

Direct Synthesis of 1-Indanones via Pd-Catalyzed Olefination and Ethylene Glycol-Promoted Aldol-Type Annulation Cascade

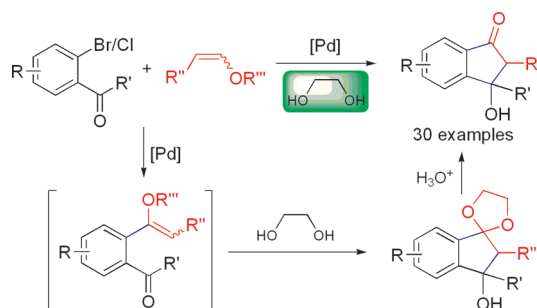
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ABSTRACT



A wide range of multisubstituted 1-indanones of potential pharmaceutical use were synthesized in a one-pot fashion in moderate to excellent yields via palladium catalysis in ethylene glycol. The Heck reaction first installs an enol functionality on the aromatic ring; this is followed by an ethylene glycol promoted aldol-type annulation with a neighboring carbonyl group, resulting in the formation of various 1-indanones.

Indanone and related indan structures constitute the core of a large number of bioactive natural products and pharmaceutically interesting molecules (Figure 1).¹ Some representative examples include the pterosin family, known for their cytotoxic and antibacterial activities,^{1b} the antihypertensive drug (+)-Indacrinone,^{1k} the antidepressant Indatraline,^{1j} the HIV protease inhibitor Indinavir,¹ⁱ and the acetylcholinesterase inhibitor Donepezil (Aricept).^{1h}

Several methods have been reported to access the indanone framework, including intramolecular Friedel–Craft cyclization,² hydroacylation of 2-formyl styrenes,³ isomerization of α -aryl-propargyl alcohols followed by cyclization,⁴ and other procedures.⁵ However, most of these require preformed substrates via multistep synthesis. Recently, Hallberg and Larhed reported a simple one-pot Heck–aldol annulation reaction between salicylaldehyde triflates and 2-hydroxy-ethyl vinyl ether, affording indanone ketals in moderate yields.⁶

In the course of our study into regioselective Heck reactions,⁷ we discovered that the Pd(OAc)₂-dppp-catalyzed [dppp = 1,3-bis(diphenylphosphino)propane] arylation of

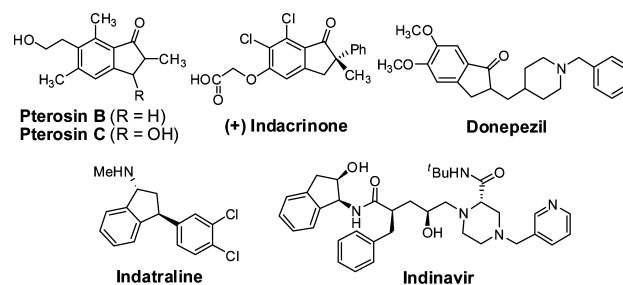
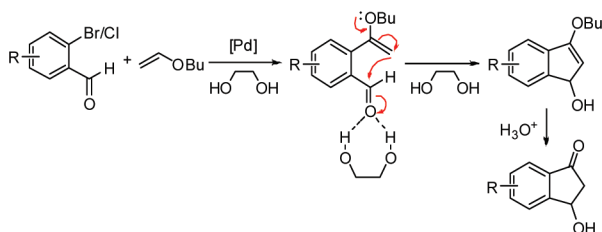


Figure 1. Representative examples of indanone and indan-containing compounds.

electron-rich olefins proceeds efficiently in alcohol solvents, especially ethylene glycol (EG), furnishing branched olefins in excellent selectivity.^{7a,b} In continuing the research, we thought that if readily available 2-halobenzaldehydes were used to arylate the cheap *n*-butyl vinyl ether, the resulting branched vinyl ether products might undergo intramolecular nucleophilic attack at the carbonyl group,⁸ yielding 1-indanones in a one-pot fashion (Scheme 1). To realize this

Scheme 1. Working Hypothesis for Accessing 1-Indanones



seemingly easy, Heck–aldol-type cascade, the use of EG as solvent could be the key, as it would be expected to facilitate both the Heck arylation^{7a,b} and the nucleophilic attack

(1) (a) Mahalingam, A. K.; Axelsson, L.; Ekegren, J. K.; Wannberg, J.; Kihlström, J.; Unge, T.; Wallberg, H.; Samuelsson, B.; Larhed, M.; Hallberg, A. *J. Med. Chem.* **2010**, *53*, 607. (b) Wessig, P.; Teubner, J. *Synlett* **2006**, 1543, and references therein. (c) Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932. (d) Yao, W.; Wasserman, Z. R.; Chao, M.; Reddy, G.; Shi, E.; Liu, R.-Q.; Covington, M. B.; Arner, E. C.; Pratta, M. A.; Tortorella, M.; Magolda, R. L.; Newton, R.; Qian, M.; Ribadeneira, M. D.; Christ, D.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2001**, *44*, 3347. (e) Nagle, D. G.; Zhou, Y.-D.; Park, P. U.; Paul, V. J.; Rajbhandari, I.; Duncan, C. J. G.; Pasco, D. S. *J. Nat. Prod.* **2000**, *63*, 1431. (f) Hong, B. C.; Sarshar, S. *Org. Prep. Proced. Int.* **1999**, *31*, 1. (g) Lago, M. A.; Luengo, J. I.; Peishoff, C. E.; Elliot, J. D. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1996; Vol. 31, p 81. (h) Sugimoto, H.; Imura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821. (i) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443. (j) Bøgesø, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817. (k) deSolms, S. J.; Woltersdorf, O. W., Jr.; Cragoe, E. J., Jr. *J. Med. Chem.* **1978**, *21*, 437.

(2) For recent examples, see: (a) Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* **2004**, *45*, 1741. (b) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316, and references therein.

(3) Kundu, K.; McCullagh, J. V.; Morehead, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 16042.

(4) (a) Shintani, R.; Yashio, K.; Nakamura, T.; Okamoto, K.; Shimada, T.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 2772. (b) Shintani, R.; Takatsu, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 3735.

(5) (a) Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804. (b) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2006**, *8*, 3379. (c) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 9253. (d) Petriguet, J.; Roisnel, T.; Grée, R. *Chem.—Eur. J.* **2007**, *13*, 7374. (e) Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett.* **2008**, *10*, 1783.

(6) (a) Bengtson, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 5854. (b) Arefalk, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2005**, *70*, 938.

(7) (a) Ruan, J.; Iggo, J. A.; Berry, N. G.; Xiao, J. *J. Am. Chem. Soc.* **2010**, *132*, 16689. (b) Zeynab, H.; Ruan, J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 5555. (c) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510. (d) Mo, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152. (e) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751.

(8) For intermolecular aldol-type reactions of vinyl ethers, see: Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

through hydrogen bonding with the halide anions and the carbonyl oxygen.^{9,10} We report herein that 1-indanones can indeed be readily accessed via this cascade reaction.

Using 2-bromobenzaldehyde (**1a**) and *n*-butyl vinyl ether (**2a**) as substrates and reaction conditions similar to those established for other aryl bromides,^{7b} we quickly found that under the catalysis of Pd-dppp in EG, the indanone (**3a**) could be isolated in an excellent yield of 85% following acid hydrolysis (entry 1, Table 1). To our surprise, however, the

Table 1. Screening Reaction Conditions for the Cascade Reaction^a

entry	Pd(OAc) ₂ (mol %)	solvent	yield (%) ^b
1	1	EG	85
2	1	EG	86 ^c
3	2	DMF	<5
4 ^d	2	DMF	42
5	2	DMSO	<5

^a Reaction conditions: (1) **1a** (1 mmol), **2a** (3 mmol), Pd(OAc)₂ (1 mol %), dppp (1.5 mol %), Et₃N (1.5 mmol), solvent (4 mL), 115 °C, 16 h; (2) 3 M HCl, rt, 1 h. ^b Isolated yields of **3a**. ^c No acid hydrolysis; isolated yields of **3aa**. ^d 1.5 mmol [H₂NⁱPr₂][BF₄] was added.

indanone ketal (**3aa**) was isolated in 86% yield when the acid treatment was omitted (entry 2), indicative of **3a** being formed from **3aa**. Apart from the mechanistic implication, this provides a simple method for synthesizing ketal-protected indanones, which were obtained in moderate yields via Hallberg and Larhed's method.^{6a} For comparison, the reaction was also performed in DMF and DMSO. As can be seen from Table 1, little desired product was formed (entries 3 and 5), most likely due to the Heck arylation being sluggish.^{7a,b} Introducing the hydrogen bond donor [H₂NⁱPr₂][BF₄], which has been shown to promote the Heck reaction,^{7d} led to an increased but still unsatisfactory yield of 42% for **3a** (entry 4), indicating that EG is highly effective in catalyzing both the Heck and annulation reactions.

Under the reaction conditions established above (entry 1, Table 1), we then explored the reactions of **2a** with a range of 2-bromobenzaldehydes (**1a–h**). As summarized in Table 2, the reaction afforded good to excellent yields of 3-hydroxy-1-indanones (**3a–h**), tolerating electronically different substituents on the aromatic ring. However, when salicylaldehyde triflate was used,⁶ **3a** was obtained only in 12% yield, due to decomposition of the triflate in EG.

With the success in aryl bromides, we turned our attention to the chloride analogues. However, under the same condi-

(9) Ethylene glycol is an excellent hydrogen bond donor: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003.

(10) The carbonyl may be activated through a single-point hydrogen bonding; see ref 7a. Also see: Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

Table 2. Heck–Aldol Annulation Reaction of ArBr (**1a–h**) with *n*-Butyl Vinyl Ether (**2a**)^a

entry	ArBr	product	yield (%) ^b
1			85
2			87
3			65
4			70
5			84
6			85
7			82
8			80

^a Reaction conditions: (1) **1** (1 mmol), **2a** (3 mmol), Pd(OAc)₂ (1 mol %), dppp (1.5 mol %), Et₃N (1.5 mmol), EG (4 mL), 115 °C, 16 h; (2) 3 M HCl, rt, 1 h. ^b Isolated yields.

tions as those for the bromides, the reaction of 2-chlorobenzaldehyde (**1i**) with **2a** led to only 6% of indanone **3a**. A slightly higher yield of 15% was obtained at 145 °C. We have recently shown that the Pd(OAc)₂-4-MeO-dppp system [4-MeO-dppp = 1,3-bis(bis(4-methoxyphenyl)phosphino)propane] is very efficient for the Heck arylation with various aryl chlorides in EG.^{7a} Bearing this in mind, we changed the ligand from dppp to 4-MeO-dppp and were gratified to obtain **3a** in 70% isolated yield at 145 °C at a catalyst loading of 2 mol % (entry 1, Table 3). The yield (55%) was lower at 115 °C. Subsequently, other substituted 2-chlorobenzaldehydes **1j–q** were examined. The results are shown in Table 3. As can be seen, moderate to good yields of indanones **3** were obtained, albeit slightly lower than those from the bromides. Worthy of noting is that the sterically more demanding substrates **1j** and **1o–q** successfully underwent the Heck-annulation cascade, affording good yields (entries 2, 7–9). Also of interest is that 6-chloro-3-hydroxy-1-indanone **3j** was formed in 50% yield (entry 4),

Table 3. Heck–Aldol Annulation of ArCl (**1i–q**) with **2a**^a

entry	ArCl	product	yield (%) ^b
1			70
2			62
3			51
4			50
5			53
6			72
7			70
8			63
9			65

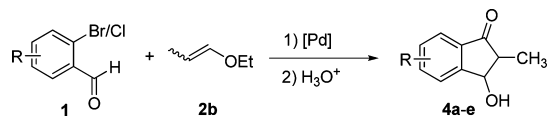
^a Reaction conditions: (1) **1i–q** (1 mmol), **2a** (3 mmol), Pd(OAc)₂ (2 mol %), 4-MeO-dppp (3 mol %), Et₃N (1.5 mmol), EG (4 mL), 145 °C, 16 h; (2) 3 M HCl, rt, 1 h. ^b Isolated yields.

showing that the sterically less accessible *ortho*-chloride is more reactive when using 2,4-dichlorobenzaldehyde (**1l**).

To extend further the substrate scope, we next investigated the reaction of a bulkier vinyl ether, 1-ethoxyprop-1-ene (**2b**), with various 2-halobenzaldehydes **1** under the same conditions for the respective halides. These reactions required a longer reaction time of 20 h, however. As shown in Table 4, a range of 2-methyl-3-hydroxy-1-indanones **4a–e** were produced in moderate yields, as a mixture of *cis*- and *trans*-isomers. The reaction provides a straightforward way for the total synthesis of pterosins.^{1b}

2'-Haloaryl ketones were also demonstrated to be viable substrates, affording quaternary alcohols (Table 5). Using the ketones **5a–g** as substrates, 3-hydroxy-1-indanones **6a–d** were obtained in moderate to good yields; even the bulky 2'-bromo- or 2'-chlorobenzophenones underwent the annulation (entries 3 and 7). There are only a few methods for synthesizing 3,3'-

Table 4. Heck–Aldol Annulation of ArX with 1-Ethoxyprop-1-ene (**2b**)^a



entry	ArBr/ArCl	product	yield (%) ^b
1			55
2			40
3			58
4			55
5			50
6			45

^a The reaction conditions were the same as those in Table 2 for aryl bromides and Table 3 for aryl chlorides, except for using **2b** and 20 h reaction time. ^b Isolated yields.

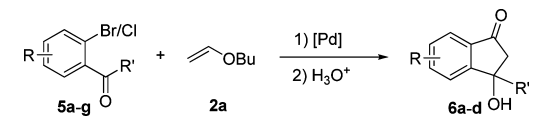
disubstituted 1-indanones,^{2b,4b,5b} and to the best of our knowledge, this is the first time that 1-indanones bearing a quaternary 3-hydroxy functionality have been reported.

As aforementioned, the reaction of **1a** with **2a** in EG led to **3aa** being isolated in high yield, instead of the cyclic enol ether shown in Scheme 1, if acid hydrolysis was not performed (entry 2, Table 1). Taking this into account, a mechanism for the cascade reaction is suggested (Scheme 2). The Heck reaction affords the branched enol ether product, which undergoes nucleophilic attack at the carbonyl group activated by EG via hydrogen bonding.^{9,10} The resulting oxonium ion reacts with EG, giving rise to a mixed ketal. Elimination of BuOH under acid catalysis then leads to **3aa**, and finally, acidic treatment of **3aa** forms **3a**. Similar mixed and cyclic ketals have previously been observed when the Heck reaction was run in diols.¹¹

In summary, we have developed a new protocol for the one-pot synthesis of pharmaceutically interesting, multisubstituted 1-indanones. The protocol centers on a Heck–aldol cascade, with Pd catalyzing the Heck arylation while EG facilitates both the arylation and the aldol-type annulation. Further study into the mechanism and enantioselective synthesis of 3-hydroxy-1-indanones is underway.

(11) McConville, M.; Blacker, J.; Xiao, J. *Synthesis* **2010**, 349.

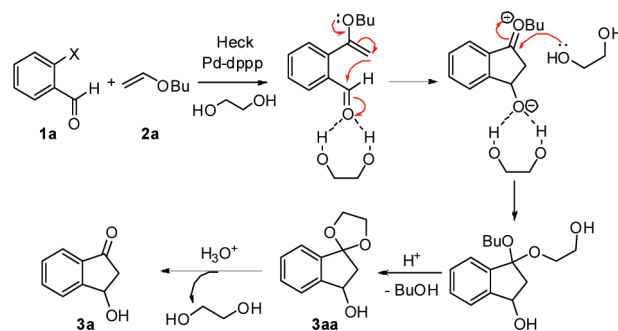
Table 5. Heck–Aldol Annulation of 2'-Haloaryl Ketones (**5a–g**) with **2a**^a



entry	ArBr/ArCl	product	yield (%) ^b
1			78
2			73
3			50
4			75
5			55
6			72
7			40

^a The reaction conditions were the same as those in Table 4. ^b Isolated yields.

Scheme 2. Suggested Mechanism for the Heck–Aldol Annulation



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Supporting Information Available: Experimental details and characterization data of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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