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Palladium-Catalyzed Internal Nucleophile-Assisted Hydration–Olefin Insertion Cascade: Diastereoselective Synthesis of 2,3-Dihydro-1*H*-inden-1-ones

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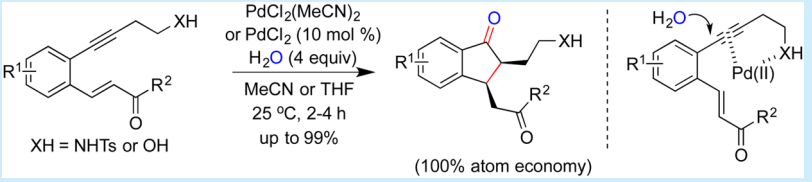
Supporting Information



ABSTRACT: A novel palladium-catalyzed hydration–olefin insertion cascade assisted by internal nucleophiles was developed for the synthesis of biologically significant 2,3-dihydro-1*H*-inden-1-ones under mild conditions. A detailed mechanistic study revealed that the assistance of the internal nucleophiles is crucial to trigger the cascade reaction via nucleopalladation of the alkyne moiety. The overall reaction is equivalent to regioselective hydration of alkynes followed by intramolecular Michael addition. This highly efficient and 100% atom-economical domino sequence afforded *cis*-2,3-disubstituted 2,3-dihydro-1*H*-inden-1-ones in excellent yields (up to 99%) with complete diastereoselectivity.

Palladium-catalyzed domino processes have emerged as promising approaches for the construction of complex molecules by creating several carbon–carbon, carbon–heteroatom bonds and rings through a single synthetic operation.[1,2] These sequential one-pot reactions including domino, cascade, or tandem processes, in general, are considered to be an alternative often superior to classical multistep syntheses since they offer step and atom economy, waste minimization, and the creation of molecular complexity and diversity among other additional advantages.[3] Indeed, on several occasions, molecules that cannot be accessed through conventional methods could be synthesized by means of cascade reactions. Although a large number of strategies including palladium catalysis were employed to initiate these sequential processes, over the past two decades nucleopalladation-initiated cascade reactions were found to be expedient to achieve diverse products elegantly.[4] In particular, intramolecular nucleophilic cyclization of alkynes in the presence of palladium catalysts and the subsequent domino reactions were considered to be a prominent strategy to access complex molecules.[5,6]

2,3-Dihydro-1*H*-inden-1-ones are key structural fragments of a variety of natural products of biological significance represented by the antibacterial and cytotoxic 2-methyl-2,3-dihydro-1*H*-inden-1-ones, pterosin B (**1a**) and C (**1b**)[7] and the polyphenol family of natural compound pauciflorol F (**2**) (Figure 1).[8] In addition, a large number of these analogues

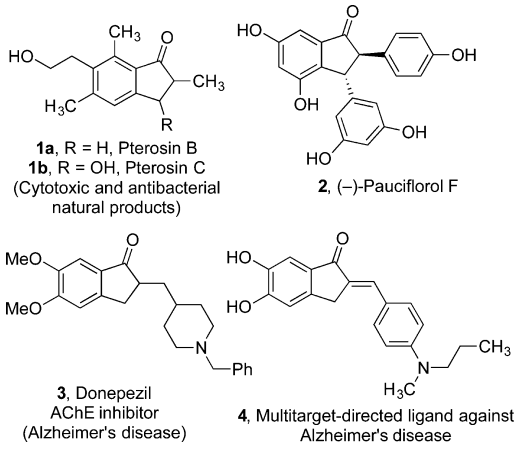


Figure 1. Representative 2,3-dihydro-1*H*-inden-1-one natural products and bioactive compounds.

display a wide range of biological activities. For instance, donepezil (**3**), the Food and Drug Administration (FDA) approved drug used for the treatment of Alzheimer' s disease, acts as an AChE inhibitor,[9] and compound **4** was identified as a multitarget-directed ligand against Alzheimer's disease that

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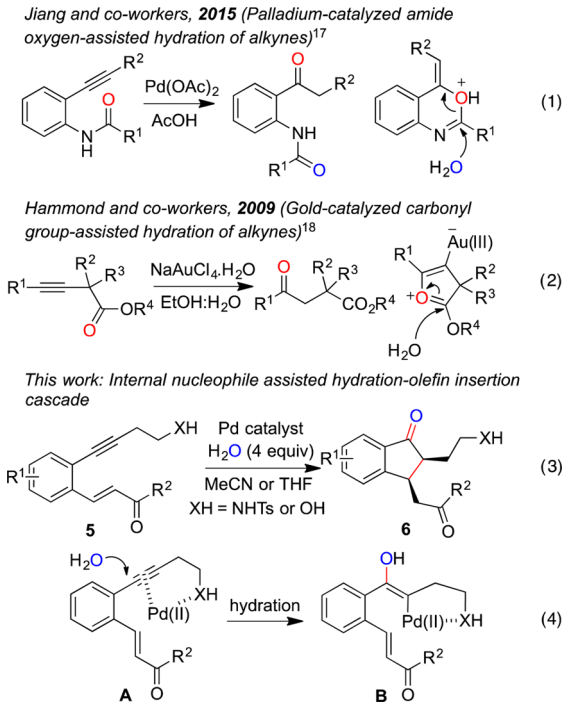
could inhibit self-induced Aβ aggregation.[10] Additional notable biological significance of 2,3-dihydro-1*H*-inden-1-ones includes the cytotoxicity against MCF-7 and estrogen-dependent breast cancer cells[11] and potent aromatase inhibitory activity for breast cancer therapy.[12] Although a considerable number of approaches were developed for the synthesis of 2,3-dihydro-1*H*-inden-1-ones including the direct intramolecular Friedel−Crafts reaction,[13] efficient straightforward synthetic methods toward these compounds are rather limited.[14,15]

Hydration of alkynes is a highly synthetically significant strategy enabling the generation of the ubiquitous and versatile carbonyl functionality.[16] However, the majority of these protocols were restricted to terminal alkynes and often encountered regioselectivity issues for unsymmetrical internal alkynes. Recently, Jiang and co-workers developed an interesting mild procedure involving palladium-catalyzed, amide oxygen-assisted hydration of alkynes regioselectively (Scheme 1, eq 1).[17]

Scheme 1. Pd- and Au-Catalyzed, Neighboring Group-Assisted Hydration of Alkynes

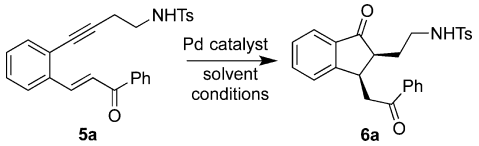


Another notable example for the neighboring group assisted regioselective hydration of alkynes includes the gold-catalyzed carbonyl group-assisted procedure reported by Hammond and co-workers (Scheme 1, eq 2).[18] Inspired by these carbonyl oxygen-assisted hydration reactions, we envisaged a palladium-catalyzed, internal nucleophile (NHTs, OH) assisted hydration−olefin insertion cascade for the synthesis of 2,3-dihydro-1*H*-inden-1-ones **6** starting from the readily accessible alkynes **5** bearing a Michael acceptor (Scheme 1, eqs 3 and 4). To the best of our knowledge, this is a unique example of a palladium-catalyzed, neighboring group assisted cascade reaction for the synthesis of 2,3-dihydro-1*H*-inden-1-ones.

To test the feasibility of the proposed domino sequence, the synthesized alkyne **5a** (SI) was treated with 10 mol % of $Pd(OAc)_2$ in various solvents and $PdCl_2(PPh_3)_2$ in acetonitrile in the presence of four equivalents of water. However, only traces of the expected product **6a** were observed even after 24 h.

To our delight, $Pd(OTf)_2$ in acetonitrile triggered the cascade smoothly to afford 2,3-dihydro-1*H*-inden-1-one **6a** in 83% yield in 5 h at 25 °C. Further exploration of catalyst revealed that $PdCl_2$ and $PdCl_2(MeCN)_2$ were found to be excellent to furnish the product in nearly quantitative yields in acetonitrile in a span of 2 h reaction time (Table 1, entries 1−3). Other tested solvents

Table 1. Optimization of Reaction Conditions for the NHTs-Assisted Cascade Reaction[a]



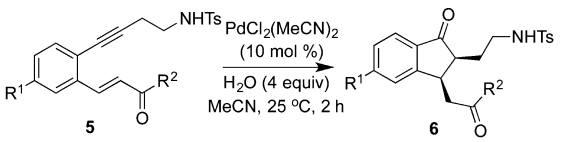
entry	catalyst (10 mol %)	solvent	reaction time (h)	yield of **6a**[b] (%)
1	$Pd(OTf)_2$	MeCN	5	83
2	$PdCl_2$	MeCN	2	94
3[c]	$PdCl_2(MeCN)_2$	MeCN	2	96, 94[d]
4	$Sc(OTf)_3$	MeCN	24	73

[a]All reactions were carried out with **5a** (0.25 mmol), water (4 equiv), and catalyst (10 mol %) in 3 mL of solvent at 25 °C. [b]Isolated yield. [c]Optimized reaction conditions. [d]5 mol % of catalyst was used.

including dioxane, THF, DCM, and DCE furnished the products in high yields compared to toluene and ethanol (see the SI for detailed optimization). Interestingly, the Lewis acid $Sc(OTf)_3$ was also able to catalyze the cascade reaction, albeit in lower yield (73%, entry 4). Finally, we tested the reaction with decreased catalyst loading (5 mol %) and found that the product was obtained in comparable yield after relatively longer reaction time (5 h, 94%, entry 3).

Having optimized the reaction conditions for the domino sequence, we then explored the scope and limitations of the protocol with a number of substrates, and the results are summarized in Scheme 2. Initially, we investigated the nature of

Scheme 2. Substrate Scope for the NHTs-Assisted 2,3-Dihydro-1*H*-inden-1-one Synthesis



6a, R^1 = H, R^2 = Ph (96%); **6b**, R^1 = H, R^2 = 4-OMe-C_6H_4- (94%)
6c, R^1 = OMe, R^2 = 3,4-$(OMe)_2$-C_6H_3- (97%)
6d, R^1 = OMe, R^2 = Ph (82%); **6e**, R^1 = OMe, R^2 = 2,4-$(Cl)_2$-C_6H_3- (97%)
6f, R^1 = OMe, R^2 = 2-Naph (95%); **6g**, R^1 = OMe, R^2 = 2-Furyl (96%)
6h, R^1 = OMe, R^2 = *n*-Pr (99%); **6i**, R^1 = H, R^2 = Me (84%)

the R^2 substituents and discovered that, besides the unsubstituted phenyl group, both electron-donating and -withdrawing substituents were well tolerated to afford the products in excellent yields (**6a−c** and **6e**). Likewise, naphthyl (**6f**) and 2-furyl (**6g**) substituents were also equally effective. In addition, alkyl substituents at the R^2 position afforded the corresponding 2,3-dihydro-1*H*-inden-1-one in good to excellent yields (**6h** and **6i**). The reaction was equally effective when strong electron-releasing substituents (R^1) were placed on the aromatic ring. The *cis* stereochemistry of the 2,3-disubstituted 2,3-dihydro-1*H*-inden-1-ones **6** was confirmed by ^1H NMR coupling constant values ($J_{H_2-H_3}$ = 3.3 Hz).

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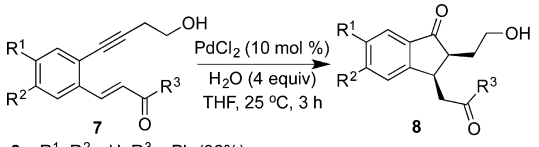
With these positive results in hand, in order to explore the generality of the nucleophile-assisted cascade, we next investigated the domino sequence with a substrate tethered with a hydroxyl nucleophile **7a**. Although success was obtained with the NHTs substituent, the preliminary results with the hydroxyl substrate **7a** were discouraging. Treatment of compound **7a** with $PdCl_2(MeCN)_2$ under the previously optimized reaction conditions furnished a mixture of 2,3-dihydro-1*H*-inden-1-one **8a** (18%) and the diastereomeric spiroketal **9** being the latter the major product (59%). Promisingly, changing the solvent to THF inverted the product ratio to provide compound **8a** as the major product with an isolated yield of 72%. A brief solvent screening involving DCM, toluene, and dioxane resulted in no significant improvement. Interestingly, the reaction in 1:1 THF/H_2O eliminated the spiroketal completely and yielded 83% of the product **8a**. Subsequently, another promising catalyst identified in Table 1, $PdCl_2$, also afforded only the expected product in 86% yield. Final screening of solvents in the presence of $PdCl_2$ and other catalysts such as $Pd(OAc)_2$, $Pd(OTf)_2$, and $PdCl_2(PPh_3)_2$ were not effective in further improving the reaction (see the SI for detailed optimization).

Next, we studied the scope of the hydroxyl-assisted domino reaction as shown in Scheme 3. Similar to the NHTs-assisted

Scheme 3. Substrate Scope for the Hydroxyl-Assisted 2,3-Dihydro-1*H*-inden-1-one Synthesis



8a, R^1, R^2 = H, R^3 = Ph (86%)
8b, R^1, R^2 = H, R^3 = 4-OMe-C_6H_4- (75%)
8c, R^1, R^2 = H, R^3 = 4-Cl-C_6H_4- (73%)
8d, R^1, R^2 = H, R^3 = 2,4-$(Cl)_2$-C_6H_3- (70%)
8e, R^1, R^2 = H, R^3 = 2-Naph (78%)
8f, R^1, R^2 = H, R^3 = Me (81%)
8g, R^1 = Me, R^2 = H, R^3 = Ph (81%)[a]
8h, R^1 = Me, R^2 = H, R^3 = 2-Thienyl (84%)[a]
8i, R^1 = H, R^2 = OMe, R^3 = Ph (62%)[a]
8j, R^1,R^2 = -OCH_2O-, R^3 = 2-Thienyl (65%)[a]

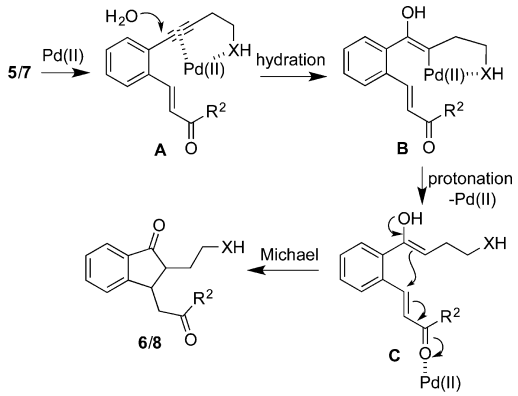
[a]The reactions were carried out with **7** (0.5 mmol), water (4 equiv), $PdCl_2$ (10 mol %), and $InCl_3$ (10 mol %) in 6 mL of THF at 25 °C for 4 h.

reactions, the hydroxyl group was also effective in assisting the cascade reaction to yield the corresponding 2,3-dihydro-1*H*-inden-1-ones **8** in good yields. The R^2 positions tolerated a wide variety of substituents including aryl, heteroaryl, naphthyl, and methyl groups, and the other aryl ring was also replaced by methyl, methoxyaryl, and piperonyl units.

A plausible mechanism for the internal nucleophile-assisted, palladium-catalyzed cascade process is shown in Scheme 4. Initial coordination of the palladium(II) species with the alkyne moiety of compound **5/7**, assisted by the tethered nucleophile, followed by regioselective hydration affords intermediate **B**. Subsequent protonation of intermediate **B** furnishes enol **C**, which undergoes intramolecular Michael addition to afford the products **6/8**. Alternatively, olefin insertion of intermediate **B** followed by protonation would afford the products.

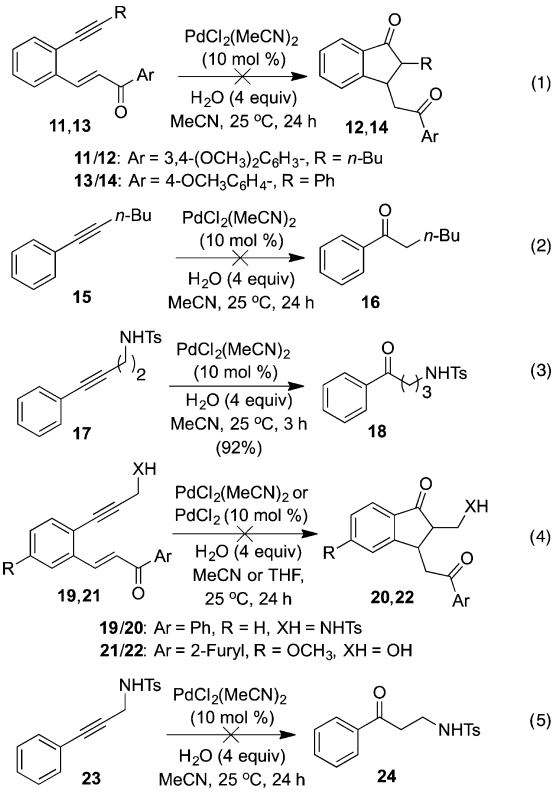
In order to understand the mechanism of the reaction and to demonstrate the significance of the internal nucleophile assistance in the cascade process, we carried out a set of control

Scheme 4. Proposed Mechanism for the Nucleophile-Assisted Cascade Reaction



experiments (Scheme 5). The 1-hexyne- and phenylacetylene-derived substrates **11** and **13** completely failed to afford 2,3-

Scheme 5. Control Experiments to Support the Proposed Mechanism



dihydro-1*H*-inden-1-ones **12** and **14**, respectively, under the optimized reaction conditions (Scheme 5, eq 1). Similarly, alkyne **15** did not provide the corresponding hydration product **16** (Scheme 5, eq 2). However, as shown in eq 3, a simple alkyne bearing the NHTs substituent **17** furnished the corresponding ketone **18** in 92% yield in 3 h. These results revealed that the presence of the internal nucleophile is a crucial prerequisite to trigger the cascade reaction. In the absence of the tethered nucleophile no product formation was noticed, thus confirming the progress of the reaction via species **A** and **B**. Subsequently, the reactivity of alkynes **19**, **21**, and **23**, which are expected to generate strained four-membered coordination intermediates,

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were also tested under the optimized conditions, and no cyclized products were formed even after 24 h (Scheme 5, eqs 4 and 5). Thus, the position of the tethered nucleophile in the alkyne chain is pivotal to trigger the cascade. Although the proposed mechanism is convincing and supported by the control experiments, the intramolecular nucleopalladation-initiated mechanism involving a dihydropyrrole/dihydrofuran intermediate cannot be completely ruled out (see the SI for a detailed mechanism).

The formation of spiroketal **9** could be explained through a dihydrofuran intermediate generated via palladium-catalyzed nucleopalladation followed by protonation steps (SI). Although one of the diastereomeric spiroketals **9a** was isolated and characterized, the second diastereomer was inseparable in pure form.

In conclusion, we have developed a highly efficient palladium-catalyzed domino sequence equivalent to the regioselective hydration of alkynes followed by intramolecular Michael addition for the synthesis of 2,3-dihydro-1*H*-inden-1-ones under mild conditions. Mechanistic studies revealed that the assistance of the tethered nucleophiles (NHTs and OH) is essential to trigger the hydration−olefin insertion cascade to afford the target compounds in excellent yields. Furthermore, the reaction was found to be highly diastereoselective, furnishing only the *cis* diastereomer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01623.

Experimental procedures, detailed optimization, characterization data, alternative mechanism, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor J. Carlos Menéndez on the occasion of his 56th birthday.

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