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Journal

Organic Letters, 19(10)

ISSN

1523-7060

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Publication Date

2017-05-19

DOI

10.1021/acs.orglett.7b00958

Peer reviewed

Brønsted Acid-Catalyzed Intramolecular Hydroarylation of β-Benzylstyrenes

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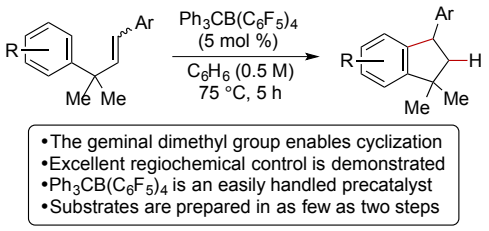
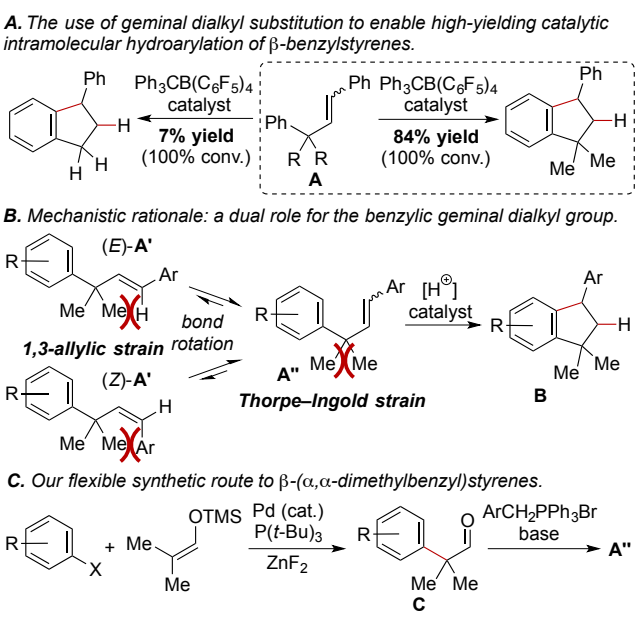
Supporting Information Placeholder

ABSTRACT: Using triphenylmethylium tetrakis(pentafluorophenyl)borate as a convenient Brønsted acid precatalyst, β-(α,α-dimethylbenzyl)styrenes are shown to cyclize efficiently to afford a variety of new indanes that possess a benzylic quaternary center. The geminal dimethyl-containing quaternary center is proposed to be necessary to arm the substrate for cyclization through steric biasing.



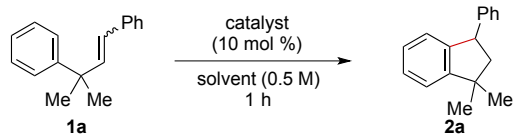
The hydroarylation of alkenes[1] is the most direct means by which to synthesize alkylarenes.[2] Catalytic intramolecular Friedel–Crafts-type electrophilic alkene hydroarylation reactions are useful for the synthesis of many types of benzocycloalkanes,[3] but such methods require the desired ring closure to outcompete intermolecular side reactions. Thus, there are relatively few strategies for Friedel–Crafts-type benzocyclopentane (indane[4]) synthesis , presumably in part due to the challenging trajectory of electrophilic aromatic attack required to achieve the formal 5-*endo-trig* cyclization.[5,6,7] Perhaps the most common strategy is the Friedel–Crafts-type cyclization of remote alcohols, which can be difficult to prepare in modular fashion.[4a,7] In contrast, a method for indane synthesis using strictly aliphatic (unoxidized) substrates has not yet been developed. Herein, we describe our investigation of electrophilic cyclizations of β-benzylstyrenes (**A**, Scheme 1A). The complication of intermolecular side reactions is made abundantly clear considering that the simplest β-benzylstyrene, **A** (R = H), affords just 7% yield of the cyclized product. Fortunately, installation of a geminal dimethyl group (R = Me) enabled cyclization of **A** to outcompete intermolecular side reactions, resulting in excellent yield (inset, Scheme 1A). This disparity suggests that the geminal dialkyl group assists cyclization through conformational activation of the substrate via both 1,3-allylic strain (**A'**) and Thorpe–Ingold strain (**A''**, Scheme 1B).[8] Based on this exciting lead, we devised a rapid synthesis of β-(α,α-dimethylbenzyl)styrenes to enable modification of either of the two aromatic rings, as well as the substituents on the benzylic carbon atom (Scheme 1C). This route consists of a zinc enolate cross-coupling to produce benzylic quaternary center-containing benzaldehydes (**C**),[9] followed by Wittig olefination. Thus, in just three steps total, we can prepare a wide variety of indanes that contain benzylic geminal dimethyl-containing quaternary centers. Benzylic geminal dimethyl quaternary centers are medicinally significant because they are metabolically robust compared to benzylic methylenes.[10] In materials, 1-aryl-3,3-dimethylindanes like **B** have been used in microporous polymers[11a] and as composites in thermoplastics.[11b]

Scheme 1. Intramolecular Hydroarylation of β-Benzylstyrenes: Challenges and Opportunities



At the outset of our study, we used β-benzylstyrene **1a** as a model substrate and evaluated a series of Brønsted and Lewis acids for their propensity to catalyze intramolecular hydroarylation (Table 1). Initially, we found that 10 mol % of *p*-toluenesulfonic acid monohydrate did not efficiently consume substrate **1a** at 80 °C, but full conversion could be realized at 135 °C (entries 1 and 2). In comparison, under otherwise identical conditions, 85% aqueous sulfuric acid converted the substrate much less efficiently (entry 3), while 37% aqueous hydrochloric acid failed to convert the substrate appreciably (entry 4). The evaluation of a stronger Brønsted acid, namely trifluoromethanesulfonic acid, was more fruitful, with the solvents benzene, toluene, and dichloromethane affording diminishing yields of indane **2a**, the former providing nearly quantitative yield of product (entries 5–7). Turning our attention to Lewis acids, transition metal complexes fared no better than Brønsted

Table 1. Optimization of the Intramolecular Hydroarylation of β-(α,α-Dimethylbenzyl)styrene [a]



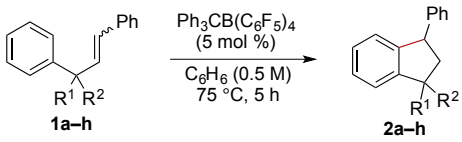
entry	catalyst or precatalyst	solvent	temp (°C)	conv (%)[b] of **1a**	yield (%)[b] of **2a**
1	*p*-TsOH•H_2O	C_6H_6	80	7	6
2	*p*-TsOH•H_2O	C_6H_6	135	100	71
3	H_2SO_4 (85 wt % aq)	C_6H_6	135	60	50
4	HCl (37 wt % aq)	C_6H_6	135	<5	0
5	HOTf	CH_2Cl_2	0→rt	100	60
6	HOTf	PhMe	0→rt	100	85
7	HOTf	C_6H_6	0→rt	100	>95
8	$Ph_3PAuOTf$	C_6H_6	135	<5	0
9	$Pd(OAc)_2$	TFA/DCM	100	100	58
10	TMSOTf	C_6H_6	40	100	91
11	$Ph_3CB(C_6F_5)_4$	C_6H_6	75	100	>95
12[c]	$Ph_3CB(C_6F_5)_4$	C_6H_6	75	10	0
13	$Ph_3CB(C_6F_5)_4$	C_6H_6	rt	<5	0

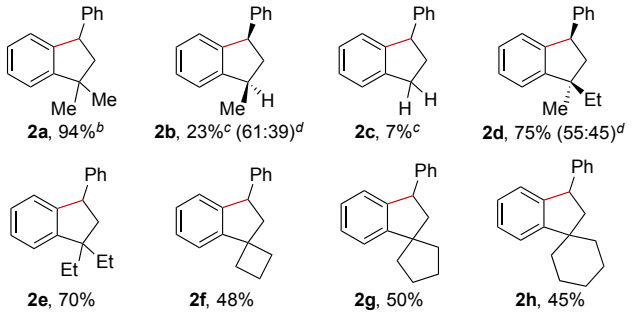
[a] Reactions were conducted on 0.1 mmol scale in a sealed vial. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] 10 mol % of triethylamine was used in this case.

acids: $Ph_3PAuOTf$ failed to engage the starting material at all (entry 8), while a modest 58% yield was realized using $Pd(OAc)_2$ in the presence of trifluoroacetic acid (entry 9). Main group Lewis acids fared much better, with trimethylsilyltriflate (TMSOTf) delivering **2a** in 91% yield at just 40 °C (entry 10). Excellent yield was also achieved using a triphenylmethylium (tritylium) Lewis acid salt, specifically commercially available tritylium tetrakis(pentafluorophenyl)borate (TPFPB), which delivered indane **2a** virtually quantitatively at temperatures as low as 75 °C (entry 11). Notably, other tritylium salts, including Ph_3CBF_4, Ph_3CSnCl_5, and Ph_3CPF_6, resulted in little or no conversion of **1a** at 75 °C, presumably due to their observed insolubility. No product was detected in the presence of triethylamine (entry 12), which suggests that this variant is catalyzed by the *in situ*-generated Brønsted acid H–TPFPB.[12] Finally, no conversion was observed when the tritylium salt was used at ambient temperature (entry 13). Although lower reaction temperatures are possible using either trifluoromethanesulfonic acid (entry 7) or trimethylsilyltriflate (entry 10), they are noxious, difficult to measure reliably, prone to decomposition, and volatile, whereas the tritylium TPFPB salt is an easily handled solid.

Utilizing the tritylium TPFPB precatalyst, we next systematically probed the importance of the geminal dialkyl effect on empowering the cyclization of β-benzylstyrenes (Table 2). Affirmatively, whereas **2a** is readily formed in excellent yield on 1.0 mmol scale using 5 mol % of the precatalyst at [**1a**] = 0.5 M, diminishing yields resulted as methyl groups were removed from the benzylic position. Specifically, despite complete substrate conversion, monomethyl indane **2b** was obtained in just 23% yield, while, as mentioned previously, desmethylated **2c** was barely observed. Of note, *cis*-**2b** was formed with slight preference over *trans*-**2b**. We then evaluated the scope of benzylic dialkyl substituents on β-benzylstyrenes **1**.

Table 2. The Influence of Alkyl Substitution at the Benzylic Position of β-Benzylstyrenes [a]



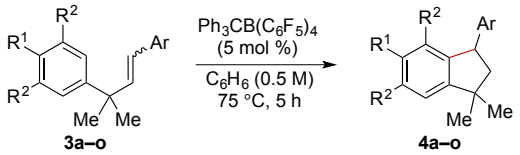


[a] Reactions were conducted on 0.25 mmol scale unless otherwise noted, and monitored by TLC. In each case, the starting material was fully consumed within 5 hours. Yields refer to isolated product unless otherwise noted. [b] Reaction was conducted on 1.0 mmol scale. [c] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Ratio of diastereomers as determined by ^{1}H NMR of the crude reaction mixture; the major diastereomer is depicted.

To that end, 1,1-ethylmethyl-3-phenylindane **2d** was formed in good yield, albeit as a 55:45 mixture of diastereomers. Diethyl indane **2e** was also formed in good yield, while cycloalkyl-containing β-benzylstyrenes **1f**–**1h** afforded diminished yields of the corresponding hydroarylation products **2f**–**2h**. The attenuated yields of **2f**–**2h** also support our hypothesis of an enabling Thorpe–Ingold effect, because angle compression is diminished for cyclic alkanes compared to acyclic ones.[8]

Our next aim was to investigate the functional group tolerance of the reaction conditions on hydroarylations of substituted **β-(α,α-dimethylbenzyl)styrenes** (Table 3). In general, the tritylium TPFPB catalyst fully converted substrates containing a wide variety of functional groups, with the exception of Lewis basic alkoxyl or hydroxyl groups. However, in such cases, triflic acid may be used—for example, **3a** was converted to indane **4a**, albeit in low yield (entry 1). Also in the R^1 position, non-basic substituents, such as methyl (entry 2) and halogens, including bromine, chlorine, and fluorine (entries 3–5), were effectively hydroarylated in the presence of the trityl TPFPB salt. In contrast, a substrate bearing a trifluoromethyl substituent (**3f**) was fully consumed, but a complex mixture of undesired products resulted (entry 6). A phenyl-substituted substrate (**3g**) afforded 31% hydroarylation yield when using triflic acid as catalyst (entry 7); surprisingly, no cyclization occurred in the presence of the trityl TPFPB precatalyst. Excellent yields were obtained for *meta*-dimethoxy- and *meta*-dimethyl-substituted substrates (entries 8 and 9), the former also requiring triflic acid as catalyst. Methoxy, methyl, chloro, and trifluoromethyl-containing substrates afforded only modest yields in the styrene para-position (entries 10–13), whereas a m-chloro substituent delivered indane **4n** in fair yield in the presence of 15 mol % of tritylium TPFPB (entry 14). Lastly, in moving beyond substituted arenes (styrenes), we found that substrate **3o**, which contains a 2-naphthyl substituent, afforded 69% yield of hydroarylation product **4o** (entry 15). regioselectivity of this reaction.

Table 3. Scope of the Intramolecular Hydroarylation of β-(α,α-Dimethylbenzyl)styrenes[a]



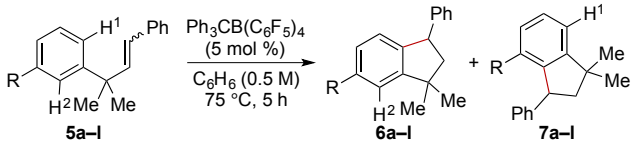
entry	substrate ID	R^1	R^2	Ar	Yield (%) of **4**
1	**3a**	OMe	H	Ph	29[b,c]
2	**3b**	Me	H	Ph	76
3	**3c**	Br	H	Ph	62
4	**3d**	Cl	H	Ph	65
5	**3e**	F	H	Ph	52
6	**3f**	CF_3	H	Ph	0
7	**3g**	Ph	H	Ph	31[c]
8	**3h**	H	OMe	Ph	93[c]
9	**3i**	H	Me	Ph	91
10	**3j**	H	H	(*p*-OMe)C_6H_4	15[c]
11	**3k**	H	H	(*p*-Me)C_6H_4	28
12	**3l**	H	H	(*p*-Cl)C_6H_4	46
13	**3m**	H	H	(*p*-CF_3)C_6H_4	41[b,d]
14	**3n**	H	H	(*m*-Cl)C_6H_4	73[e]
15	**3o**	H	H	2-naphthyl	69

[a] Starting material was fully consumed within 5 hours. Yields refer to isolated product unless otherwise noted. [b] ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction employed 10 mol % of trifluoromethanesulfonic acid as catalyst at 0 °C for 1 h. [d] Reaction employed 0.6 equivalents of trifluoromethanesulfonic acid for 1 h. [e] Reaction employed 15 mol % of $Ph_3CB(C_6F_5)_4$.

We next evaluated the outcomes of intramolecular hydroarylations in which two regioisomeric indane products are possible (Table 4). The cyclization of *t*-Bu-substituted substrate **5a** formed the least-hindered cyclization product, 6-*tert*-butylindane **6a**, exclusively (entry 1). Cyclization also favored the 6-substituted regioisomer in >2:1 ratio for methoxy (entry 2),[13] fluoro (entry 3), and hydroxyl (entry 4) substituted β-benzylstyrenes, which is consistent with cyclization at the more nucleophilic position.[14] In contrast to the *t*-Bu-bearing substrate (entry 1), the analogous *i*-Pr-substituted substrate **5e** cyclized with only a modest preference for indane **6e**. As alkyl substituents became even less bulky (entries 6 and 10), the 4-alkylindanes **7f** and **7j** were formed preferentially.[15] Other halogenated substrates (**5g** and **5i**) and a phenyl-substituted substrate (**5h**) all favored the formation of the corresponding 4-substituted indane regioisomers **7g**–**7i** (entries 7–9). Finally, bicyclic arene-containing substrates **5k** and **5l** (Table 4, bottom) delivered the corresponding sterically congested isomers **7k** and **7l** in near exclusivity.

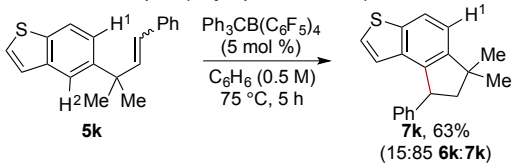
We have demonstrated the feasibility and utility of catalytic intramolecular hydroarylations of β-(α,α-dimethylbenzyl)styrenes. These reactions are readily accomplished with an easily handled trityl TPFPB precatalyst, or catalytic triflic acid. We are currently pursuing the development of new methods based on the utility of α,α-dimethylbenzyl-substituted alkenes, while also working to better understand the mechanism of the reaction, including the relative contributions of steric and electronic effects upon the

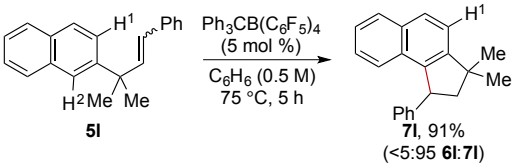
Table 4. Assessing the Regioselectivity of Intramolecular Hydrorylations of β-(α,α-Dimethylbenzyl)styrenes[a]



entry	substrate ID	R	Yield (%) of **6**+**7**	rr[b] (**6**:**7**)
1	**5a**	*t*-Bu	88	>95:5
2[c]	**5b**	OMe	91	81:19
3	**5c**	F	85	78:22
4[c]	**5d**	OH	70	67:33
5	**5e**	*i*-Pr	83	60:40
6	**5f**	Et	78	50:50
7	**5g**	Cl	91	40:60
8	**5h**	Ph	98	35:65
9	**5i**	Br	96	35:65
10	**5j**	Me	70	33:67

additional examples (major product shown)





[a] Starting material was fully consumed within 5 hours. Yields refer to the sum of regioisomers. [b] rr = regioisomeric ratio, which was determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Reaction employed 10 mol % of trifluoromethanesulfonic acid as catalyst for 1 h.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This research was funded by the University of California, Merced.

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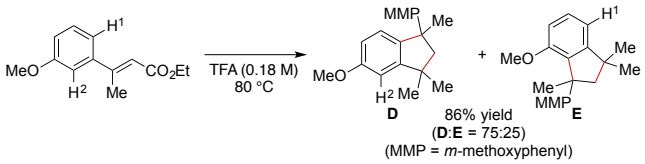
(13) The regioselectivity of the cyclization of **5b** matches the regioselectivity observed in the decarboxylative cyclodimerization of α-methyl-*m*-methoxy ethyl cinnamate, which is also proposed to form indanes via the following formal 5-*endo-trig* cyclization (see: Gopi Krishna Reddy, A.; Satyanarayana, G. *J. Org. Chem.* **2016**, *81*, 12212):



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(15) The regioselectivity of the cyclization of **5j** closely matches the regioselectivity observed in the cyclodimerization of α,*m*-dimethylstyrene, which is also proposed to form indanes via the following formal 5-*endo-trig* cyclization (see: Petropoulos, J. C.; Fisher, J. J. *J. Am. Chem. Soc.* **1958**, *80*, 1938):