtained (Figure S10 and SI41), the concentration of aldehyde in the reaction is low, implying the existence of an equilibrium between nickel hydride species and aldehyde. Deuterium labeling studies were designed to elicit additional information.

https://doi.org/10.1021/acs.orglett.2c01862
Org. Lett. 2022, 24, 4804–4809

When the deuterium-labeled alcohol **1al** was subjected to the standard reaction, we observed the ketone **4al** with 47% deuterium incorporation, indicating a reversible reaction between the intermediate aldehyde **7** and nickel hydride species **8** (Scheme 3). Formation of trace of secondary alkyl

Scheme 3. Deuterium Labeling Studies



alcohol **11** is indicative of the presence of transient nickel hydride species. Variable-time normalization analysis (VTNA) revealed this is first order with respect to all reactants/reagents, emphasizing their role in the rate-limiting step (Figure 2).

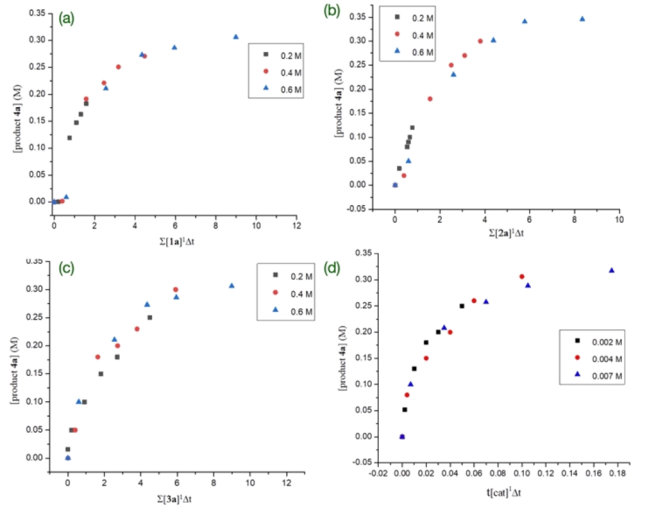


Figure 2. Kinetic studies.

On the basis of our findings and data from the literature, Figure 3 proposes a mechanistic hypothesis. When $NiCl_2 \cdot 6H_2O$ and alcohol **1** are mixed, the intermediate aldehyde (III) and the nickel hydride complex are generated via a four membered transition state (II). Following aldol condensation of aldehyde (III) with aryl methyl ketone **2**, the intermediate

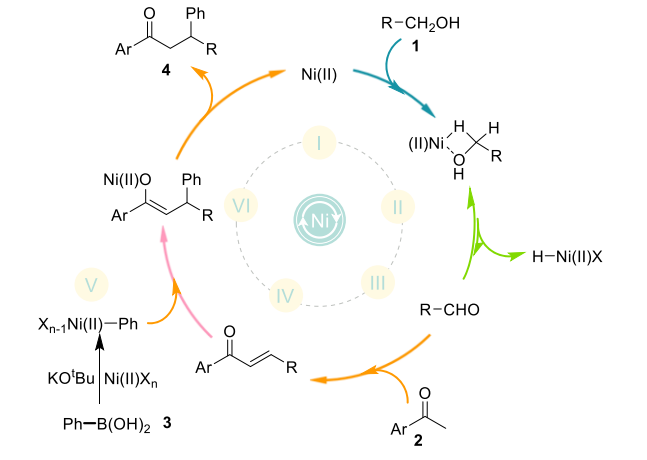


Figure 3. Mechanistic hypothesis.

enone (IV) could be formed. Concurrently, a base promoted transmetalation of boronic acid **3** via boronate complex may result in the nickel intermediate V, followed by a 1,4-addition to yield the final product **4**, as illustrated in Figure 3.

To summarize, for the first time, we successfully intercepted the intermediate nickel hydride species from a hydrogen borrowing strategy and used them in the synthesis of *β,β*-disubstituted ketones. The developed multicomponent reaction does not require sophisticated or added ligands, is capable of generating molecules with diverse functional groups, and was used to synthesize medicinally significant molecules. The presence of nickel hydride species and its equilibrium with the aldehyde were identified in preliminary mechanistic studies. Kinetic studies revealed that 1,4-addition is a rate-limiting step. Our laboratory is currently conducting additional research to broaden the scope of the methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01862.

Experimental details, characterization data of compounds, crystallographic data, and computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ramesh Rasappan − *School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Vithura, Thiruvananthapuram, Kerala 695551, India;* orcid.org/0000-0002-3209-3315; Email: rr@iisertvm.ac.in

Authors

Venkadesh Balakrishnan − *School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Vithura, Thiruvananthapuram, Kerala 695551, India*

Anirban Ganguly − *School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Vithura, Thiruvananthapuram, Kerala 695551, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c01862

Author Contributions

The manuscript was written through contributions of all authors. V.B. and A.G. performed the experiments. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank CSIR (Council of Scientific and Industrial Research) 02(0409)/21/EMR-II and IISER Trivandrum for financial support. V.B. and A.G. acknowledge IISER Trivandrum for fellowships.

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