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Addition of Arylboronic Acids to Arylpropargyl Alcohols en Route to Indenes and Quinolines

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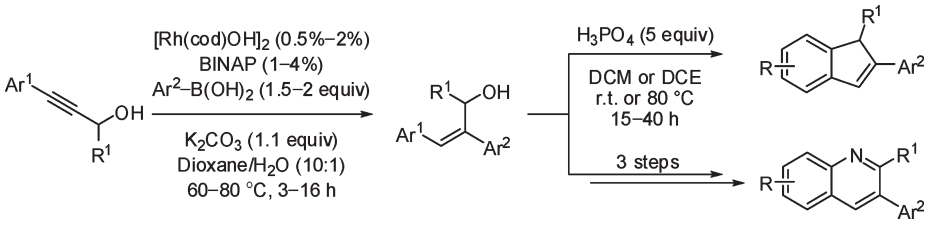
ABSTRACT



A regio- and stereoselective rhodium-catalyzed synthesis of trisubstituted allylic alcohols is described. The utility of these synthons is demonstrated in a convenient synthesis of indenes and quinolines.

Carbometalation of easily accessible propargylic alcohols provides a good access point to substituted allylic alcohols.[1,2] Various metals can promote arylation and alkylation of internal alkynes, but most protocols require the use of highly reactive and sensitive organometallic reagents.[2] Rhodium-catalyzed arylation of alkynes with boronic acids bypasses this obstacle.[3,4] Since the report of this reaction by Hayashi and our work on unsymmetrical alkynes,[4,5] some applications of this chemistry have been reported; however unprotected propargylic alcohols are not well studied.[3d] In this work we describe a rhodium-catalyzed arylation of aryl-substituted propargylic alcohols, which takes place in high yields and regio- and stereoselectivity. Furthermore, we show that the resulting allylic alcohols can be used in a one-step synthesis of indenes and as an access point to quinolines, both of which are useful classes of molecules.[6,7]

Although rhodium-catalyzed arylation of internal alkynes has the potential to be useful, the regioselectivity is

(1) For reviews on carbometalation of alkynes, see: (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841–870. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. (c) Fallis., A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899–5913. (d) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698–4745.

(2) Synthesis of allylic alcohols from propargylic alkynes - From propargylic alcohols and nucleophiles: (a) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989–2992. (b) Tessier, P. E.; Nguyen, N.; Cly, M. D.; Fallis, A. G. *Org. Lett.* **2005**, *7*, 767–770. (c) Denmark, S. E.; Pan., W. *Org. Lett.* **2003**, *5*, 1119–1122. (d) Zhang, X.; Lu, Z.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2009**, *7*, 3258–3263. (e) Oh, C. H.; Jung, H. H.; Kim, K. S.; Kim., N. *Angew. Chem., Int. Ed.* **2003**, *42*, 805–808. (f) Gupta, A. K.; Kim, K. S.; Oh, C. H. *Synlett* **2005**, 457–460. From propargylic alcohols and aryl halides: (g) Durandetti, M.; Hardou, L.; Clément, M.; Maddaluno, J. *Chem. Commun.* **2009**, 4753–4755. (h) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972–6975. (i) Cacchi, S.; Fabrizi, G.; Moro, L.; Pace, P. *Synlett* **1977**, 1367–1370. (j) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Eur. J. Org. Chem.* **2000**, 4099–4108. Selected examples of alternative reactivity of propargylic alcohols and boronic acids: (k) Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 5573–5575. (l) Dheur, J.; Sauthier, M.; Castanet, Y.; Mortreux, A. *Adv. Synth. Catal.* **2010**, *352*, 557–561.

(3) Hayashi, T.; Inoue, K.; Tamiguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918–9919. (b) Matsuda, T.; Makino, M.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4608–4611. (c) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, U.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766–5771. (d) Acardi, A.; Aschi, M.; Chiarini, M.; Ferrara, G.; Marinelli, F. *Adv. Synth. Catal.* **2010**, *352*, 493–498.

(4) For reviews on reactions featuring rhodium catalyzed arylation of alkynes, see: (a) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217–224. (b) Youn, S. W. *Eur. J. Org. Chem.* **2009**, 2597–2605.

(5) (a) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123–125. (b) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762–769. (c) Tsui, G. T.; Lautens, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8938–8941.

(6) Reviews on the use of indenes: (a) Kuninobu, Y.; Nishina, Y.; Kawata, A.; Shouho, M.; Takai, K. *Pure Appl. Chem.* **2008**, *80*, 1149–1154. (b) Enders, M.; Baker, R. W. *Curr. Org. Chem.* **2006**, *10*, 937–953. (c) Huffman, J. W.; Padgett, L. W. *Curr. Med. Chem.* **2005**, *12*, 1395–1411. (d) Stradiotto, M.; McGlinchey, M. J. *Coord. Chem. Rev.* **2001**, *219–221*, 311–378. (e) O'Connor, J. M.; Casey, C. P. *Chem. Rev.* **1987**, *87*, 307–318. (f) Coates, G. W.; Waymouth, R. M. *Science* **1995**, *267*, 217–219.

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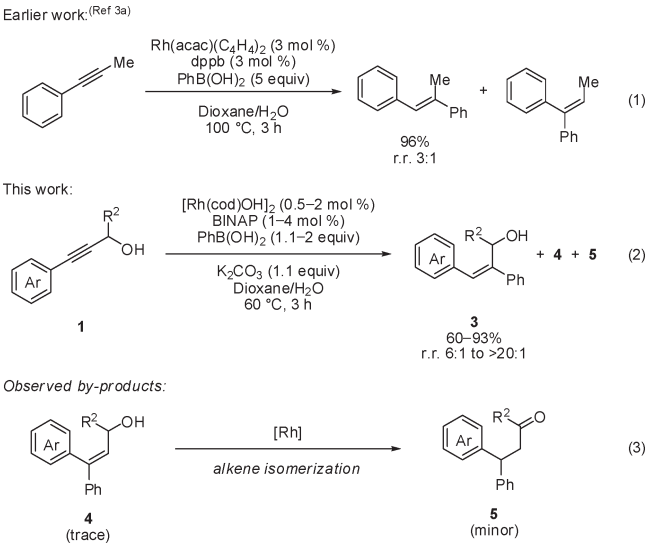
often problematic and two products are generally obtained.[8] From previous reports, the selectivity is only moderate for aryl alkyl substituted alkynes (eq 1, Scheme 1). However, considering the utility of substituted allylic alcohols we were interested in reexamining the arylation of alkynes bearing reactive functional groups such as **1** (eq 2, Scheme 1).

Scheme 1



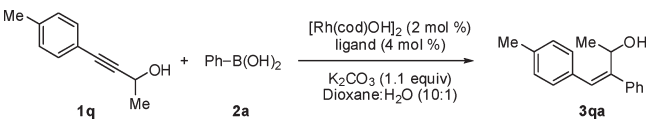
Following optimization, we observed that the rhodium/BINAP catalyst facilitated higher regioselectivity when using potassium carbonate as a base (Table 1). The apparent regioselectivity was very high (> 20:1), but upon closer examination we observed that the minor regioisomer **4** was converted to the corresponding ketone **5**, presumably through a rhodium-catalyzed isomerization of the alkene (eq 3, Scheme 1). Nevertheless the true regioisomeric ratios were higher than alkyne arylations using other bidentate phosphine ligands (entries 1–4, Table 1), and we could access the pure products **3** in good yields. With substrate **1** and a rhodium/BINAP catalyst system the reaction proceeded efficiently with mild heating, which allowed us to reduce the arylboronic acid loading to 2 equiv or lower. It is noteworthy that we observe improved yields with an increasing scale of the reaction (entries 5–7).

It was surprising that for most substrates the reaction was complete within 3 h at 60 °C, considering that the original report of the rhodium-catalyzed alkyne arylation required higher temperatures.[3a] In order to examine whether the free alcohol played a role in this rate enhancement, we looked at substrates **1b**, **1c**, and **1d** (eqs 4 and 5).

(7) Reviews on quinolines: (a) Larsen R. D. In *Science of Synthesis*; Black D. St. C., Ed.; Georg Thieme Verlag KG: Stuttgart, 2005, pp 389–660. (b) Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Polanski, J. *Cur. Med. Chem.* **2010**, *17*, 1960–1973. (c) Kumar, S.; Bawa, S.; Gupta, H. *Mini-Rev. Med. Chem.* **2009**, *9*, 1648–1654. (d) Madapa, S.; Tusi, Z.; Batra, S. *Curr. Org. Chem.* **2008**, *12*, 1116–1183.

(8) Substrates with highly hindered (i.e., TMS, *t*-Bu) or electron-withdrawing groups (C(O)R) are an exception.

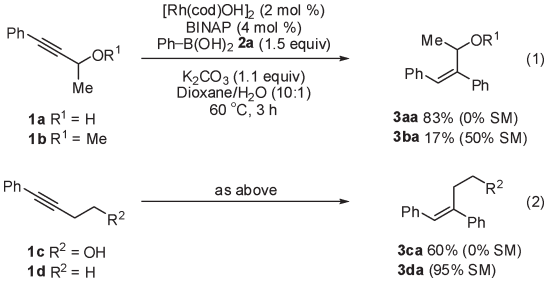
Table 1. Optimization of Reaction Conditions[a]



entry	ligand	scale (mmol)	yield (%)[b]	r.r.[c]	**3**:**4**:**5**[c]
1	dppp	0.25	(63)	4.3:1	81:10:9
2	dppb	0.25	(46)	3.3:1	76:6:18
3	dppf	0.25	(67)	4.6:1	82:2:16
4	BINAP	0.25	(53)	8.3:1	89:0:11
5[d]	BINAP	0.5	64	9:1	90:4:6
6[d]	BINAP	1	80	10:1	91:3:6
7[d]	BINAP	2	76	10:1	91:4:5

[a] $[Rh]_2$, ligand, and base are premixed at 50 °C for 15 min, then substrates are added, and reaction is heated at 60 °C for 3 h. [b] Isolated yields, NMR yield in parentheses. [c] r.r. is determined from crude NMR. [d] 4-$ClC_6H_4B(OH)_2$ **2f** used as nucleophile to give product **3qf**.

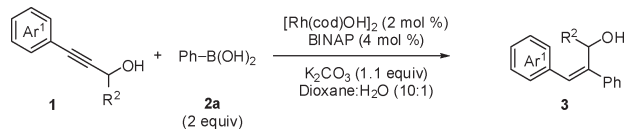
The standard substrate **1a** was completely consumed in 3 h. The methylated substrate, **1b**, gave partial conversion and considerable formation of an unidentified byproduct, showing that the free hydroxyl group was important for the reaction. The homologue **1c** gave the product in lower yield, but complete consumption of starting material was observed. An alkyl-substituted alkyne **1d** did not react, and the starting material could be reisolated. These control experiments indicate that the free alcohol improves the rate of reaction considerably. The nature of this effect is not established at this point, but coordination of the heteroatom with the rhodium center is a possibility.



During the investigation of the scope of this reaction, we found that a variety of substituents were tolerated on the aromatic ring of the propargylic substrate (Table 2). No strong effect of electronics on the regioselectivity was observed (entries 1, 4, and 5); however substrates with a smaller R^2 substituent reacted with higher regioselectivity (entries 1, 12, 13). Notably, at reduced catalyst loading (0.5 mol % $[Rh]_2$) the reaction proceeded in comparable yields and slightly higher selectivity (Table 2, entry 3 and Table 3, entry 2).[9]

(9) In an experiment using alkyl substituted propargyl alcohol (2-pentyne-1-ol) full conversion was observed but considerable decomposion was noted and the product was isolated in 35% yield and an r.r. of 1:1.77.

Table 2. Effect of Propargylic Acohol Modification on Arylation Reaction[a]



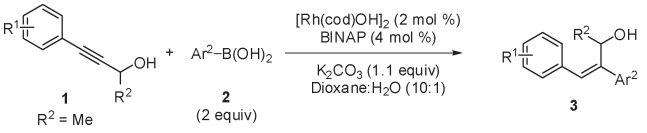
entry	Ar^1	R^2	**3**	time (h)	yield (%)[b]	r.r.[c]
1	H	H	**3ea**	3	70	20:1
2	H	Me	**3aa**	3	84	9:1
3[d]				16	73	14:1
4	4-$MeOC_6H_4$	Me	**3fa**	3	91	10:1
5	4-$CF_3C_6H_4$	Me	**3ga**	3	87	12:1
6	3,5-$MeO_2C_6H_3$	Me	**3ha**	3	93	16:1
7	4-$Me_2NC_6H_4$	Me	**3ia**	3	70	10:1
8	3,5-$Me_2C_6H_3$	Me	**3ja**	3	83	19:1
9[e]		Me	**3ka**	3	73	7:1
10[e]		Me	**3la**	3	76	7:1
11	2-$MeOC_6H_4$	Me	**3ma**	3	74	>20:1
12	4-$CF_3C_6H_4$	H	**3na**	19	71	>20:1
13	4-AcC_6H_4	H	**3oa**	7.5	75	>20:1
14	3,5-$MeO_2C_6H_3$	*i*-Pr	**3pa**	3	73	10:1

[a] See Table 1 for reaction conditions. [b] Isolated yield of major regioisomer. [c] r.r. determined from crude NMR; r.r = **3**:(**4**+**5**). [d] Reaction conditions: $[Rh]_2$ (0.5 mol %), BINAP (1 mol %), K_2CO_3 (1.1 equiv) were mixed at 50 °C for 15 min. Substrates **1** and **2** (1.5 equiv) were added, and the reaction was heated to 60 °C for 16 h. 0.4 M concentration. [e] 75 °C.

A number of different arylboronic acids could be utilized giving products in high yields (Table 3). More electron-rich boronic acids reacted faster, but electron-neutral and -poor substituents also gave products in good yields. *Ortho*-substitution was not well-tolerated, furnishing products in lower yields (entries 10 and 11). With heptenylboronic acid as the nucleophile a mixture of two isomers was obtained (entry 12).

With a convenient, stereo- and regioselective synthesis of substituted allylic alcohols in hand, we envisioned that the appended alcohol moiety could react in an intramolecular Friedel–Crafts alkylation under acidic conditions to give indenes **6** (eq 6).[6,10] The vast majority of related literature examples utilize benzylic or doubly benzylic alcohols to facilitate carbocation formation and unsubstituted or alkyl-substituted allylic alcohols generally give poor

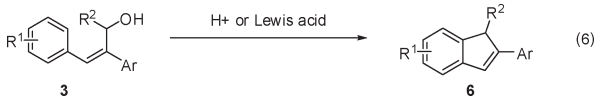
Table 3. Effect of Boronic Acid Variation on Reaction[a]



entry	R^1	Ar^2	**3**	yield (%)[b]	r.r.[c]
1	H	4-Me-3-$MeOC_6H_3$	**3ab**	84	7.5:1
2[d]				83	10:1
3	4-MeO	3,4-$MeO_2C_6H_3$	**3 fc**	73	8:1
4	4-Me	3,4-$MeO_2C_6H_3$	**3qc**	91	10:1
5	3,5-MeO_2	4-$TBSOC_6H_4$	**3hd**	81	17:1
6	4-Me	3-thiophenyl	**3qe**	70	>20:1
7	H	4-ClC_6H_4	**3af**	87	13:1
8	4-Me	4-ClC_6H_4	**3qf**	80	10:1
9	H	3-$NO_2C_6H_4$	**3ag**	83	16:1
10[e]	H	2-FC_6H_4	**3eh**	77	>20:1
11[e]	H	2-MeC_6H_4	**3ei**	60	13:1
12	H	*E*-CH=CHC_5H_{11}	**3aj**	66[f]	1.8:1

[a] See Table 1 for reaction conditions. [b] Isolated yield of major regioisomer. [c] r.r. determined from crude NMR, r.r = **3**:(**4**+**5**). [d] See Table 2 subscript *d* for reaction conditions. [e] R^2 = H. [f] Combined yield for two regioisomers.

results.[10] Furthermore, typically only very electron rich aryl groups react in these cyclizations.



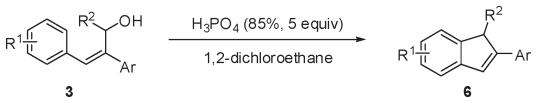
In order to affect this transformation we screened several Bronsted and Lewis acid promoters. However, most strong acids led to formation of an inseparable mixture of products, including the desired indene and an elimination byproduct. Phosphoric acid in dichloromethane gave a clean reaction, albeit over a relatively long reaction time. To remedy this, the reaction solvent was switched to 1, 2-dichloroethane, and the reaction was conducted at 80 °C. Remarkably, the transformation remained selective even at elevated temperatures.

We examined the scope of the transformation (Table 4). Electron-rich substrates cyclized faster, however substrates with electron-neutral substituents or unsubstituted substrates still reacted in high yield (entries 9–11). The presence of electron-donating groups on either aromatic ring improved the reaction rate (entries 7 and 8). Notably, the reaction still furnished the desired product with a nitro-substituted substrate **3ag** (entry 12). A substrate **3ei** bearing a primary alcohol cyclized very efficiently under these conditions (entry 11). A phenolic TBS group was tolerated, even though acidic conditions are commonly used to cleave this protecting group (entry 2),[11] demonstrating the relatively milder nature of these biphasic conditions.

Considering the importance of nitrogen-containing heterocycles in the pharmaceutical industry we were also interested in converting our allylic alcohol products to

(10) (a) Smith, C. D.; Rosocha, G.; Mui, L.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 4716–4727. (b) Buchholz, H. A.; Höfer, J.; Noltemeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1763–1770. (c) Jeong, I. H.; Park, Y. S.; Kim, M. S.; Song, Y. S. *J. Fluor. Chem.* **2003**, *120*, 195–209. (d) Lim, H. N.; Ji, S.-H.; Lee, K.-J. *Synthesis* **2007**, 2454–2460. (e) Zhou, X.; Zhang, H.; Xie, X.; Li, Y. *J. Org. Chem.* **2008**, *73*, 3958–3960. (f) Guo, S.; Liu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2064–2070. (g) Li, G.; Wang, E.; Chen, H.; Li, H.; Liu, Y.; Wang, P. G. *Tetrahedron* **2008**, *64*, 9033–9043. (h) Cosmo, R.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 1499–1509. (i) Sonntag, M.; Strohriegl, P. *Tetrahedron* **2006**, *62*, 8103–8108. (j) Wang, J.; Zhang, L.; Jing, Y.; Huang, W.; Zhou, X. *Tetrahedron Lett.* **2009**, *50*, 4978–4982. (k) Zhang, X.; Teo. W. T. Chan, P. W. H. *Org. Lett.* **2009**, *11*, 4990–4993. (l) Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732–3735.

Table 4. Scope of Friedel–Crafts Alkylation Products[a]



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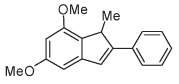
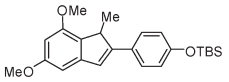
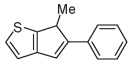
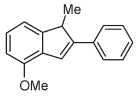
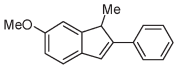
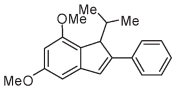
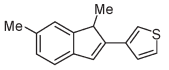
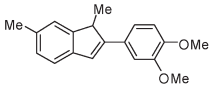
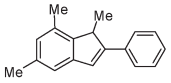
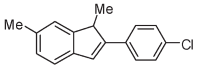
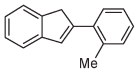
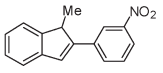
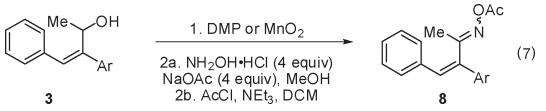
entry	product		temp (°C)	time (h)	yield (%)[b]
1[c]		**6ha**	rt	240	91
2			80	16	90
2		**6hd**	80	22	78
3[c]		**6la**	rt	17	69
4		**6ma**	80	15	85
5		**6fa**	80	15	82
6		**6pa**	80	50	87
7		**6qe**	80	16	82
8[c]		**6qc**	rt	80	66
9		**6ja**	80	40	80
10		**6qf**	80	40	74
11		**6ei**	80	44	88
12		**6ag**	80	44	65

[a] H_3PO_4 (85%) was added to a solution of alcohol in 1,2-dichloroethane. The reaction was monitored by TLC. [b] Isolated yields. [c] Dichloromethane used as a solvent.

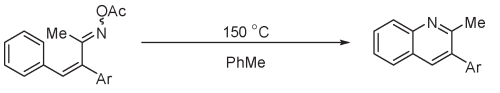
quinolines.[6] To affect this annulation an *O*-acetyloxime group could be installed after oxidation of the alcohols to the ketones to yield **8** (eq 7).



3 8 (7)

We initially examined palladium-catalyzed cyclizations of **8** based on a report by Hartwig.[12] However, we observed that the formation of quinoline occurred in the absence of palladium, under thermal conditions. Heating the *O*-acetyloximes in either toluene or dioxane at 150 °C afforded the desired quinoline products **9**. 6π-Electrocyclizations of methyl and acetyl oximes are known to occur under irradiation, although most examples feature cyclic substrates to facilitate the cyclization.[13] Since the arylation reaction provides products with defined stereochemistry at the alkene, irradiation is not necessary for alkene isomerization and the electrocyclization can occur under thermal conditions (Scheme 2). We found that electron-neutral and -poor substrates provided the highest yields, but product was also obtained with an electron-rich substrate in modest yield.

Scheme 2. Synthesis of Quinolines[14]



8
8a Ar = Ph
8b Ar = 4-Me-3-MeOC$_6$H$_3$
8c Ar = 3-NO$_2$C$_6$H$_4$
8d Ar = 4-Cl-C$_6$H$_4$

9
9a 68%
9b 55%
9c 79%
9d 73%

In conclusion, we have reported a rhodium-catalyzed arylation of unprotected arylpropargylic alcohols. This transformation led to synthetically useful products, the utility of which was demonstrated in a facile synthesis of indenes and quinolines.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Starting material (0.1 mmol) was placed in a microwave tube, and toluene was added (1 mL). The vial was sealed with a Teflon lined septum and placed in a 150 °C oil bath. Isolated yields.