

A Dual Catalytic Strategy for Forging sp^2 - sp^3 & sp^3 - sp^3 Architectures via β -Scission of Aliphatic Alcohol Derivatives

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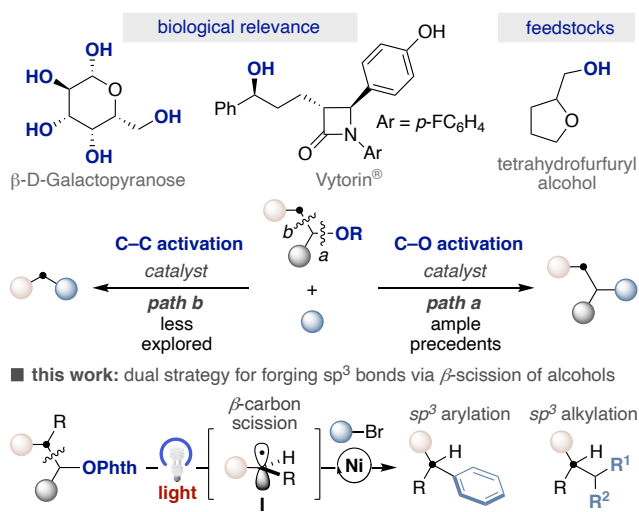
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Supporting Information Placeholder

ABSTRACT: A dual platform for forging sp^2 - sp^3 & sp^3 - sp^3 carbon bonds via catalytic β -scission of aliphatic alcohol derivatives with both aryl and alkyl halides is disclosed. This protocol is distinguished by its wide substrate scope and broad applicability, even in the context of late-stage functionalization.

Metal-catalyzed cross-coupling reactions have offered innovative solutions to forge sp^3 architectures,¹ thus providing medicinal chemists a new tool to increase structural diversity for improving clinical success.² At present, these protocols rely primarily on prefunctionalizations at the targeted sp^3 site, such as well-defined organometallics,¹ organic halides,¹ or C-O/C-N electrophiles^{3,4}, among others.⁵ Driven by these observations, chemists have been challenged to design bond formations with non-functionalized sp^3 C-H or C-C linkages. Despite the advances realized in the former,⁶ the activation of unstrained sp^3 C-C bonds still remains problematic due to their covalent nature and directionality, making these transformations thermodynamically and kinetically uphill.⁷

Scheme 1. Aliphatic Alcohol Motifs as sp^3 Counterparts.



Recent years have witnessed the design of bond-forming strategies with naturally occurring aliphatic alcohols as native adaptative sp^3 handles, hence providing novel pathways for molecular assembly via sp^3 C-O activation (Scheme 1, *path a*).⁸ In contrast, the use of unactivated aliphatic alcohols as sp^3 synthons via β -C scission has received much less attention, with isolated C-C bond-formations occurring by reaction of open-shell species with activated radical acceptors (*path b*).⁹ At the outset of our investigations, a generic platform aimed at interfacing β -scission and the modularity offered by transition metals with organic halide counterparts was an attractive but as yet unrealized scenario.¹⁰ If successful, the combination of these disciplines might provide a new technique to rapidly forge sp^3 architectures from simple precursors with the advantage of producing useful chemicals for downstream applications. Herein, we describe the realization of this goal, resulting in a modular and widely applicable protocol for forging sp^3 architectures with *N*-phthalimide

ethers (OPhth) derived from aliphatic alcohols and aryl/alkyl halides via the intermediacy of **I**, even in the context of late-stage functionalization (*bottom*).

Table 1. Optimization of the Reaction Conditions.^a

entry	deviation standard conditions	3a (%) ^b
1	none	84 (77) ^c
2	L2 instead of L1	74
3	L3 instead of L1	8
4	L4 instead of L1	2
5	L5 instead of L1	16
6	using Ni(COD) ₂	51
7	using THF instead of NMP	61
8	using PhMe instead of NMP	3
9	no 4-CzIPN	63
10	no L1 , no Ni, HE or in the darkness	0

^a **1a** (0.10 mmol), **2a** (0.15 mmol), NiBr₂·diglyme (10 mol%), **L1** (15 mol%), 4-CzIPN (2 mol%), HE (0.15 mmol), K₂CO₃ (0.10 mmol) in NMP (0.25 M) at 40 °C for 18 h. ^b

^c Isolated yield.

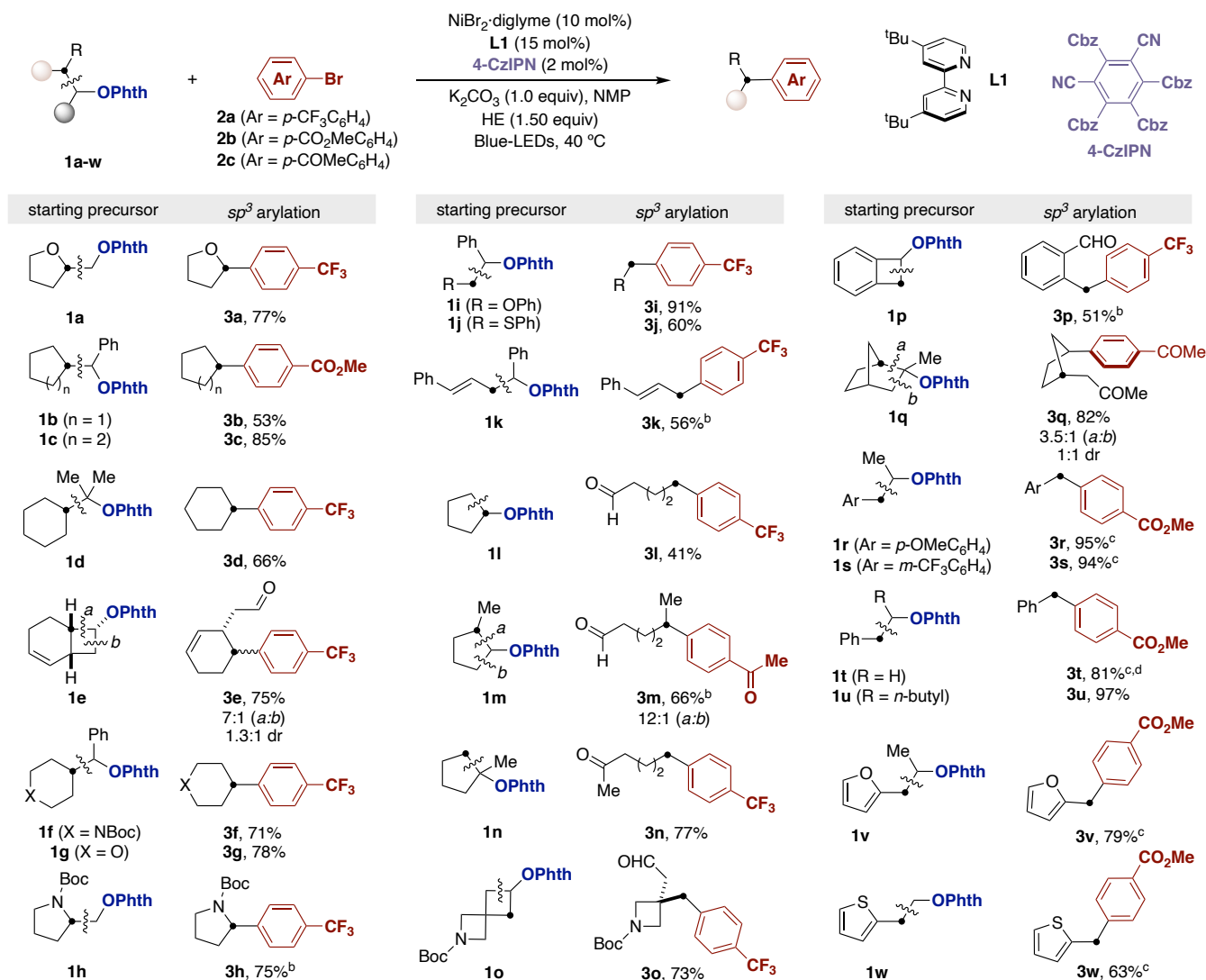
L1: R¹=H; R²=*t*-Bu
L2: R¹=H; R²=OMe
L3: R¹=H; R²=CO₂Me
L4: R¹=Me; R²=OMe
L5: R¹=*t*-Bu; R²=*t*-Bu

^a **1a** (0.10 mmol), **2a** (0.15 mmol), NiBr₂·diglyme (10 mol%), **L1** (15 mol%), 4-CzIPN (2 mol%), HE (0.15 mmol), K₂CO₃ (0.10 mmol) in NMP (0.25 M) at 40 °C for 18 h. ^b

Table 2. Dual Catalytic *sp*³ Arylation via β -Scission of Aliphatic Alcohol Derivatives.^a

¹⁹F-NMR yields using 1-fluoro-3-nitrobenzene as internal standard. ^c Isolated yield.

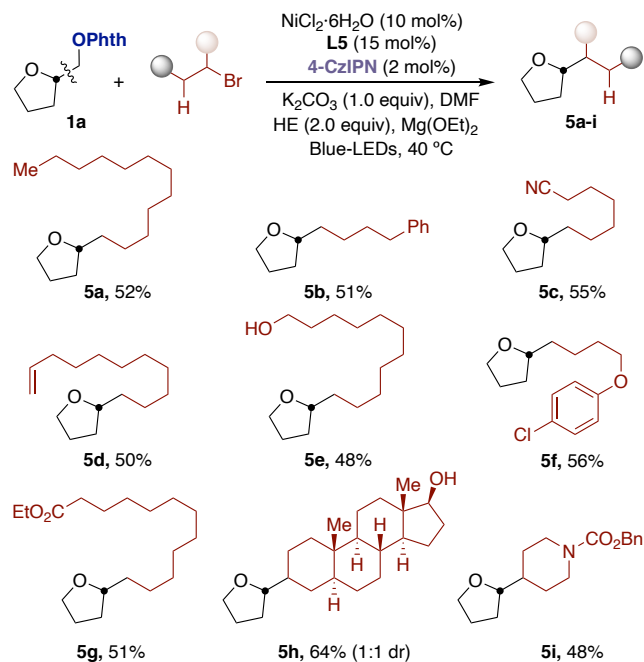
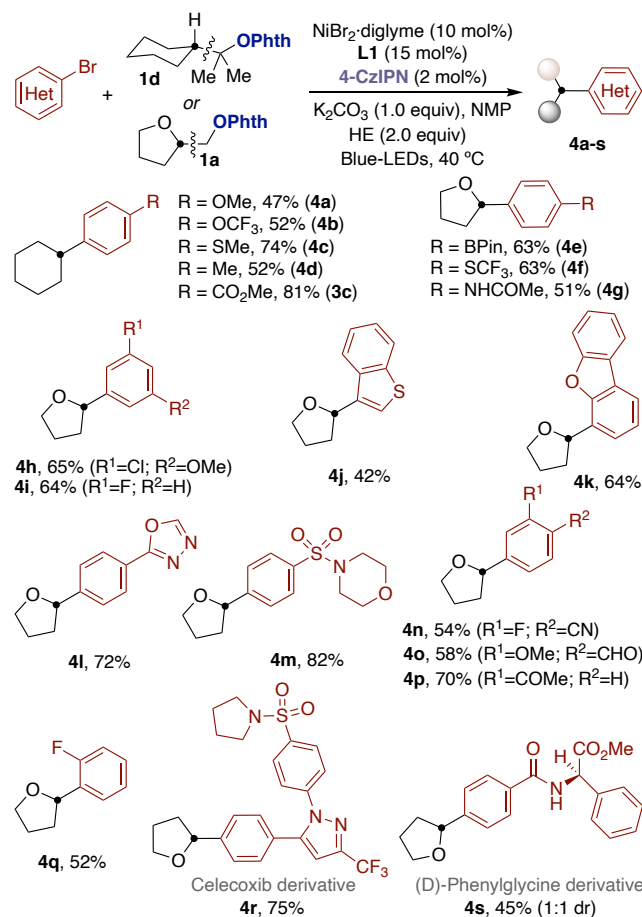
We began our investigations by evaluating the arylation of **1a** – readily synthesized on a large scale from tetrahydrofurfuryl alcohol feedstock in quantitative yield – with **2a** via β -scission (Table 1). After considerable optimization,¹¹ the best results were accomplished with 4-CzIPN as photocatalyst in the presence of Hantzsch ester (HE) under blue light-emitting diodes (LEDs) irradiation with a Ni/**L1** regime at 40 °C, obtaining **3a** in 77% isolated yield. As expected, the nature of the ligand had a non-negligible impact on reactivity, with 4,4'-di-*tert*butyl-bipyridine (**L1**) being particularly suited for the targeted C–C bond-forming event (entries 2-5). As shown in entries 6-8, lower yields of **3a** were found when utilizing nickel precatalysts and solvents other than NiBr₂·diglyme and NMP. Interestingly, **3a** could also be within reach in the absence of 4-CzIPN, albeit in lower yields (entry 9). While tentative, this observation suggests that an electron donor-acceptor (EDA) complex between **1a** & HE might come into play prior to β -scission.¹² Further control experiments revealed that the presence of Ni/**L1**, HE under visible light irradiation was critical for success (entry 10).



^a As Table 1 (entry 1), using aryl halide (0.20 mmol); Isolated yields, average of at least two independent runs.^b Using **1** (2.0 equiv), HE (2.0 equiv). ^c Using HE (2.50 equiv), TBAB (0.10 mol). ^d Using Ph-HE (2.50 equiv).

Next, we turned our attention to exploring the preparative scope of our protocol. As evident from the results compiled in Table 2, the β -scission/ sp^3 arylation event could be conducted with equal ease for a wide variety of differently substituted *N*-phthalimido substituted ethers derived from primary, secondary and tertiary aliphatic alcohols. As shown for **3k**, **3r**, **3s**, **3t** and **3u**, the protocol can be conducted with homoallylic or homobenzylic alcohols, giving rise to a formal sp^3 arylation at the benzylic or allylic site. Even cyclic alcohols with different ring sizes could be employed as substrates – including spirocyclic or bridged motifs – thus resulting in aliphatic carbonyl compounds via a ring-opening arylation event (**3e**, **3l-3q**).¹³ Notably, β -scission took place preferentially at the more substituted carbon, an observation that can tentatively be ascribed to the inherent stability of the resulting open-shell intermediate. As shown for **3v** and **3w**, the presence of electron-rich furans or thiophenes does not interfere with productive C–C bond-formation.

Table 3. Scope of Aryl Bromides.^a



^a **1a** (0.40 mmol), alkyl bromide (0.20 mmol), NiCl₂·6H₂O (10 mol%), **L5** (15 mol%), HE (0.40 mmol), K₂CO₃ (0.20 mmol), Mg(OEt)₂ (0.20 mmol) in DMF (0.125 M) at 40 °C for 20 h; Isolated yields, average of two independent runs.

^a As Table 1 (entry 1), using aryl halide (0.20 mmol); Isolated yields, average of at least two independent runs.

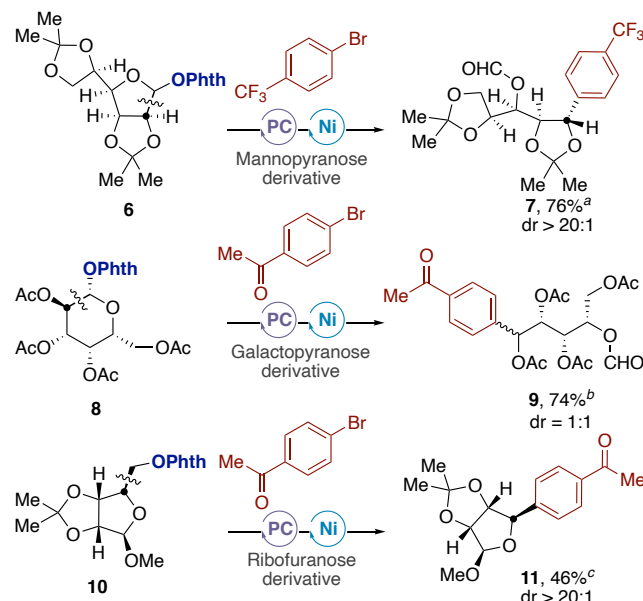
Our β -scission/ sp^3 arylation was found to be widely applicable to an array of aryl halides regardless of the electronic and steric environments of the arene (Table 3), even in the presence of *ortho*-substituents (**4q**). Note, however, that electron-deficient substrates generally provided better yields of the corresponding sp^3 -arylated products. The generality of the method was further illustrated by an excellent chemoselectivity profile, as ketones (**4p**), nitriles (**4n**), sulfonamides (**4m**, **4r**), amides (**4g**, **4s**), esters (**3c**, **4s**) or aldehydes (**4o**) were well-accommodated. Notably, the presence of sulfur-, oxygen- or even nitrogen-containing heterocycles posed no problems (**4j**, **4k**, **4l**, **4r**). The last example is particularly noteworthy, as the presence of nitrogen donors might a priori interfere with **L1** for binding to the Ni center.¹⁴ In addition, the presence of boronic esters (**4e**) and aryl halides (**4h**, **4i**, **4n**, **4q**) was perfectly compatible with productive sp^3 - sp^2 C-C bond-formation, thus leaving ample room for further functionalization via conventional cross-coupling reactions.¹⁵ Interestingly, Celecoxib or Phenylglycine derivatives were easily within reach by reacting **1a** with the corresponding aryl halide (**4r**, **4s**).

Table 4. Dual Catalytic sp^3 Alkylation via β -Scission.^a

Encouraged by these results, we wondered whether our protocol could be extended to build up sp^3 architectures by utilizing unactivated alkyl halides as counterparts.¹ We anticipated that the proclivity of in situ generated alkyl metal species for parasitic β -hydride elimination and the intrinsic electronic differences between aryl- and alkyl-Ni(II) complexes arising from oxidative addition to Ni(0)(**L1**) would make the recombination of the latter with electron-rich open-shell species **I** (Scheme 1) particularly problematic.¹ Indeed, a close inspection into the literature data reveals that the means to forge sp^3 - sp^3 bonds with unactivated alkyl halides still remains an elusive endeavor in the catalytic C-C bond-cleavage arena. Interestingly, although a Ni/**L1** regime failed to provide even traces of the targeted sp^3 - sp^3 bond-forming event, a protocol based on the Ni/**L5** couple delivered the corresponding sp^3 frameworks, thus revealing a non-negligible impact of the ligand denticity on reactivity (Table 4). As shown, a wide variety of unactivated alkyl halides possessing nitriles (**5c**), alkenes (**5d**), aliphatic alcohols (**5e**, **5h**), esters (**5g**, **5i**) or aryl halides (**5f**) could be tolerated. Although in comparatively lower yields than those shown in Table 3, these results should be interpreted against the challenge that is addressed in the sp^3 coupling arena. Scheme 2 further illustrates the synthetic applicability of our protocol. Specifically, we found that various saccharide derivatives could be employed as substrates for enabling a synergistic β -scission/ sp^3 bond-forming reaction, resulting in densely functionalized **7**, **9** and **11**, even with a high diastereoselectivity profile. Taken together, the results illustrated in Tables 2-4 and Scheme 2 stand as a

testament to the attractiveness of our β -scission/ sp^3 bond-formation, thus revealing an untapped potential for forging structurally-different sp^3 architectures from abundant aliphatic alcohol derivatives under mild conditions, even in the context of late-stage functionalization.

Scheme 2. Functionalization of Saccharides via β -Scission.

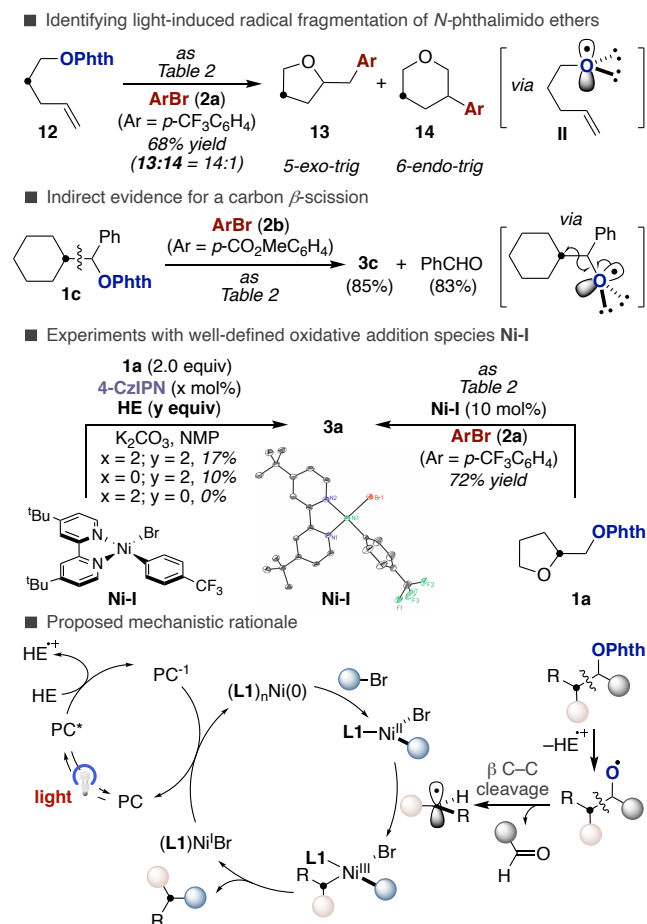


Conditions: as for Table 1 (entry 1). ^a **6** (0.30 mmol) and aryl bromide (0.20 mmol). ^b **8** (0.30 mmol) and aryl bromide (0.20 mmol). ^c **10** (0.40 mmol) and aryl bromide (0.20 mmol).

While unraveling all of the intricacies of our β -scission/ sp^3 bond-formation should await further investigations, preliminary studies revealed an association constant of 2.9 M^{-1} of HE with **1a**,¹¹ thus implying that an EDA complex between these species might be formed prior to homolytic cleavage.¹² Radical fragmentation of this entity was supported by exposure of **12** to our optimized reaction conditions, giving rise to both **13** and **14** (14:1 ratio). The formation of these products can be interpreted on the basis of a 5-*exo*-trig or 6-*endo*-dig cyclization from an in situ-generated oxygen-centered radical intermediate **II** (Scheme 3).^{16,17} In addition, 83% conversion to benzaldehyde was found by reacting **1c** with methyl 4-bromobenzoate, thus indirectly confirming the β -scission from species of type **II** en route to open-shell alkyl radical intermediates (*middle*).¹¹ Stoichiometric experiments with **Ni-I** – readily obtained by oxidative addition of **2a** to $\text{Ni}(\text{cod})_2/\text{L1}$ – revealed that sp^3 bond-formation required the presence of HE, thus contributing to the prevailing perception that donor-acceptor complexes are critical for success (*bottom left*).¹² As expected, **Ni-I** turned out to be catalytically competent as reaction intermediate, giving rise to **3a** in 72% yield (*bottom right*). On the basis of these results, we tentatively propose a dual catalytic manifold consisting of interfacing alkyl radical intermediates generated upon β -scission with the

corresponding oxidative addition aryl- or alkyl- $\text{Ni}(\text{II})$ species (Scheme 3, *bottom*). C–C bond-forming reductive elimination from a $\text{Ni}(\text{III})$ entity then delivers the targeted sp^3 framework and $\text{Ni}(\text{I})$ intermediates. A final single-electron transfer from the reduced form of 4-CzIPN – obtained by reductive quenching with HE – to $\text{Ni}(\text{I})$ recovers back the propagating $\text{Ni}(\text{0})$ catalysts.

Scheme 3. Mechanistic Experiments.



In summary, we have developed a new catalytic blueprint for forging sp^3 architectures from abundant aliphatic alcohols as adaptative nucleophilic handles by combining light-induced β -scission with Ni catalysts. This technology offers an unconventional manifold for enabling sp^3 -arylation and sp^3 -alkylation events with an excellent chemoselectivity and application profile under mild conditions, even within the context of late-stage functionalization of advanced intermediates. Further extensions to other related processes are currently underway.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectral and crystallographic data (PDF)

Data for Ni-I (CCDC-2039340) (CIF)

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