# Nickel-Catalyzed Direct Addition of Diorganozinc Reagents to Phthalimides: Selective Formation of Gamma-Hydroxylactams

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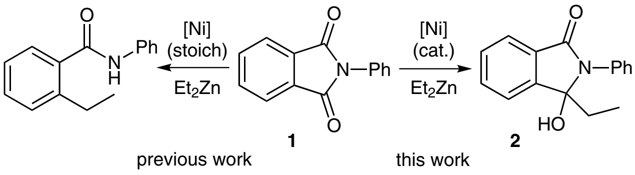
**Abstract:** The nickel-catalyzed addition of diorganozinc reagents to phthalimides proceeds with excellent selectivity to provide 3-substituted-3-hydroxyisoindolin-1-one products. These 3-hydroxy-γ-lactams are produced cleanly in high yield with numerous examples of imide substitution and a broad range of diorganozinc reagents that are prepared and utilized without purification.

**Key words:** imide, catalysis, lactams, organometallic reagents, nickel

The development of transition-metal-catalyzed coupling methodologies has a continual influence on the evolution of synthetic organic chemistry.[1] In addition to the development of previously unknown transformations and couplings, transition-metal catalysis can provide greater control over known reactions through the use of less forceful reaction conditions, ultimately allowing the use of a broader range of substrates. For example, the reaction of strongly nucleophilic organometallic reagents, such as Grignards[2] and organolithiums,[3] with imides is well precedented. These reactions, however, are often plagued by uncontrolled multiple nucleophile additions to generate complex mixtures of products. The controlled addition of a single alkyl or aryl nucleophile would offer a clear route to the formation of 3-substituted 3-hydroxyisoindolin-1-ones, a structural motif found in numerous natural products[4] and bioactive compounds,[5] including chlorthalidone, which is a diuretic utilized to treat hypertension.[6] Access to these 3-hydroxy-γ-lactams has been achieved through a number of procedures,[7,8] including recent routes utilizing alkynyl benzoic acids[9] or rhodium-catalyzed oxidative acylation,[10] but these methods generally fail to demonstrate broad substrate scope for nitrogen, backbone, and/or 3-carbon substitution.

In previous work, our group reported the nickel-mediated decarbonylative coupling of diorganozinc reagents and phthalimides to generate *ortho*-substituted benzamides (Scheme 1).[11] While tolerant of a wide variety of functionality on both the diorganozinc and phthalimide reagents, this methodology is significantly limited by the lack of catalyst turnover. In the process of exploring potential catalytic conditions for this decarbonylative transformation, we observed the nickel-catalyzed direct addition of diethylzinc to *N*-phenylphthalimide (**1**) to selectively generate *N*-phenyl-3-hydroxyisoindolin-1-one (**2**; Scheme 1). Due to the previously mentioned observation of this skeleton in natural products and other bioactive molecules, we pursued the optimization and full exploration of this reactivity. Herein, we present the development of a nickel-catalyzed methodology for the cNickel-Catalyzed Addition of Diorganozinc Reagents to Phthalimidesoupling of phthalimides with diorganozinc reagents that leads to selective mono-addition of the organometallic with a broad range of imide and nucleophile substitution for the selective preparation of 3-substituted 3-hydroxyisoindolin-1-ones.



**Scheme 1**

In the presence of 10 mol% $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) and 11 mol% $PPh_3$ in THF at 55 °C, diethylzinc cleanly adds to *N*-phenylphthalimide, providing the direct addition product **2** in 81% isolated yield. In the process of reaching these optimized conditions, numerous experiments were performed to ascertain the role of the various components of this transformation (Table 1). In the absence of nickel, under otherwise standard conditions, no product was observed (entry 2). A number of ligands provide the product in low yields, while also generating the decarbonylation product (entries 3–5).[12] In contrast, the use of $Ph_3P$ provided the 3-hydroxyisoindolin-1-one exclusively with high yield. The use of bench-stable $Ni(acac)_2$ (acac = acetylacetonate) as the catalyst required a slight excess of diethylzinc in order to generate the proposed Ni(0) active catalyst, but provided the desired product in a nearly identical yield to that obtained with $Ni(COD)_2$ (entry 6). In optimizing reaction conditions, alternative solvents, nucleophiles, and temperatures were also explored.

With the development of the optimized conditions, our efforts turned toward exploration of the substrate scope. A series of N-substituted phthalimides was prepared and tested for reactivity (Table 2). Aromatic substrates containing a variety of substituents were found to be compatible with the reaction conditions, providing good to excellent yields. The reaction was tolerant of a significant

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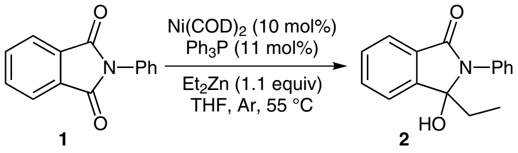
**Table 1** Optimization of the Nickel-Catalyzed Direct Addition



| Entry | Conditions (deviation from standard)[a] | Yield of **2** (%) |
|---|---|---|
| 1 | none | 81 |
| 2 | no Ni source | 0 |
| 3 | no ligand | <5 |
| 4 | ligand = bipy | <5 |
| 5 | ligand = pyridine | 12 |
| 6 | metal = Ni(acac)$_2$, Et$_2$Zn (1.5 equiv) | 80 |
| 7 | 1,4-dioxane at 95 °C | 65 |
| 8 | EtZnBr instead of Et$_2$Zn | 8 |
| 9 | 25 °C | 40 |

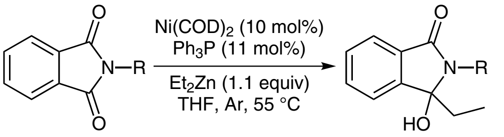
[a] Standard conditions: **1** (0.5 mmol), Ni(COD)$_2$ (10 mol%), Ph$_3$P (11 mol%), Et$_2$Zn (0.55 mmol), 55 °C, THF, Ar atmosphere.

range of functional groups, including those that are not compatible with more reactive organometallic species, such as aryl esters and *N*-aryl halides (entries 7 and 8).

To date the reactivity has been limited to relatively electron-deficient aryl-substituted phthalimides.[13] N-Alkyl or N-aryl species containing electron-releasing functionality, such as *N*-benzyl or *N*-4-methoxyphenyl phthalimides, provide little or no product when subjected to standard reaction conditions; the starting imides, or the corresponding amide acid generated from hydrolysis during workup, are recovered. Likewise, imides with saturated backbones, such as 2,3-dimethylsuccinimide, failed to react under the standard conditions.

In addition to elaboration of the phthalimide substituents, the scope of diorganozinc reagents was also explored. Commercially available reagents worked smoothly, but the availability of commercial diorganozinc reagents is quite limited. It was therefore paramount that the reaction proceeds efficiently with nucleophiles prepared and utilized with minimum purification. To address this requirement, a solution of diphenylzinc, prepared through lithium–halogen exchange of bromobenzene and subsequent reaction with ZnCl$_2$, was utilized as the nucleophilic reagent under Ni(COD)$_2$/Ph$_3$P catalysis. By utilizing imide **10** under otherwise standard reaction conditions, the desired product of this reaction was obtained in 82% yield compared to 84% yield obtained with commercially available Ph$_2$Zn (Scheme 2). It should be emphasized that the diorganozinc reagents were utilized as prepared as a solution in THF, suggesting no deleterious effects of residual organics and salts formed during nucleophile preparation.

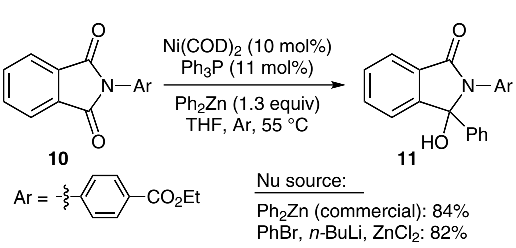
**Table 2** Scope of the Reaction with Respect to *N*-Phthalimide Substitution[a]



| Entry | R | Product | Yield (%) |
|---|---|---|---|
| 1 | Ph | **2** | 81 |
| 2 | 3-MeC$_6$H$_4$ | **3** | 82 |
| 3 | 4-MeC$_6$H$_4$ | **4** | 78 |
| 4 | 4-EtC$_6$H$_4$ | **5** | 93 |
| 5 | 4-*i*-PrC$_6$H$_4$ | **6** | 81 |
| 6 | 3,5-(F$_3$C)$_2$C$_6$H$_3$ | **7** | 68 |
| 7 | 4-EtO$_2$CC$_6$H$_4$ | **8** | 86 |
| 8 | 4-ClC$_6$H$_4$ | **9** | 66[b] |

[a] Standard conditions: Imide (0.5 mmol), Ni(COD)$_2$ (10 mol%), Ph$_3$P (11 mol%), Et$_2$Zn (0.55 mmol), 55 °C, THF, Ar atmosphere.

[b] Yield by GC/MS analysis. Separation from the elimination product generated by dehydration proved difficult and led to significantly reduced isolated yield.

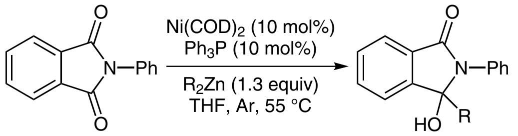


**Scheme 2** Use of commercial diphenylzinc versus that prepared and utilized without purification

With the successful demonstration of nucleophiles prepared in situ, a broad range of diorganozinc reagents was explored as coupling partners (Table 3). Steric aspects of the nucleophiles appear to have a modest effect, because the coupling proceeds efficiently with *ortho*-, *meta*-, and *para*-substituted aryl nucleophiles with only minor influence on the yield (entries 1–6). The functional group tolerance includes typical ether, thioether and trifluoromethyl moieties, but also extends to more exotic nucleophiles, such as aryl fluoride and bromide (entries 11 and 13). The bromide is formed via the diarylzinc reagent prepared from 1-bromo-4-iodobenzene. An alkyl ester nucleophile, utilized without purification following generation from zinc chloride and (1-ethoxycyclopropoxy)trimethylsilane,[14] also readily adds to imide **1** with excellent conversion, but isolation is complicated by the propensity of the product to undergo dehydration to generate a mixture of alkenes.

As illustrated by the optimization studies, this reaction is extremely sensitive to the electronic nature of both the

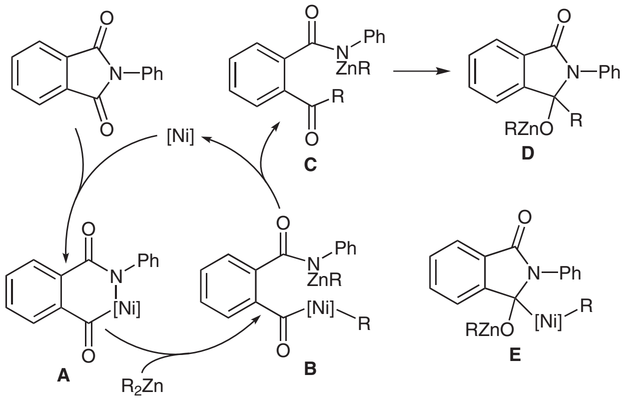
**Table 3** Scope of the Reaction with Prepared Diorganozinc Nucleophiles[a]



| Entry | R | Product | Yield (%) |
|---|---|---|---|
| 1 | 4-MeC$_6$H$_4$ | **12** | 82 |
| 2 | 3-MeC$_6$H$_4$ | **13** | 81 |
| 3 | 2-MeC$_6$H$_4$ | **14** | 65 |
| 4 | 4-MeOC$_6$H$_4$ | **15** | 76 |
| 5 | 3-MeOC$_6$H$_4$ | **16** | 78 |
| 6 | 2-MeOC$_6$H$_4$ | **17** | 60 |
| 7 | 4-MeSC$_6$H$_4$ | **18** | 85 |
| 8 | 4-*t*-BuC$_6$H$_4$ | **19** | 80 |
| 9 | 2-naphthyl | **20** | 33 |
| 10 | 4-F$_3$CC$_6$H$_4$ | **21** | 76 |
| 11 | 4-FC$_6$H$_4$ | **22** | 75 |
| 12 | 3,5-(F$_3$C)$_2$C$_6$H$_3$ | **23** | 85 |
| 13 | 4-BrC$_6$H$_4$ | **24** | 56[b] |

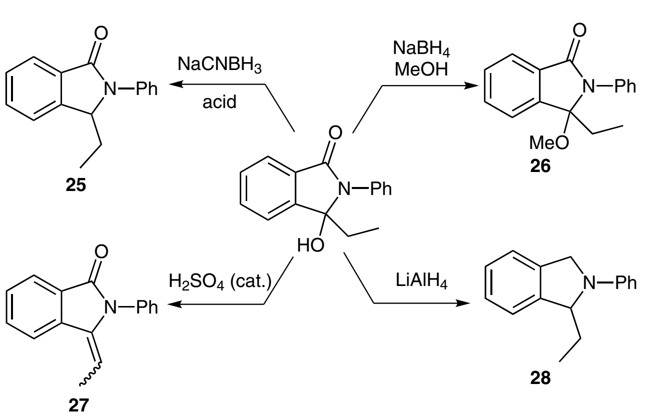
[a] Standard conditions: **1** (0.5 mmol), Ni(COD)$_2$ (10 mol%), Ph$_3$P (11 mol%), Ar$_2$Zn (0.68 mmol), 55 °C, THF, Ar atmosphere.
[b] Yield by GC/MS analysis.

phthalimide substituents and the ligand. This sensitivity is similar to that observed in our previous decarbonylation methodology, and in conjunction with the lack of multiple addition products, suggests a shared mechanistic pathway. As such, it is proposed that the reaction proceeds via a nickel metalacycle rather than through direct nucleophilic attack (Scheme 3). Oxidative addition of the nickel(0) catalyst into the imide provides nickel(II) metalacycle **A**. This metalacycle can subsequently undergo decarbonylation as it does under catalysis with bipy, ultimately leading to the catalytically dormant nickel(0)-carbonyl species, or react with the diorganozinc reagent through transmetallation. Under catalysis with Ph$_3$P, the latter pathway dominates, presumably due to destabilization of the nickel-carbonyl intermediate through the use of the more π-accepting phosphine ligand. Zinc amide species **B** then undergoes subsequent reductive elimination to form amide salt **C**. Free ketoacid has not been observed under any reaction conditions, leading to the assumption that intermediate **C** undergoes rapid intramolecular cyclization to generate lactam **D** prior to the acidic workup, which results in formation of the 3-hydroxy-γ-lactam. It is also possible that intermediate **B** undergoes cyclization to form **E** prior to reductive elimination, although this seems less likely due to the relative electrophilicity of metal acyl complex **B** and ketone **C**. Studies are underway to evaluate this catalytic cycle and the influence of electronic effects on the proposed divergence of paths.



**Scheme 3** Proposed mechanism

As outlined in Scheme 4, the product 3-hydroxyisoindolin-1-ones can be further diversified through a variety of reactions. Treatment with sodium cyanoborohydride leads to 3-alkyl-1-isoindolinones **25**,[3] whereas treatment of the same species with sodium borohydride in alcoholic solvents generates 3-alkoxy esters **26**.[3,15] Treatment of the 3-hydroxyisoindolin-1-ones with acid results in the dehydration product, generating a *cis*/*trans* mixture of the corresponding alkenes **27**. Finally, treatment of the products with lithium aluminum hydride results in reduction of the substrate to the corresponding 1-substituted isoindole **28**. These examples demonstrate the versatility of the substituted γ-lactams and illustrate the potential utility of the newly developed methodology.



**Scheme 4** Elaboration of 3-substituted-3-hydroxyisoindolin-1-ones

In summary, the coupling of N-substituted phthalimides with diorganozinc reagents has been demonstrated by utilizing nickel(0) catalysis.[16] Diorganozinc reagents generated from aryl bromides and used without purification can be utilized to generate a broad range of substituted 3-hydroxyisoindolin-1-ones in good to excellent yield. Efforts to understand the mechanistic interconnection of this methodology with decarbonylative cross-coupling are ongoing.

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) Due to the strength of the nickel–carbonyl bond, decarbonylation leads to deactivation of the catalyst and results in low yields of the desired products.

(13) It should be noted that with the use of electron-deficient heteroatom-containing N-substituted imides, such as *N*-(2-pyridyl)phthalimide, uncatalyzed addition of diorganozinc nucleophiles was observed.

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(15) Base, such as $NaBH_4$ or NaOMe, is required for the formation of **26**. No reaction was observed in the absence of base under otherwise identical reaction conditions.

(16) **Direct Addition of $Et_2Zn$ to Phthalimides; Typical Procedure:** $Ph_3P$ (13.1 mg, 0.055 mmol) and *N*-phenylphthalimide (111.6 mg, 0.50 mmol) were combined with a stirbar in an oven-dried 25 mL round-bottomed flask. The flask was transferred into an inert atmosphere glove box, where $Ni(COD)_2$ (14.0 mg, 0.051 mmol) was added. The flask was sealed with a septum and removed from the glove box, whereupon THF (2 mL) was added, followed by $Et_2Zn$ (56.5 μL, 0.55 mmol, 1.1 equiv). The solution was then brought up to temperature in a 55 °C oil bath and stirred for 16 h. Upon completion of the reaction, the mixture was cooled to r.t., the septum was removed and $Et_2O$ (15 mL) was added. The addition of 2 M aq HCl (15 mL) quenched the reaction, which was then extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography (hexane–EtOAc, 4:1) to provide **2** (81% yield).

**Direct Addition with Diorganozinc Reagents Generated In Situ; Typical Method:** 1-Bromo-4-*tert*-butylbenzene (230 μL, 1.33 mmol) was added to an oven-dried 10-mL round-bottomed flask, sealed with a septum, evacuated and refilled with Ar (×3) and dissolved in THF (2 mL). The reaction mixture was cooled to –78 °C, *n*BuLi (2.5 M in hexanes, 536 μL, 1.34 mmol) was added dropwise and the mixture was stirred at –78 °C for 1 h. In a separate flask, $ZnCl_2$ (92.1 mg, 0.68 mmol) was dried by heating under vacuum and then dissolved in THF (1 mL). This solution was then added to the solution of ArLi, still at –78 °C. The reaction was removed from the cold bath and allowed to warm to r.t. while stirring for 30 min.

In a separate 25 mL round-bottomed flask, *N*-phenylphthalimide (112 mg, 0.50 mmol) and $Ph_3P$ (14.2 mg, 0.054 mmol) were combined and transferred into an inert atmosphere glove box, where $Ni(COD)_2$ (14.1 mg, 0.051 mmol) was added. This flask was sealed with a septum and removed from the glove box, whereupon THF (2 mL) was added, followed by the $Ar_2Zn$ solution. The solution was then brought up to 55 °C in an oil bath and stirred for 16 h. Upon completion of the reaction, the mixture was cooled to r.t., the septum was removed and $Et_2O$ (15 mL) was added. The addition of 2 M aq HCl (15 mL) quenched the reaction, which was then extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane–EtOAc, 9:1) to provide **19** as a white solid (80% yield).