DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

2-Methyltetrahydrofuran (2-MeTHF): A Green Solvent for Pd–NHC-Catalyzed Amide and Ester Suzuki–Miyaura Cross-Coupling by N–C/O–C Cleavage

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. The palladium-NHC-catalyzed (NHC = N-heterocyclic carbene) Suzuki–Miyaura cross-coupling of amides and esters via highly chemoselective N–C(O) and O–C(O) cleavage with aryl boronic acids using green, sustainable and eco-friendly 2-methyltetrahydrofuran (2-MeTHF) is reported. A variety of amides and aryl esters were coupled with aryl boronic acids in high to excellent yields. This method employs commercially-available, air- and moisture-stable Pd(II)–NHC precatalysts. Crucially, the use of 2-MeTHF leads to the highest TON reported to date in amide N–C(O) bond cross-coupling. This operationally-simple protocol was utilized in the synthesis a bioactive ketone intermediate, emphasizing the potential of 2-MeTHF as a green solvent in unconventional amide bond disconnection. Given the tremendous importance of amide bond cross-coupling strategies and the drive to maintain full sustainability in cross-coupling processes, we expect that the synthetic method will be of broad interest.

Keywords: 2-MeTHF; Suzuki–Miyaura; cross-coupling; C–N activation; C–O activation; Pd-NHCs

Introduction

The central importance of the amide functional group in chemistry and biology[1,2] has spurred the development of an arsenal of catalytic methods for functionalization of amides by transition-metal-catalyzed N–C(O) cleavage.[3–8] It is estimated that more than 75% of drug candidates feature an amide bond, with more than two-third of new FDA drug approvals containing an amide, thus presenting unique opportunites in the modification of pharmaceuticals.[9,10] The ground-state-destabilization manifold of amides has been further translated into the activation of esters via initial insertion into the O–C(O) bond.[11,12] The cross-coupling products of these technologies yield chemicals that are highly attractive in academic and industrial sectors because traditionally inert amide or ester bonds are converted into acyl-metal intermediates using catalytic protocols with significantly improved chemoselectivity and atom economy.[13]

Meanwhile, in recent years, much attention has focused on cross-coupling reactions in environmentally friendly media.[14,15] Remarkably, organic solvents constitute up to 90% of the non-aqueous waste generated in pharmaceutical industry, and the major waste stream in academic laboratories.[16] Given the tremendous potential of amide bond cross-coupling technologies, it is surprising that catalytic methods using green solvents are to date unknown.

In 2017, our laboratory introduced the use of Pd(II)–NHC precatalysts for amide N–C bond cross-coupling.[4a] This catalytic system proved to be the most reactive in cross-coupling of amides reported to date.[3a] To improve sustainability and green profile of amide bond cross-coupling, herein, we report the first method to perform palladium-catalyzed Suzuki–Miyaura cross-coupling of amides and esters via highly chemoselective N–C(O) and O–C(O) cleavage using green, sustainable and eco-friendly 2-methyltetrahydrofuran (2-MeTHF)[17,18] (Figure 1). Considering the reduced environmental impact of 2-MeTHF and the fact that this solvent is obtained from renewable resources, the combination of biorelevant amide cross-coupling with sustainable 2-MeTHF offers an attractive protocol for industrial and academic applications. It should be further noted that this protocol is compatible with the [Pd(IPr)(1-*t*-Bu-ind)Cl] precatalyst.[4h]

In a broader context, this Update reports the first example of N–C(O) and O–C(O) cross-coupling in green solvents, and demonstrates the generality of these reactions with respect to both coupling partners. This protocol using favorable green 2-MeTHF could be readily performed on a preparative gram scale at low catalyst loading. Important features of our study

include: (1) The developed method employs commercially-available, air- and moisture-stable Pd(II)–NHC precatalysts;[19,20] (2) the high solubility of the base in 2-MeTHF leads to the highest TON reported to date for amide N–C(O) bond cross-coupling; (3) this operationally-simple protocol allows for the cross-coupling of a variety of amides and aryl esters with aryl boronic acids in high to excellent yields, including one-pot activation/cross-coupling of secondary amides; (4) the method was utilized in the synthesis a bioactive ketone intermediate, emphasizing the potential of 2-MeTHF as a green solvent for unconventional amide bond disconnection.

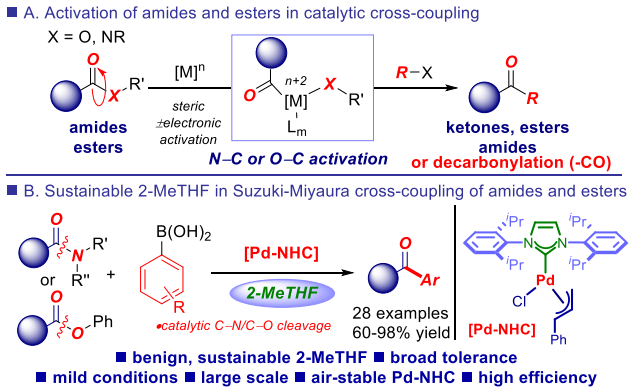


Figure 1. (a) Activation of Amides and Esters. (b) Sustainable 2-MeTHF in Suzuki–Miyaura Cross-Coupling of Amides and Esters.

Results and Discussion

Amide bond cross-coupling provides new opportunities to elaborate the stable amide linkage into valuable chemicals.[1–3] 2-MeTHF has been regarded as a very attractive solvent for organometallic reactions.[17] Unlike THF, 2-MeTHF is produced from bioresources, furfural or levulinic acid, which is indispensable in decreasing waste generation in chemical and pharmaceutical sectors.[18] More importantly, inorganic bases are more soluble in 2-MeTHF than in THF,[17a,b] which leads to high efficiency in select organometallic processes. Water helps to activate the Pd–NHC catalyst system.[21]

We focused our efforts on the Suzuki–Miyaura cross-coupling of *N*-Boc activated secondary amides[8] (Ar = Ph, R = Ph, RE = 9.7 kcal/mol; RE = resonance energy; Winkler-Dunitz parameters: τ = 18.8°; χ_N = 18.9°) using various Pd-NHC precatalysts. The optimized process (eq 1) employs [Pd(IPr)(cin)Cl] (3 mol%) (cin = cinnamyl)[22] in the presence of K_2CO_3 (3 equiv) in 2-MeTHF under exceedingly mild room temperature conditions. Interestingly, a base screen revealed K_2CO_3 to be superior to KOH, K_3PO_4 and KF under these conditions. Importantly, the cross-coupling could be carried out efficiently using only a slight excess of boronic acid (1.2 equiv). Finally, we established that

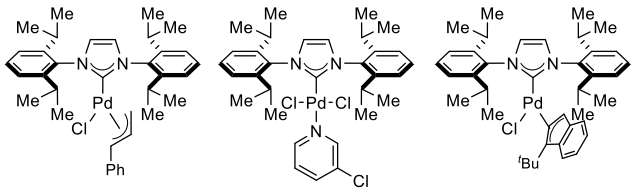
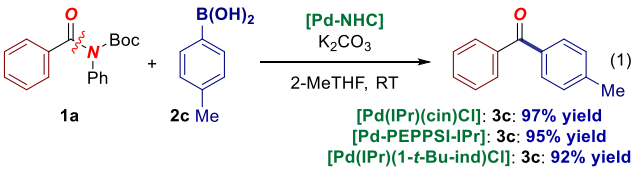


Figure 2. Structures of Pd(II)-NHC Precatalysts for Suzuki–Miyaura Cross-Coupling in Ecofriendly 2-MeTHF.

Equation 1. Effect of Precatalysts on the Suzuki–Miyaura Cross-Coupling of Amides in Ecofriendly 2-MeTHF.[a]



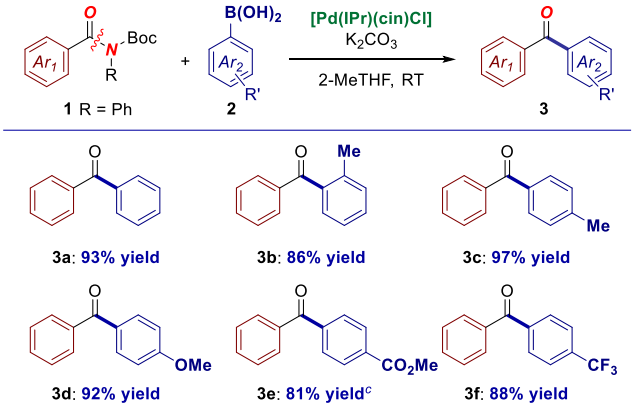
[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (1.2 equiv), Pd-NHC (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5 equiv), 2-MeTHF (0.25 M), 23 °C, 15 h.

the reaction could be carried our with other commercially-available Pd(II)–NHC precatalysts (Pd-PEPPSI-IPr,[23] 95%; Pd(IPr)(1-*t*-Bu-ind)Cl,[24] 92%) (Figure 2), highlighting the potential of 2-MeTHF as a general solvent for amide bond cross-coupling. It also should be noted that the amount of waste is an important consideration in evaluating sustainability in addition to the toxicity of solvents and reagents used.[18c] We note that under the standard conditions (eq 1, **1a**, [Pd(IPr)(cin)Cl], 3 mol%, 2-MeTHF, RT), 98% yield is obtained using 1.2 equiv of K_2CO_3, consistent with facile transmetallation under these conditions.

With optimal conditions in hand, the scope of the amide bond cross-coupling in 2-MeTHF was next evaluated. The conditons using 3.0 equiv of base were selected for comparison purposes.[4a] As shown in Schemes 1-3, a variety of boronic acids and amides can be deployed in this sustainable cross-coupling protocol. As revealed in Scheme 1, these mild conditions are compatible with electronically-diverse boronic acids, including electron-neutral (**3a**, **3c**), electron-donating (**3d**) and deactivating electron-withdrawing groups (**3e**, **3f**). Steric-hindrance is well-tolerated (**3b**). The functional group tolerance towards an alkyl ester should be noted (**3e**) as this substrate would be problematic in the addition of hard organometallic reagents to Weinreb amides.[25] As shown in Scheme 2, this method was found to be effective with diverse amides, including sterically-hindered (**3b'**), electronically-deactivated (**3d'**), containing electrophilic functional groups (**3e'**) as well as those containing fluorinated moieties (**3f'**,**3g**) and heterocycles (**3h**) that constitute common motifs in pharmaceutical chemistry.[26]

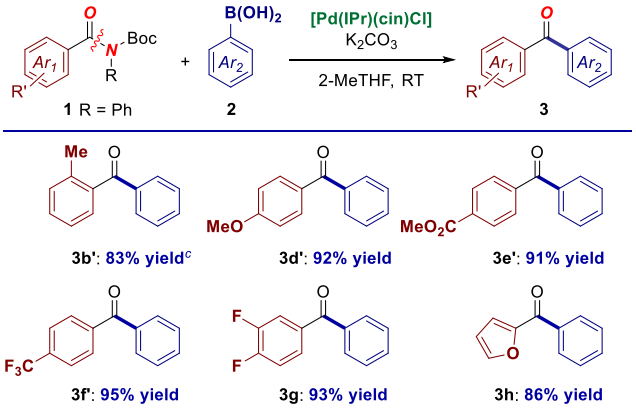
To test the limits of this cross-coupling process using sustainable 2-MeTHF, we systematically

Scheme 1. Scope of the Suzuki–Miyaura Cross-Coupling of Amides in Ecofriendly 2-MeTHF: Amides.[a,b]



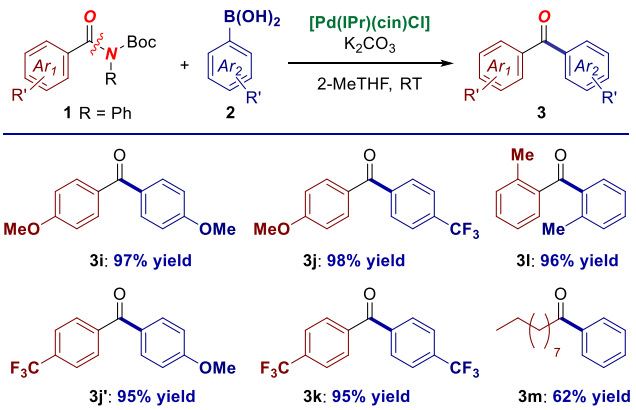
[a]Conditions: Amide (1.0 equiv), Ar-B(OH)$_2$ (1.2 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), 2-MeTHF (0.25 M), 23 °C, 15 h. [b]Isolated yields. [c]Ar-B(OH)$_2$ (2.0 equiv).

Scheme 2. Scope of the Suzuki–Miyaura Cross-Coupling of Amides in Ecofriendly 2-MeTHF: Boronic Acids.[a,b]



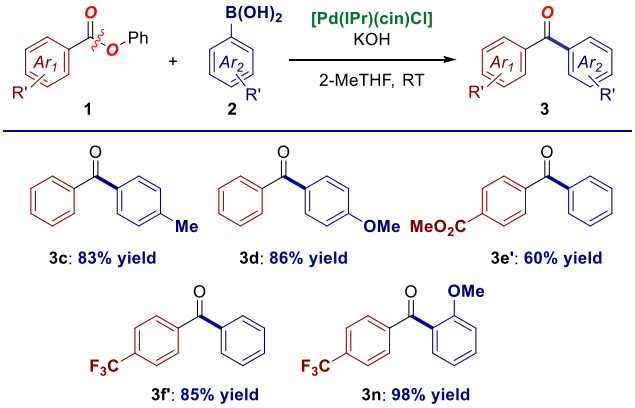
[a]Conditions: Amide (1.0 equiv), Ar-B(OH)$_2$ (1.2 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), 2-MeTHF (0.25 M), 23 °C, 15 h. [b]Isolated yields. [c]Ar-B(OH)$_2$ (2.0 equiv).

Scheme 3. Scope of the Suzuki–Miyaura Cross-Coupling of Amides in Ecofriendly 2-MeTHF: Further Examples.[a,b]



[a]Conditions: Amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), 2-MeTHF (0.25 M), 23 °C, 15 h. [b]Isolated yields.

Scheme 4. Scope of the Suzuki–Miyaura Cross-Coupling of Esters in Ecofriendly 2-MeTHF.[a,b]



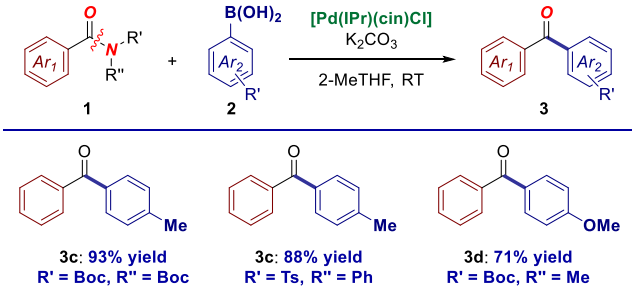
[a]Conditions: Ester (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%), KOH (3.0 equiv), H_2O (5.0 equiv), 2-MeTHF (0.25 M), 23 °C, 15 h. [b]Isolated yields.

examined cross-coupling of electronically-matched/mismatched electrophile/ nucleophile couples (Scheme 3). It is now established that the rate- determining step in amide cross-coupling involves transmetallation,[21] while electronic-substitution of the amide affects amidic resonance.[8] We found that all combinations (**3i**, **3j**, **3j'**, **3k**) gave the ketone products in excellent 95-98% yields, attesting to the generality of this sustainable catalytic protocol. Note that this includes the challenging combination of cross-coupling of electronically-deactivated amide with electronically-deactivated boronic acid (**3j**).[11b,4h] We also found that the notoriously difficult bis-ortho-methyl substituted biaryl ketone (**3l**) could be prepared in excellent yield. Furthermore, the cross-coupling of an alkyl amide (**3m**) can be carried out, demonstrating that this system catalyzes the reaction of aliphatic amides. It is worthwhile to note that the use of various *N*-alkyl-*N*-Boc derivatives is typically feasible using Pd(II)–NHCs due to similar amidic resonance of the amide bond.[3a] Activated alkanecarboxamides are limited to primary and secondary alkanecarboxamides.

We then turned our attention to the cross-coupling of aryl esters. Electronic-destabilization of the O–C(O) bond in aryl esters enables synthetically appealing catalytic cross-coupling by C–O acyl cleavage.[3a,4h,11] Interestingly, we found that 2-MeTHF is suitable for the selective Suzuki–Miyaura cross-coupling of phenolic esters. In this case, the inexpensive KOH was found to be the preferred base. As shown in Scheme 4, these conditions are compatible with the cross-coupling of sterically- and electronically-varied ester/boronic acid combinations, affording ketone products in good to excellent yields using [Pd(IPr)(cin)Cl] as catalyst. The exquisite chemoselectivity for the cross-coupling of an aryl ester in the presence of its alkyl counterpart is noteworthy (**3e'**).

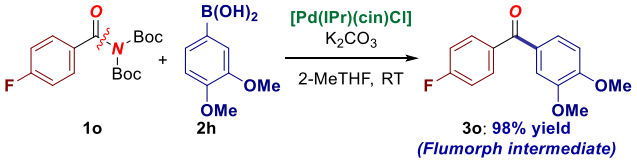
Pleasingly, the optimized conditions allow for the cross-coupling of diverse amides, including *N*,*N*-Boc$_2$ amides (Scheme 5, entry 1) that are readily

Scheme 5. Scope of Amides in the Suzuki–Miyaura Cross-Coupling in Ecofriendly 2-MeTHF.[a,b]

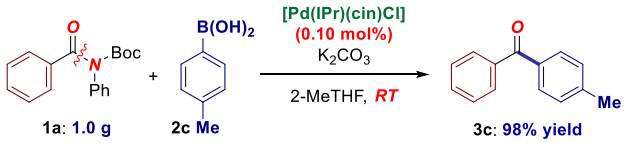


[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), 2-MeTHF (0.25 M), 23 °C, 15 h.. [b]Isolated yields.

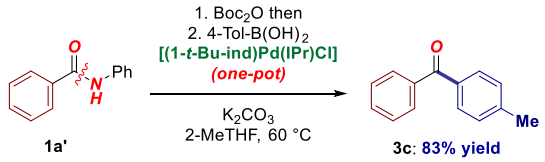
Scheme 6. Synthesis of Flumorph Intermediate by the Amide Suzuki–Miyaura Cross-Coupling in 2-MeTHF.



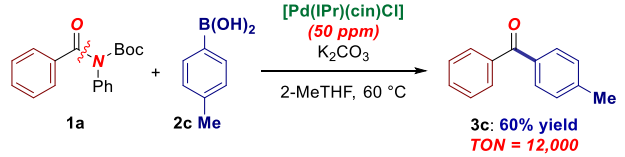
Scheme 7. Scale-up at Low Catalyst Loading in 2-MeTHF.



Scheme 8. One-Pot N-Activation/Amide Cross-Coupling in 2-MeTHF.



Scheme 9. Determination of TON in 2-MeTHF.



prepared from unactivated primary amides as well as *N*-Ar/Ts sulfonamides (entry 2) and *N*-alkyl/Boc carbamates (entry 3). Thus, this green protocol allows one to take advantage of different amide bond precursors and activation mechanisms.[3,8] It should be noted that the acyl-cross-coupling manifold is fundamentally different from decarbonylative cross-coupling amides. In general, the acyl cross-coupling is at present at much more evolved stage of development than decarbonylative cross-couplings. Our results establish that the most useful examples of N-acyclic amides that could be prepared directly from common acyclic amides (*N*-R/Boc, *N*-R/Ts, *N*-Boc$_2$) are compatible with the cross-coupling protocol in ecofriendly 2-MeTHF.

To further demonstrate the generality of this sustainable cross-coupling, we applied this method to the synthesis of a bioactive ketone intermediate in the commercial preparation of Flumorph,[27] a promising new generation pesticide (Scheme 6). As shown, the high cross-coupling efficiency at room temperature emphasizes the potential of 2-MeTHF as a green solvent in unconventional amide bond disconnection.

Pleasingly, the cross-coupling of amide (**1a**) proceeded on a gram scale in 98% yield using only 0.10 mol% of the air-stable [Pd(IPr)(cin)Cl] catalyst, demonstrating the scalability of this new cross-coupling protocol (Scheme 7).

Furthermore, one-pot activation/cross-coupling is feasible as illustrated by the reaction of N-Ph-benzamide (Scheme 8). The use of [Pd(IPr)(1-*t*-Bu-ind)Cl][23] gave slightly better reactivity in this instance. The one-pot activation/cross-coupling establishes facile and sustainable generation of metal-acyl moieties from secondary amides.

Finally, encouraged by the high cross-coupling reactivity observed in 2-MeTHF, we explored reactions using lower catalytic loadings. We found that the cross-coupling of amide (**1a**) is feasible at 50 ppm [Pd] loading (TON = 12,000, 60 °C, 2-MeTHF, 2.0 M) (Scheme 9). It is clear that the high turnover is possible through the improved solubility of K_2CO_3 (1.2 equiv) in 2-MeTHF that enables more concentrated solutions.[17] This represents the highest TON reported to date in amide cross-coupling, and shows the advantage of using environmentally-friendly 2-MeTHF over THF (TON <2,000).

Conclusions

In summary, this Update reports the first method to perform cross-coupling of unconventional amide and ester electrophiles in green solvents. We have demonstrated the utility of green, sustainable and renewable 2-methyltetrahydrofuran as an attractive solvent for the palladium-NHC-catalyzed Suzuki–Miyaura cross-coupling of amides and esters. This operationally-convenient method employs commercially-available, air- and moisture-stable Pd(II)-NHC precatalysts, and is compatible with a wide range of amides and boronic acid components. The potential of these cross-couplings has been demonstrated in large-scale synthesis, one-pot activation/cross-coupling and the synthesis a bioactive ketone intermediate. More broadly, the use of 2-methyltetrahydrofuran creates two opportunities in amide bond cross-coupling: (1) it enables the use of ecofriendly, sustainable processes for the catalytic generation of metal-acyl moieties, and, (2) it takes advantage of the beneficial physico-chemical properties of 2-MeTHF, enabling highly efficient cross-coupling. Considering the importance of amide bond cross-coupling strategies and clear advantages gained from using sustainable solvents in cross-

coupling protocols, we expect that the method will find broad application in organic synthesis.

Experimental Section

General Information. General methods have been published.[4b]

General Procedure for the Suzuki-Miyaura Cross-Coupling of Amides in EcoFriendly 2-MeTHF. An oven-dried vial equipped with a stir bar was charged with an amide substrate (neat, 1.0 equiv), potassium carbonate (typically, 3.0 equiv), boronic acid (typically, 1.2 equiv), [Pd(IPr)(cin)Cl] (Neolyst CX31, typically, 3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (typically, 0.25 M) and water (typically, 5.0 equiv) were added with vigorous stirring at room temperature and the reaction mixture was stirred for the indicated time. After the indicated time, the reaction mixture was diluted with EtOAc (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

Representative Procedure for the Suzuki-Miyaura Cross-Coupling of Amides in EcoFriendly 2-MeTHF (1.0 g scale). An oven-dried vial equipped with a stir bar was charged with *tert*-butyl benzoyl(phenyl)carbamate (3.36 mmol, 1.00 g, 1.0 equiv), potassium carbonate (10.10 mmol, 1.395 g, 3.0 equiv), *p*-tolylboronic acid (6.73 mmol, 0.915 g, 2.0 equiv), [Pd(IPr)(cin)Cl] (0.10 mol%, 2.2 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (1.0 M) and water (16.80 mmol, 0.303 g, 5.0 equiv) were added with vigorous stirring at room temperature and the reaction mixture wasstirred for 15 h at room temperature. After the indicated time, the reaction mixture was diluted with EtOAc (20 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product; 98% (0.647 g).

Acknowledgements

Rutgers University and the NSF (CAREER CHE-1650766) are gratefully acknowledged for support. The Bruker 500 MHz spectrometer was supported by the NSF-MRI grant (CHE-1229030). P.L. thanks the China Scholarship Council (No. 201606350069).

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