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# Sustainable Synthetic Methods: Domino Construction of Dihydropyridin-4-ones and β-Amino Esters in Aqueous Ethanol

**Peter J. Alaimo,* Robert O'Brien III, Adam W. Johnson, Sarah R. Slauson, Jeannette M. O'Brien, Elizabeth L. Tyson, Amanda-Lynn Marshall, Colleen E. Ottinger, Jon G. Chacon, Lorien Wallace, Corey Y. Paulino, and Sarah Connell**

*Department of Chemistry, Seattle University, 901 12th Avenue,*
*Seattle, Washington 98122*

*alaimop@seattleu.edu*

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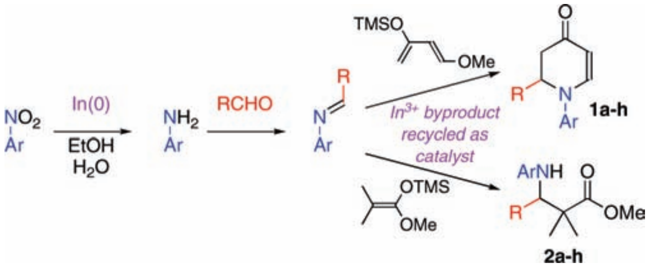
## ABSTRACT



**Domino reactions were designed to allow the byproduct of an upstream reaction to be internally recycled to catalyze a downstream reaction in a one-pot tandem sequence. Nitroarene reduction by $In^0$ generates an amine and $In^{III}$ byproducts. Addition of aldehyde followed by Danishefsky's diene or silyl ketene acetal provides access to dihydropyridin-4-ones or β-amino esters, respectively, in yields that are comparable or superior to the reported stepwise reactions.**

Over the past 15 years, the development of "green" synthetic methods has become an important frontier in chemistry; a key objective is to eliminate the adverse environmental effects of chemical synthesis.[1] Toward this end, progress has been made using reusable catalysts, renewable resources, and alternative solvents such as water, sc-$CO_2$, and ionic solvents.[2] Other advances include eliminating the generation of toxic byproducts through discovery of safer reagents, developing more efficient reactions (e.g., catalyzed reactions) that do not require large energy inputs, and using domino reaction cascades where the product of one reaction becomes the starting material for the next step in situ.[3] The domino strategy minimizes waste by reducing the number of purification steps—the stage where the most waste is generated. Herein we describe our efforts to advance sustainable synthetic methods by designing a rare example[4] of a domino cascade that *internally recycles* an upstream reaction *byproduct* to provide a *catalyst* for a downstream reaction.[5] We disclose two versions of this strategy, which we expect will be applicable to a range of transformations.

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(1) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686.

(2) (a) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (b) Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746. (c) Miao, W.; Chan, T. H. *Acc. Chem. Res.* **2006**, *39*, 897.

(3) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.

(4) An interesting example of internal recycling was reported by Loh where an $In^0$-mediated Barbier-type aldehyde allylation reaction generated a γ-adduct, which rearranged to an α-adduct in an $In^{3+}$-catalyzed manner. (a) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y *Tetrahedron Lett.* **2001**, *42*, 8705. (b) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958.

(5) A conceptually unique but related strategy called cascade catalysis refers to the use of several different catalysts in one-pot procedures to catalyze mechanistically distinct steps of a cascade reaction. The approach presented here is fundamentally different but could, in theory, be used in combination with cascade catalysis.

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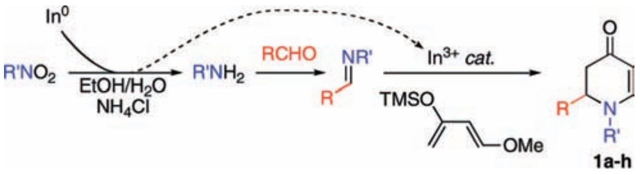
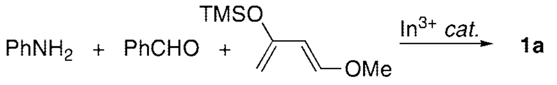
We identified dihydropyridin-4-ones as a family of targets to showcase the strategy because these compounds are of great practical importance. In addition to being found in alkaloids and enzyme inhibitors, these scaffolds are key building blocks for numerous heterocycle syntheses because of their vinylagous amide moiety.[6] To assemble dihydropyridin-4-ones, we reasoned that the $In^0$-mediated reduction of nitroarenes followed by aldimine formation (upon addition of aldehyde) would start the domino sequence (Scheme 1). Performing the reduction in the presence of $NH_4Cl$ should generate $InCl_3$ as the reaction byproduct. The Lewis acidic $InCl_3$ complex is now poised to assemble the product by catalyzing the aza-Diels−Alder reaction between the imine and the added diene. This sequence tests our hypothesis that the $InCl_3$ generated in situ is internally recycled to catalyze the cycloaddition reaction, since aza-Diels−Alder reactions between Danishefsky's diene and aldimines require a catalyst. We focused our studies on the $In^0/In^{3+}$ redox couple for the following reasons: (i) $In^0$ is a selective three-electron reductant, (ii) $In^{3+}$, an oxidation product of $In^0$, has been shown to be a competent Lewis acid catalyst,[7,8] and (iii) both $In^0$ and $In^{3+}$ are water-tolerant reagents,[9] allowing the domino cascade to be performed in environmentally benign media.

**Scheme 1.** Domino Nitroarene Reduction−Aldimine Formation−Aza-Diels−Alder Reaction Using Danishefsky's Diene



We first optimized the published procedure for $In^0$-mediated nitrobenzene reduction,[9] which calls for 7 equiv of $In^0$ in a mixture of saturated aq $NH_4Cl$/ethanol.[10] Since only 2 equiv of $In^0$ should provide the six electrons needed, and since lower $[NH_4Cl]$ might lessen acid-mediated diene degradation, we sought to decrease the amount of $In^0$ and $NH_4Cl$ used. In fact, the reduction proceeds in higher yield and purity with decreased $In^0$ equivalents and a lower $[NH_4Cl]$; common byproducts found using 7 equiv of $In^0$, such as nitrosobenzene, azobenzene, and azoxybenzene, are almost entirely absent from reactions using 2−4 equiv of $In^0$ and 1−5 M $NH_4Cl$. Thus, we performed all subsequent reactions using these modified conditions.

We also investigated the latter part of the cascade, the three-component aza-Diels−Alder reaction of aniline, benzaldehyde, and Danishefsky's diene (eq 1), with the goal of identifying reaction conditions compatible with the previous nitrobenzene reduction step. This aza-Diels−Alder reaction has been reported under the following conditions: in anhydrous $CH_3CN$ ($In(OTf)_3$-catalyzed),[7] in water/MeOH ($HBF_4$-catalyzed),[11] in water (AgOTf-catalyzed),[12] and on soluble solid support [$Zn(ClO_4)_2$-catalyzed].[13] Because this reaction has also been reported to proceed in the *absence* of added Brønsted or Lewis acid in methanol,[14] we tested whether catalyst was required. We found that the desired cycloaddition reaction requires catalyst[15] and that various indium salts are competent catalysts in aqueous alcoholic media, consistent with the findings of Frost, Akiyama, and Kobayashi.[7,11,12] The significance of these results is that (i) the aza-Diels−Alder reaction outcompetes diene degradation under these conditions and (ii) nitroarene reduction and the Diels−Alder reaction can be conducted under similar reaction conditions in one pot.



(1)

The key experiment involved testing whether the reduction step can be combined with imine formation and cycloaddition in one-pot. When the nitrobenzene reduction and the three-component aza-Diels−Alder reaction were conducted in one pot (by reacting a mixture of $PhNO_2$, $In^0$, $NH_4Cl$, PhCHO, and Danishefsky's diene in refluxing water/ethanol), we found that diene degradation resulted. However, good results were obtained by carrying out the nitroarene reduction under reflux for 5−12 h, cooling to room temperature, and then adding aldehyde followed by diene.

Best results were obtained using 5−6 equiv of aldehyde (Table 1); unreacted aldehyde could be recovered easily during column chromatography. GC−MS analysis of crude reaction mixtures revealed that $PhNO_2$ was completely

**Table 1.** Results of Domino Nitroarene Reduction−Aldimine Formation−Aza-Diels−Alder Using Danishefsky's Diene

| entry | R | R′ | product | yield (%)[a] |
|---|---|---|---|---|
| 1[b] | Ph | Ph | **1a** | 77 |
| 2[c] | Ph | Ph | **1a** | 84 |
| 3[c] | 4-(MeO)$C_6H_4$ | Ph | **1b** | 99 |
| 4[b] | 4-($O_2N$)$C_6H_4$ | Ph | **1c** | 88 |
| 5[d] | 4-($O_2N$)$C_6H_4$ | Ph | **1c** | 99 |
| 6[b] | 4-(HO)$C_6H_4$ | Ph | **1d** | 66 |
| 7[c] | 2-furanyl | Ph | **1e** | 72 |
| 8[c] | 4-(Me)$C_6H_4$ | Ph | **1f** | 67 |
| 9[d] | Ph | 4-(Cl)$C_6H_4$ | **1g** | 72 |
| 10[d] | Ph | 2-(MeO)$C_6H_4$ | **1h** | 69 |

[a] Isolated yield based on $PhNO_2$. [b] Using 1 equiv of aldehyde. [c] Using 5 equiv of aldehyde. [d] Using 6 equiv of aldehyde.

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(6) (a) Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry*, 2nd ed.; McKillop, A., Ed.; Pergamon: Oxford, UK, 1996; Vol. 5, p 37. (b) Young, D. W.; Comins, D. L. *Org. Lett.* **2005**, *7*, 5661.

(7) Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621.

(8) Loh, T.-P.; Chen, S.-L. *Org. Lett.* **2002**, *4*, 3647.

(9) Moody, C. J.; Pitts, M. R. *Synlett* **1998**, 1028.

(10) While this work was in progress, Banik reported an optimized procedure. See: *Org. Synth.* **2005**, *81*, 188.

consumed and that only traces of unreacted aniline and imine remained. This procedure works well for both electron-rich and electron-poor benzaldehyde derivatives. Entry 6 is noteworthy because it shows that this method tolerates the presence of an unprotected phenol; such substrates are rarely reported in similar studies.[16] Entries 9 and 10 indicate that the reaction is tolerant of electron-donating and electron-withdrawing substituents on the nitroarene. Comparison of the reaction yields to literature values for the stepwise reactions reveals that many of our reactions provide **1** in higher overall yield. The use of aliphatic aldehydes in the reaction afforded intractable mixtures containing only 4−7% of the desired product.[17]

Since it would be useful to obtain the N−H-substituted products, we tested numerous CAN-promoted oxidative dearylationreactions of isomeric *o*-, *m*-, or *p*-methoxyphenyl products **1h**.[18] Unfortunately, all attempts at N-dearylation gave intractable mixtures containing less than 10% of the desired N−H product.[19]

Given that the nitroarene reduction is highly efficient and that the $In^{3+}$ byproduct is a potent water-compatible Lewis acid, we desired to test this internal recycling strategy on a second tandem reaction. The Mannich reaction is a valuable amine-forming reaction that provides access to synthetically and biologically important *β*-amino carbonyl compounds.[20] Furthermore, the Mannich reaction is an ideal choice for application of this method since Loh has described an elegant, asymmetric, $InCl_3$-catalyzed three-component Mannich-type reaction.[8] Therefore, as a test of the scope of this method we designed a domino reaction that would provide access to *β*-amino esters **2a−h**.

The optimized procedure involves reducing nitrobenzene with $In^0/NH_4/NH_4Cl$ in refluxing MeOH/water or EtOH/water, cooling to room temperature, adding aldehyde followed by silyl ketene acetal, and stirring for 24 h (Scheme 2; Table 2). Because we were interested in understanding the efficiency of this reaction, we conducted most experiments using only 1.2 equiv of aldehyde and 2 equiv of silyl ketene acetal. This gave isolated yields of 50−65%. Increasing the number of equivalents of aldehyde or silyl ketene acetal modestly improved the yields (entries 1 and 2). An important feature of this reaction is that it allowed the synthesis of a novel hydroxyl-containing product (entry 6) without the need for protection/deprotection; but as before, use of aliphatic aldehydes was unsuccessful.[17] CAN-promoted N-dearylation reactions of N-PMP protected *β*-amino esters have already been reported to give the desired product in high yield and purity, and thus was not repeated in this study.[21]

**Scheme 2.** Domino Nitroarene Reduction: Mannich-Type Reaction

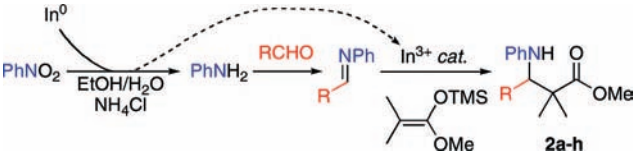

**Table 2.** Results of Domino Nitroarene Reduction: Mannich-Type Reaction Using a Silyl Ketene Acetal

| entry | R | RCHO equivalents | product | yield[a] (%) |
|---|---|---|---|---|
| 1 | Ph | 1.2 | **2a** | 60 |
| 2 | Ph | 5 | **2a** | 72 |
| 3 | 4-(MeO)$C_6H_4$ | 1.2 | **2b** | 63 |
| 4 | 4-Cl$C_6H_4$ | 1.2 | **2c** | 62 |
| 5 | 4-($O_2N$)$C_6H_4$ | 1.2 | **2d** | 61 |
| 6 | 4-(HO)$C_6H_4$ | 1.2 | **2e** | 59 |
| 7 | 2-furanyl | 1.2 | **2f** | 56 |
| 8 | 4-(Me)$C_6H_4$ | 1.2 | **2g** | 65 |
| 9 | 4-($Me_2N$)$C_6H_4$ | 1.2 | **2h** | 50 |

[a] Isolated yield based on $PhNO_2$.

These cascade reactions represent a significant step forward in the development of sustainable synthetic methods to generate valuable products in yields similar to, or better than, stepwise literature precedents. These reactions have the following noteworthy characteristics: (i) they internally recycle a reaction byproduct to perform as a catalyst,[4] (ii) they can be performed using unprotected phenolic substrates, (iii) they utilize low-toxicity solvents and reagents, and (iv) they generate nontoxic byproducts.

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(11) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831.

(12) Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 475.

(13) Guo, H.; Wang, Z.; Ding, K. *Synthesis* **2005**, 1061.

(14) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309.

(15) Reactions containing equimolar amounts of aniline, benzaldehyde, and Danishefsky's diene in aqueous $NH_4Cl$ and either ethanol or methanol were complete (monitored by TLC and GC−MS) in 5 min in the presence of 10 mol % of $In(OTf)_3$, $InCl_3$, or $InBr_3$. In the absence of an $In^{3+}$ salt, or in the presence of $In^0$ or NaOTf, <5% product was detected, even after 24 h.

(16) For example, see: Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476.

(17) Aldehydes tested include propionaldehyde, 2-methylpropionaldehyde, cyclohexanecarboxaldehyde, and pivaldehyde.

(18) Authentic samples of *m*- and *p*-methoxyphenyl products **1h** were used in these experiments. Each of the three isomers (*o*-, *m*-, and *p*-substituted **1h**) were treated with 1−8 equiv of CAN in MeCN/water or MeOH/water at temperatures ranging from −12 °C to rt, under an atmosphere of nitrogen, and also in air. All reactions afforded intractible mixtures containing a poor yield of the desired product. For leading references on N-dearylation, see: (a) Sakai, T.; Yan, F.; Uneyama, K. *Synlett* **1995**, 753. (b) Chi, Y.; Zhou, Y. G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (d) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(19) A reviewer suggested testing $PhI(OAc)_2$ as an alternative method to remove the PMP group from nitrogen. See: (a) Ibrahem, I.; Zou, W.; Casas, J.; Sunden, H.; Córdova, A. *Tetrahedron* **2006**, *62*, 357. Disappointingly, the desired deprotected product was not detected (by $^1H$ NMR spctroscopy) in these reactions.

(20) (a) Risch, N.; Arend, M.; Westermann, B. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol I, p 355 and references therein.

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**Supporting Information Available:** Experimental procedures and spectral data provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (b) Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.; Tomioka, K. *Org. Lett.* **2004**, *11*, 1721.