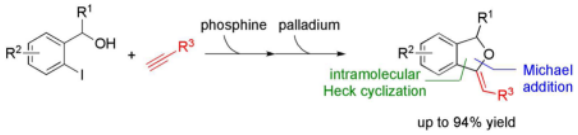
Published in final edited form as:
Org Lett. 2012 July 6; 14(13): 3264–3267. doi:10.1021/ol301154f.

Phosphine/Palladium-Catalyzed Syntheses of Alkylidene Phthalans, 3-Deoxyisoochracinic Acid, Isoochracinic Acid, and Isoochracinol

Yi Chiao Fan and **Ohyun Kwon***
Department of Chemistry and Biochemistry, University of California, Los Angeles, California, 90095-1569

Abstract



In this study we used sequential-catalysis—PPh_3-catalyzed nucleophilic addition followed by Pd(0)-catalyzed Heck cyclization—to construct complex functionalized alkylidene phthalans rapidly, in high yields, and with good stereoselectivities (E:Z ratios of up to 1:22). The scope of this Michael–Heck reaction includes substrates bearing various substituents around the alkylidene phthalan backbone. Applying this efficient sequential-catalysis, we accomplished concise total syntheses of 3-deoxyisoochacinic acid, isoochracinic acid, and isoochracinol.

The rapid and efficient transformation of simple chemical building blocks into complex molecular structures remains one of the greatest challenges in synthetic organic chemistry. Traditional one-pot/one-transformation chemical processes are less than ideal for many reasons, including time, materials, and cost. Chemists are fascinated by tandem, cascade, and sequential-catalysis processes because they eliminate the need to isolate and purify intermediates.[1] Accordingly, many groups have developed multi-catalyst systems that promote two or more chemical transformations in a single flask.[2] These multi-step/single-flask operations minimize the time and cost of delivering complex molecular architectures from simple starting materials in a facile and efficient manner.

As part of a program aimed at advancing the scope of nucleophilic phosphine catalysis[3] and realizing its potential for efficient multi-step/single-flask transformations, our group has developed a sequential-catalytic process, namely a tandem nucleophilic phosphine/palladium-catalyzed reaction sequence, for the construction of complex heterocycles from readily obtainable starting materials.

At present there are few routes available for the synthesis of highly functionalized phthalans, with most of them requiring reactions of elaborate disubstituted alkynes through iodocyclization,[4] intramolecular Michael addition,[5] or Wacker-type oxypalladation involving the use of palladium.[6] One-pot transformations, while rare,[7] are restricted in substrate scope and provide low yields and low stereoselectivity. Therefore, the challenge

ohyun@chem.ucla.edu.

Supporting Information Available: Characterization data; copies of ^1H, ^{13}C, and NOSEY NMR spectra for all compounds; representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

remains to develop concise one-pot procedures for the production of highly functionalized alkylidene phthalans with high efficiency and stereoselectivity.

In this regard, we became interested in the tertiary phosphine–assisted nucleophilic Michael addition of alcohols onto activated acetylenes to give functionalized β-benzyloxy acrylates.[8,9] With the goal of using these highly versatile β-benzyloxy acrylate intermediates for further generation of molecular complexity, we envisioned a subsequent cross-coupling event to take advantage of the compatibility of phosphines and palladium. Initially, in the presence of a phosphine, Michael addition of *o*-iodobenzyl alcohol to a propiolate generates a β-(*o*-iodobenzyloxy)acrylate. Then, employing the pre-existing phosphine as a ligand to promote the reduction of Pd(II) to Pd(0),[10] the β-(*o*-iodobenzyloxy)acrylate undergoes intramolecular Heck cyclization.[11] Joining these two transformations into a one-pot Michael–Heck procedure allows the synthesis of highly functionalized alkylidene phthalans.

We suspected that a tandem Michael–Heck approach would offer rapid access to a group of rare fungal metabolites—isoochracinol (**1**), isoochracinic acid (**2**), and 3-deoxyisoochracinic acid (**3**)—from the genus *Cladosporium*.[12] Among these compounds, 3-deoxyisoochracinic acid (**3**) exhibits antibacterial activity, inhibiting the growth of *B. subtilis*, a known cause of food poisoning (Figure 1).[13]

Before proceeding to the one-pot transformation, we investigated the efficiency of each reaction step. Slowly adding methyl propiolate into a solution of *o*-iodobenzyl alcohol and PPh_3 in MeCN under reflux under Ar provided methyl β-(*o*-iodobenzyloxy)acrylate in 99% isolated yield after purification (Scheme 1). This Michael reaction produced a 10:1 mixture of E and Z isomers, which we separated and characterized unambigiously.[14] We then subjected the mixture of β-(*o*-iodobenzyloxy)acrylates to Heck conditions, cleanly affording the target annulation product **7a**, isolated as the major (Z) isomer.[15]

To incorporate this nucleophilic phosphine-catalyzed Michael addition into a sequential-catalysis process, we explored the possibility of executing the Pd(0)-catalyzed Heck cyclization without isolation of the β-(*o*-iodobenzyloxy)acrylate intermediate. First, using PPh_3 to catalyze the Michael addition, we formed the desired Michael adduct rapidly. Next, were introduced $Pd(OAc)_2$, tetrabutylammonium chloride (TBACl), and K_2CO_3 to the same flask. After 8 h, we isolated the major cyclic alkylidene phthalan **7a** in 76% yield as the Z isomer, with complete consumption of the β-(*o*-iodobenzyloxy)acrylate intermediate **6** (Scheme 2). The one-pot procedure was operationally simpler and more efficient (76% yield) than the two-pot process (61%).

Based on the yields of our two-pot synthesis, we targeted the Heck reaction to optimize the overall reaction efficiency (Scheme 1). The reaction rate decreased dramatically, providing only a trace of product, in the absence of TBACl (Table 1, entries 1 and 2), which is known to improve the yields of Heck reactions.[16] From a screening of palladium catalysts, $Pd(OAc)_2$ appeared to be the optimal Heck cyclization catalyst in the presence of PPh_3, TBACl, and K_2CO_3 in MeCN under Ar (entry 6). To further improve the product yield, we screened several bases, with $NaHCO_3$ emerging to give the highest efficiency, providing the Heck reaction product in 80% yield (entry 8). In the subsequent one-pot procedure, we obtained the phthalan **7a** in 74% yield (Table 2, entry 1).

These conditions were also viable for reactions of the alcohol component with various substituents on the benzene ring (Table 2). Accordingly, we isolated highly functionalized alkylidene phthalans as Z isomers in good to excellent yields. Both electron-donating and -withdrawing substituents were compatible with the optimized conditions, although reactions with strongly withdrawing trifluoromethyl and nitro functionalities provided lower yields of

the desired alkylidene phthalans (entries 7 and 8). *o*-Iodobenzyl alcohols bearing substituents ortho to the iodine atom produced the corresponding alkylidene phthalans in excellent yields and high levels of stereoselectivity (entries 11 and 12).

Next, we evaluated the effects of various substituents at the benzylic position of the pronucleophile **4** (Table 3). Monosubstituted pronucleophiles afforded the corresponding alkylidene phthalans in good yields (entries 1–4). Notably, the α-(trifluoromethyl)benzyl alcohol **4p** underwent this sequential-catalysis smoothly (entry 4). The gem-dimethyl–substituted benzyl alcohol **4q** did not provide its desired product, presumably because of the steric bulk of the tertiary alcohol nucleophile (entry 5).

We also subjected an array of electron-deficient acetylenes to the optimized Michael–Heck reaction conditions (Table 4). In addition to benzyl propiolate (**5b**, entries 1–5), acetylenes with electron-withdrawing acyl and sulfonyl groups afforded their corresponding alkylidene phthalans in good yields (entries 6–10). The ethynyl phosphonate **5f** was also a suitable substrate under the reaction conditions, albeit providing the phthalan **9k** in low yield (entry 11).

Scheme 3 presents a plausible mechanism for the Michael–Heck reaction, which commences with nucleophilic addition of PPh_3 onto the electron-deficient acetylene **5a**. The resulting phosphonium vinyl anion **10** deprotonates the pronucleophile **4a** to provide the anion **11**, which undergoes conjugate addition to another molecule of the acetylene **5a** to give the intermediate **12**,[17,18] protonation of which gives the β-(*o*-iodobenzyloxy)acrylate **6**. This final protonation step produces the alkoxide **11** and propagates the reaction. The Michael adduct **6** can also be generated through an addition/elimination pathway involving **11** and **13** via **14**.

With the introduction of $Pd(OAc)_2$, the pre-existing PPh_3 becomes a ligand for Pd(II), reducing it to Pd(0). The active Pd(0) oxidatively inserts into the aryl iodide of the Michael adduct **6**, generating the arylpalladium(II) complex **15**, which undergoes carbopalladation in a 5-exo-trig manner to form **16**. After rotation around the C–C single bond, **17** undergoes stereospecific syn β-hydride elimination to generate the alkylidene phthalan **7a** and the palladium(II) halide **18**, which, after reductive elimination of HI, regenerates the active Pd(0) species.

Applying the concept of Michael–Heck sequential-catalysis, we realized brief syntheses (Scheme 4) of isoochracinol (**1**), isoochracinic acid (**2**), and 3-deoxyisoochracinic acid (**3**).[12,13] Starting from the alkylidene phthalan **9e**, global debenzylation and hydrogenation of the olefin generated the natural fungal metabolite 3-deoxyisoochracinic acid (**3**) in quantitative yield. Furthermore, benzylic oxidation[19] of 3-deoxyisoochracinic acid (**3**) with CrO_3 and AcOH afforded isoochracinic acid (**2**). BH_3·THF-mediated chemoselective reduction of the carboxylic acid moiety of isoochracinic acid (**2**) delivered isoochracinol (**1**).

In conclusion, we have developed Michael–Heck sequential-catalysis into an efficient and facile route toward highly functionalized (*Z*)-alkylidene phthalans from readily accessible *o*-iodobenzyl alcohols and electron-deficient acetylenes. The Michael–Heck technology provided the alkylidene phthalan intermediate **9e**, which allowed rapid and efficient syntheses of the natural fungal metabolites isoochracinol (**1**), isoochracinic acid (**2**), and 3-deoxyisoochracinic acid (**3**). This method provides an economical (time, materials, cost) gateway to functionalized (*Z*)-alkylidene phthalans that are amenable to the synthesis of more-complex systems, including natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the NIH (R01GM071779 and P41GM081282).

References

1. Tietze, LF.; Brasche, G.; Gericke, K. Domino Reactions in Organic Synthesis. Wiley-VCH; Weinheim, Germany: 2006.
2. For selected recent reviews on multicatalytic concepts, see: Ajamian A, Gleason JL. Angew Chem, Int Ed. 2004; 43:3754.Lee JM, Na Y, Han H, Chang S. Chem Soc Rev. 2004; 33:302. [PubMed: 15272370] Wasilke JC, Obrey SJ, Baker RT, Bazan GC. Chem Rev. 2005; 105:1001. [PubMed: 15755083] Enders D, Grondal C, Hüttl MRM. Angew Chem Int Ed. 2007; 46:1570.Chapman CJ, Frost CG. Synthesis. 2007:1.Walji AM, MacMillan DWC. Synlett. 2007:1477.
3. Reviews of phosphine catalysis: Lu X, Zhang C, Xu Z. Acc Chem Res. 2001; 34:535. [PubMed: 11456471] Valentine DH Jr, Hillhouse JH. Synthesis. 2003:317.Methot JL, Roush WR. Adv Synth Catal. 2004; 346:1035.Lu X, Du Y, Lu C. Pure Appl Chem. 2005; 77:1985.Nair V, Menon RS, Sreekanth AR, Abhilash N, Biju AT. Acc Chem Res. 2006; 39:520. [PubMed: 16906748] Ye LW, Zhou J, Tang Y. Chem Soc Rev. 2008; 37:1140. [PubMed: 18497927] Kwong CK-W, Fu MY, Lam CS-K, Toy PH. Synthesis. 2008:2307.Denmark SE, Beutner GL. Angew Chem Int Ed. 2008; 47:1560.Ye LW, Zhou J, Tang Y. Chem Soc Rev. 2008; 37:1140. [PubMed: 18497927] Aroyan CE, Dermenci A, Miller SJ. Tetrahedron. 2009; 65:4069.Kumara Swamy KC, Bhuvan Kumar NN, Balaraman E, Pavan Kumar KVP. Chem Rev. 2009; 109:2551. [PubMed: 19382806] Cowen BJ, Miller SJ. Chem Soc Rev. 2009; 38:3102. [PubMed: 19847345] Marinetti A, Voituriez A. Synlett. 2010:174.Kolesinska B. Cent Eur J Chem. 2010:1147.Wei Y, Shi M. Acc Chem Res. 2010; 43:1005. [PubMed: 20232829] Pinho e Melo TMVD. Monatsh Chem. 2011; 142:681.Lalli C, Brioche J, Bernadat G, Masson G. Curr Org Chem. 2011; 15:4108.Wang S-X, Han X, Zhong F, Wang Y, Lu Y. Synlett. 2011:2766.López F, Mascareñas JL. Chem Eur J. 2011; 17:418. [PubMed: 21207554] Zhao QY, Lian Z, Wei Y, Shi M. Chem Commun. 2012; 48:1724.Fan YC, Kwon O. List B. Phosphine Catalysis. Science of Synthesis, Asymmetric Organocatalysis, Vol 1, Lewis Base and Acid Catalysts. Georg ThiemeStuttgart2012:723–782.
4. Mancuso R, Mehta S, Gabriele B, Salerno G, Jenks WS, Larock RC. J Org Chem. 2010; 75:897. [PubMed: 20043652]
5. (a) Mukhopadhyay R, Kundu NG. Tetrahedron. 2001; 57:9475.(b) Duan S, Cress K, Waynant K, Ramos-Miranda E, Herndon JW. Tetrahedron. 2007; 63:2959. [PubMed: 18382602]
6. (a) Gabriele B, Salerno G, Fazio A, Pittelli R. Tetrahedron. 2003; 59:6251.(b) Bacchi A, Costa M, Cà ND, Fabbricatore M, Fazio A, Gabriele B, Nasi C, Salerno G. Eur J Org Chem. 2004:574.(c) Peng P, Tang BX, Pi SF, Liang Y, Li JH. J Org Chem. 2009; 74:3569. [PubMed: 19326876]
7. (a) Khan MW, Kundu NG. Synlett. 1999:456.(b) Zanardi A, Mata JA, Peris E. Organometallics. 2009; 28:4335.
8. (a) Michael A. J Prakt Chem/Chem-Ztg. 1894; 49:20.(b) Bergmann ED, Ginsburg D, Pappo R. Org React. 1959; 10:179.(c) Jung ME. Comp Org Synth. 1991; 4:1.(d) Rele D, Trivedi GK. J Sci Ind Res. 1993; 52:13.
9. Inanaga J, Baba Y, Hanamoto T. Chem Lett. 1993; 2:241.
10. Dieck HA, Heck RF. J Am Chem Soc. 1974; 96:1133.
11. Heck RF. J Am Chem Soc. 1968; 90:5518.
12. These fungal metabolites exist as racemates in nature.
13. Höller U, Gloer JB, Wicklow DT. J Nat Prod. 2002; 65:876. [PubMed: 12088431]
14. We assigned the E and Z isomers based on the coupling constants of their vinyl protons. See the Supporting Information for detailed NMR studies, including ^{1}H, ^{13}C, and NOESY NMR spectra.

15. Subjecting the minor E-phthalan to the reaction conditions led to its isomerization to the favored Z form—the major product once the reaction reached equilibrium.
16. Jeffery T. J Chem Soc, Chem Commun. 1984:1287.
17. Grossman RB, Comesse S, Rasne RM, Hattori K, Delong MN. J Org Chem. 2003; 68:871. and references therein. [PubMed: 12558409]
18. (a) Sriramurthy V, Barcan GA, Kwon O. J Am Chem Soc. 2007; 129:12928. [PubMed: 17924625] (b) Sriramurthy V, Kwon O. Org Lett. 2010; 12:1084. [PubMed: 20143856] (c) Fan YC, Kwon O. Molecules. 2011; 16:3802. [PubMed: 21546881]
19. Harrison IT, Harrison S. Chem Commun (London). 1966:752a.

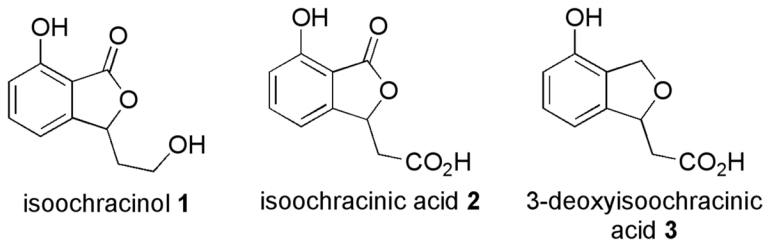
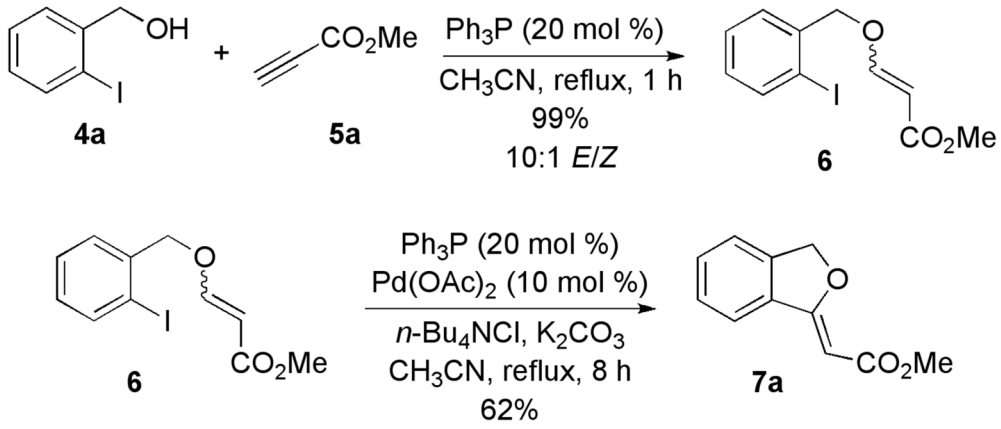
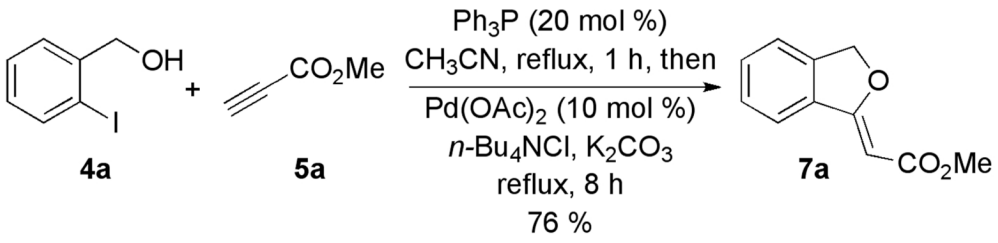


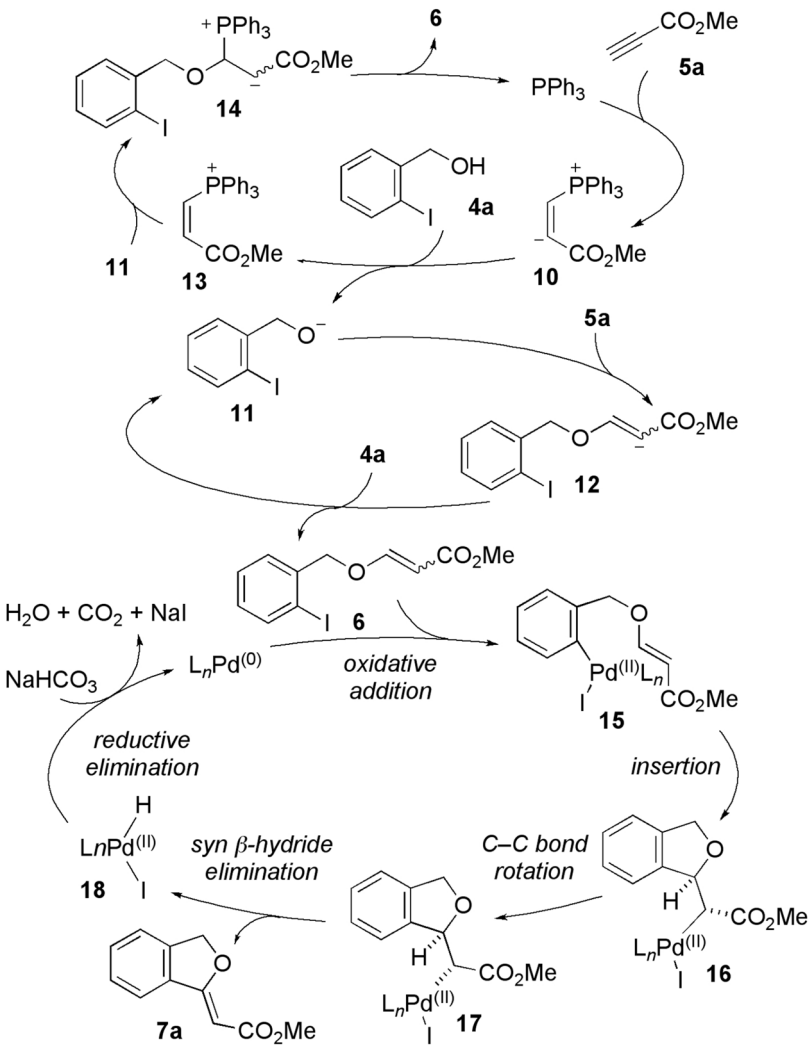
Figure 1.
Rare fungal metabolites



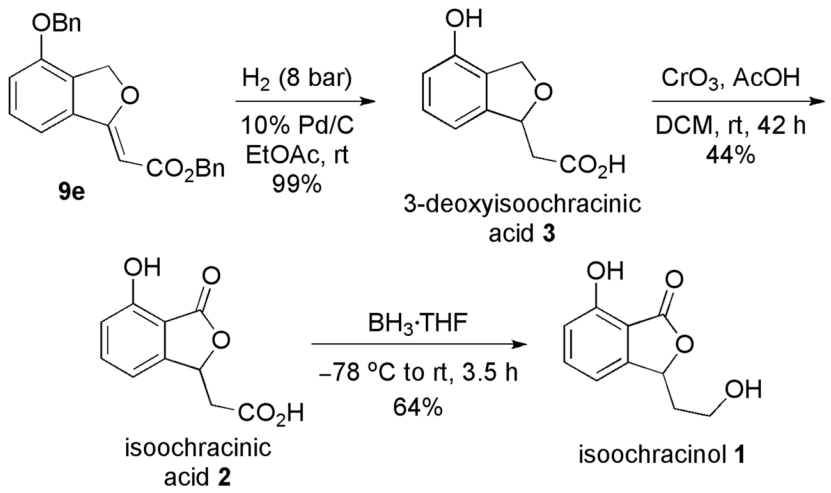
Scheme 1.
Stepwise Formation of an Alkylidene Phthalan



Scheme 2.
Preliminary Investigation of Sequential-Catalysis



Scheme 3.
Proposed Reaction Mechanism

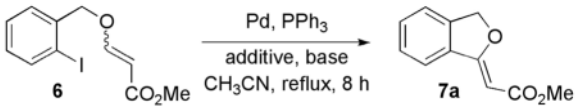


Scheme 4.

Syntheses of the Natural Products 3-Deoxyisoochracinic Acid, Isoochracinic Acid, and Isoochracinol

Table 1

Optimization of Conditions for Heck Annulation[a]



entry	palladium	additive	base	temp (°C)	yield (%)[b]
1[c]	$Pd(OAc)_2$	–	Ag_2CO_3	66	<5
2	$Pd(OAc)_2$	–	Et_3N	82	<5
3	$Pd(Ph_3P)_4$	nBu$_4$NCl	K_2CO_3	82	0
4	$Pd_2(dba)_3$	nBu$_4$NCl	K_2CO_3	82	0
5	$Pd_2(dba)_3{\cdot}CHCl_3$	nBu$_4$NCl	K_2CO_3	82	54
6	$Pd(OAc)_2$	nBu$_4$NCl	K_2CO_3	82	62
7	$Pd(OAc)_2$	nBu$_4$NCl	Ag_2CO_3	82	0
8	$Pd(OAc)_2$	nBu$_4$NCl	$NaHCO_3$	82	80
9	$Pd(OAc)_2$	nBu$_4$NCl	Et_3N	82	74
10	$Pd(OAc)_2$	nBu$_4$NCl	PMP[d]	82	59

[a] Reaction conditions: **6** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), nBu$_4$NCl (0.5 mmol), base (1 mmol), CH_3CN (10 mL), under Ar.

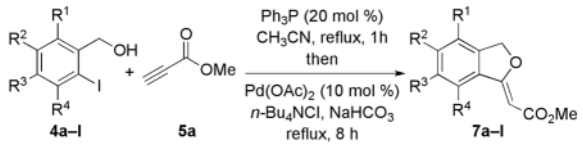
[b] Isolated yield.

[c] Reaction in THF.

[d] 1,2,2,6,6-Pentamethyl piperidine.

Table 2

Reactions of 5a with Various *o*-Iodobenzyl Alcohols



entry	Nu	R^1	R^2	R^3	R^4	E:Z[a,b]	yield (%)[c]
1	**4a**	H	H	H	H	1:3	**7a**, 74
2	**4b**	F	H	H	H	1:4	**7b**, 70
3	**4c**	H	OBn	H	H	1:3	**7c**, 65
4	**4d**	H	OMe	OBn	H	1:4	**7d**, 52
5	**4e**	H	OMe	OMe	H	1:3	**7e**, 72
6[d]	**4f**	H	OTBS	H	H	1:6	**7f**, 73
7	**4g**	H	CF_3	H	H	1:3	**7g**, 60
8	**4h**	H	NO_2	H	H	1:3	**7h**, 45
9	**4i**	H	Me	H	H	1:4	**7i**, 71
10	**4j**	H	H	Me	H	1:4	**7j**, 76
11	**4k**	H	H	H	Me	1:16	**7k**, 94
12	**4l**	H	H	H	OMe	1:22	**7l**, 91

[a] Ratio determined from the ^{1}H NMR spectrum of the crude product.

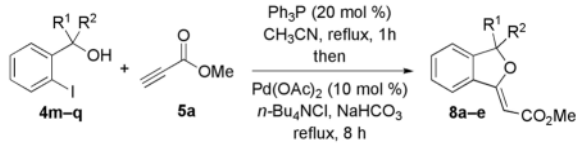
[b] The E isomers were difficult to purify and characterize, due to the presence of other byproducts.

[c] Isolated yield of the major (Z) phthalan.

[d] The phthalan **7f** was isolated as a phenol (i.e., without the protecting group).

Table 3

Reactions of 5a with Various Benzylic Alcohols



entry	Nu	R^1	R^2	E:Z[a,b]	yield (%)[c]
1	**4m**	Me	H	1:3	**8a**, 60
2	**4n**	Cyclopropyl	H	1:3	**8b**, 72
3	**4o**	Ph	H	1:5	**8c**, 60
4	**4p**	CF_3	H	1:4	**8d**, 67
5	**4q**	Me	Me	—	**8e**, 0

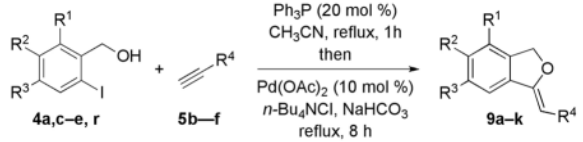
[a]Ratio determined from the ^{1}H NMR spectrum of the crude product.

[b]The E isomers were difficult to purify and characterize, due to the presence of other byproducts.

[c]Isolated yield of the major (Z) phthalan.

Table 4

Reactions with Various Electron-Deficient Acetylenes



entry	Nu	R^1	R^2	R^3	R^4	E:Z[a,b]	yield (%)[c]
1	**4a**	H	H	H	CO_2Bn, **5b**	1:5	**9a**, 78
2	**4c**	H	OBn	H	CO_2Bn, **5b**	1:3	**9b**, 51
3	**4d**	H	OMe	OBn	CO_2Bn, **5b**	1:3	**9c**, 43
4	**4e**	H	OMe	OMe	CO_2Bn, **5b**	1:4	**9d**, 67
5	**4r**	OBn	H	H	CO_2Bn, **5b**	1:5	**9e**, 62
6	**4a**	H	H	H	COMe, **5c**	1:11	**9f**, 75
7	**4c**	H	OBn	H	COMe, **5c**	1:7	**9g**, 56
8	**4e**	H	OMe	OMe	COMe, **5c**	1:3	**9h**, 69
9	**4a**	H	H	H	COPh, **5d**	1:5	**9i**, 68
10	**4a**	H	H	H	Ts, **5e**	1:3	**9j**, 51
11	**4a**	H	H	H	$PO(OPh)_2$, **5f**	1:5	**9k**, 16

[a]Ratio determined from the ^{1}H NMR spectrum of the crude product.

[b]The E isomers were difficult to purify and characterize, due to the presence of other byproducts.

[c]Isolated yield of the major (Z) phthalan.

Org Lett. Author manuscript; available in PMC 2013 July 06.