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Synthesis of Indenes via Brønsted Acid Catalyzed Cyclization of Diaryl- and Alkyl Aryl-1,3-dienes†

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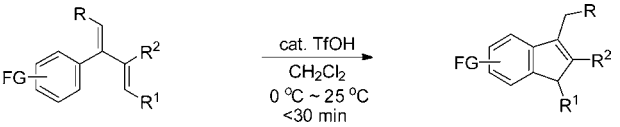
ABSTRACT



FG = H, Me, MeO, Cl, CF_3, CO_2Et, Ac
R, R^1 = H, Me, Ph R^2 = Ar, *tert*-Bu

Substituted indenes can be synthesized via the Brønsted acid catalyzed cyclization of diaryl- and alkyl aryl-1,3-dienes. In this approach, treatment of symmetric or unsymmetric diaryl- and alkyl aryl-1,3-dienes with a catalytic amount of trifluoromethanesulfonic acid gives a variety of indene derivatives in good to excellent yields under mild conditions.

Indenes are important building blocks in organic[1] and organometallic chemistry[2] and are present in many biologically and pharmaceutically active compounds.[3] Thus, the development of synthetic methods for indenes has been a significant objective in organic synthesis. To date, a variety of synthetic methods for formation of an indene ring have been reported. These include the reduction or dehydration of an indanone,[4] the cyclization of phenylvinyl derivatives or phenyl-substituted allyl alcohols,[5] the ring expansion of suitably substituted cyclopropenes,[6] or the Friedel–Crafts cyclization of tetraaryl substituted 1,3-butadienes using an excess of a Lewis acid (10 equiv).[7]

† Dedicated to Prof. Young Keun Chung on the occasion of his 60th birthday.

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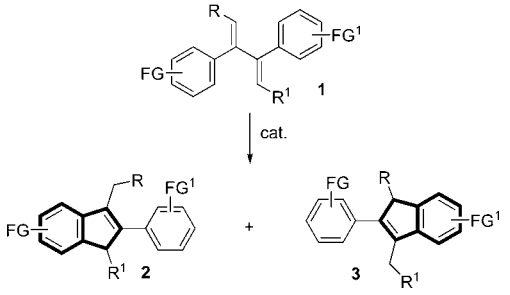
In addition, a number of transition metals, e.g., Pd,[8] Ni,[9] Pt,[10] Co,[11] Au,[12] and Fe,[13] have been used to synthesize indenes via carboannulations of alkynes. However, the introduction of a wide range of different substituents into the indene ring system often encountered difficulties, when multisubstituted indene derivatives were concerned, most especially with regard to their yields and reaction conditions.

Recently, we reported a hybrid system of gold/Brønsted acid relay catalysis for the intramolecular double hydroarylation and cyclization.[14] Moreover, as part of a synthetic project, we required a simple route to a number of indene derivatives. In this regard, we envisioned that if 2,3-diaryl-1,3-dienes **1** were treated with a variety of transition-metal catalysts or Brønsted acids, they would give indenes (**2** or **3**) via cyclization. Herein, we describe an efficient and selective synthesis of indene derivatives from symmetric or unsymmetric diaryl- and alkyl aryl-1,3-dienes through Brønsted acid catalyzed cyclization (Scheme 1).

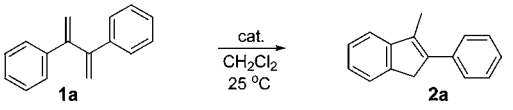
Scheme 1. Synthesis of Indenes via Intramolecular Cyclization



First, a variety of functionalized symmetric 2,3-diaryl-1,3-dienes were easily prepared through Pd-catalyzed coupling reactions of vinyl halides mediated by indium.[15] Unsymmetric diaryl- and alkyl aryl-1,3-dienes were obtained from the Pd-catalyzed cross-coupling reactions of vinyl bromides with vinyl pinacol borane.[16]

We initiated our investigation using 2,3-diphenyl-1,3-butadiene **1a** (Table 1). When **1a** was treated with Ph_3PAuCl and AgOTf (5 mol % each), the indene **2a** was obtained in 15% yield (entry 1), while use of Ph_3PAuCl and $AgSbF_6$ (5 mol % each) gave **3a** in 85% yield in DCM at 25 °C after 30 min (entry 2). The more electrophilic Au catalyst derived from $(C_6F_5)_3PAuCl$ and $AgSbF_6$ (5 mol % each) accelerated the cyclization, producing **2a** in 88% yield (DCM, 25 °C, 5 min, entry 3). The Au-catalyzed cyclization reaction needed a longer reaction time (4 h) in toluene (entry 4). In addition, $AuCl_3$ (5 mol %) in the presence of $AgSbF_6$ (15 mol %) gave a successful result (82%) in DCM (entry 5). $AgSbF_6$ (5 mol %) alone failed to catalyze the cyclization (entry 6).

Table 1. Optimization for Cyclization of 2,3-Diphenyl-1,3-butadiene



entry	cat. (mol %)	time (h)	yield (%)
1	Ph_3PAuCl (5)/AgOTf (5)	12	15 (75)[a]
2	Ph_3PAuCl (5)/$AgSbF_6$ (5)	0.5	85
3	$(C_6F_5)_3$ PAuCl (5)/$AgSbF_6$ (5)	0.08	88
4	$(C_6F_5)_3$ PAuCl (5)/$AgSbF_6$ (5)	4	84[b]
5	$AuCl_3$ (5)/$AgSbF_6$ (15)	0.5	85
6	$AgSbF_6$ (5)	12	0
7	TfOH (5)	0.08	94
8	37% HCl (25)	12	0
9	96% H_2SO_4 (25)	20	21
10	85% H_3PO_4 (25)	20	0

[a] Recovery yield of **1a**. [b] Toluene was used as a solvent.

To check the possibility of catalysis by a protic acid, we attempted the cyclization in the presence of trifluoromethanesulfonic acid (TfOH, 5 mol %), which gratifyingly gave rise to **2a** in 94% yield in DCM at 25 °C after 5 min (entry 7). However, the reaction did not give satisfactory results with protic acids such as HCl, H_2SO_4, and H_3PO_4 (entries 8–10).

To explore the scope of the present Brønsted acid catalyzed cyclization with respect to symmetric 2,3- diaryl-1,3-dienes **1**, we carried out further reactions with TfOH (5 mol %) in DCM (Table 2). Varying the electron demand of the substituents on the phenyl ring did not diminish the efficiency of cyclization. Under the optimized reaction conditions, treatment of 2,3-diaryl-1,3-butadienes **1b** and

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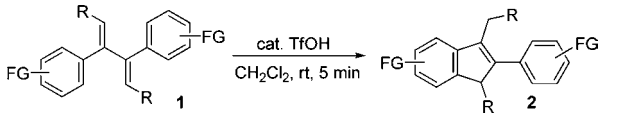
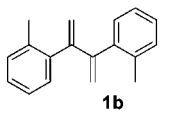
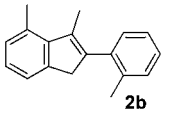
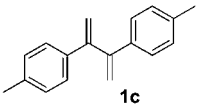
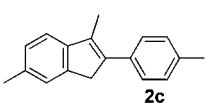
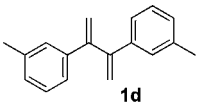
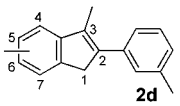
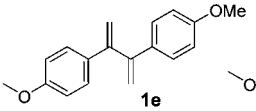
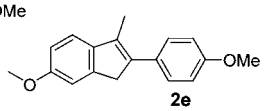
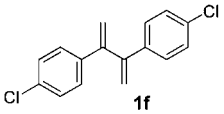
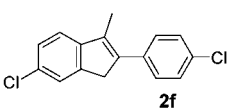
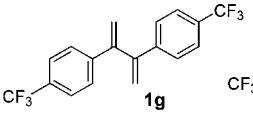
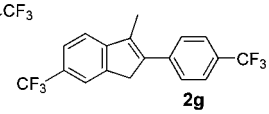
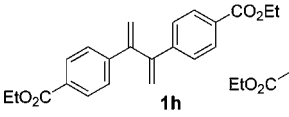
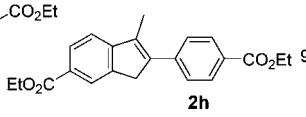
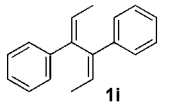
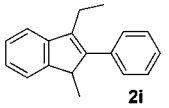
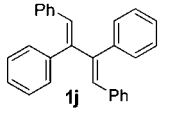
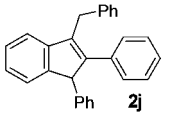
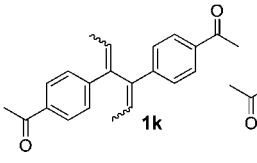
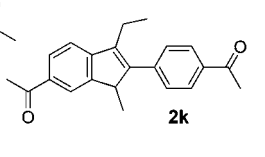
1c having a 2- or 4-methyl group with catalytic TfOH (5 mol %) gave **2b** and **2c** in 88% and 87% yields, respectively (entries 1 and 2). When 2,3-di(3-tolyl)-1,3-butadiene **1d** was employed as the substrate, theoretically, there could be two possible products from two different cyclization directions of the corresponding diene, and thus, 3,5-dimethyl-2-(3-methylphenyl)indene and 3,7-dimethyl-2-(3-methylphenyl)-indene were obtained in 35% and 50% yields, respectively (entry 3). The presence of a 4-methoxy group had little effect on either the reaction rate (5 min) or the product yield (**2e**, 88%, entry 4). 2,3-Diaryl-1,3-butadiene **1f**, having a chloride group, gave the desired indene **2f** in 80% yield (entry 5). Moreover, cyclization proceeded counter-intuitively with 1,3-dienes having electron-deficient aryl rings. When 2,3-di(4-trifluoromethylphenyl)-1,3-butadiene **1g** was subjected to the reaction conditions, the indene **2g** was obtained in 85% yield (entry 6). 2,3-Di(4-ethoxycarbonylphenyl)-1,3-butadiene **1h** underwent the Au-catalyzed cyclization reaction, producing **2h** in 97% yield albeit with a longer reaction time (30 min) in DCE at 70 °C (entry 7). The presence of a methyl or phenyl group on the terminal sp^2 carbon had little effect on the product yield. When 3,4-diphenyl-2,4-hexadiene **1i** was subjected to the optimized conditions, the desired indene (**2i**) was obtained in 95% yield (entry 8). However, 1,2,3,4-tetraphenyl-1,3-butadiene **1j** required 25 mol % TfOH and a longer reaction time (20 min) (entry 9). Encouraged by these results, we carried out the TfOH-catalyzed cyclization of a 2,3-diaryl-1,3-butadiene having an acetyl group on the phenyl ring and a methyl group on the terminal sp^2 carbon, obtaining **2k** in 75% yield, albeit after a longer reaction time (16 h) in DCE at 70 °C (entry 10). This result indicates that the carbonyl group depressed reactivity.

With this newly developed protocol in hand, we subsequently examined a variety of unsymmetric 2,3-diaryl-1,3-dienes in the Brønsted acid catalyzed cyclization (Table 3). Treatment of the 1,3-butadiene **1l** with a methyl and an ethoxycarbonyl group on the phenyl ring with 5 mol % TfOH selectively provided the desired indene **2l** in 97% yield in DCM at 0 °C after 10 min, thus greatly expanding the scope of our synthetic method (entry 1). A phenyl ring having an electron-donating group likewise selectively participated in the cyclization. 2,3-Diaryl-1,3-pentadiene **1m**, having a methyl and an acetyl group, efficiently cyclized with 5 mol % TfOH to selectively afford **2m** in 91% yield (entry 2). When a cyclization reaction was carried out with **1n** and 5 mol % TfOH, the desired indene **2n** was selectively obtained in 89% yield (entry 3). We were pleased to find that 1,3-pentadiene **1o** successfully engaged in this cyclization (entry 4). Treatment of diaryl-1,3-butadienes **1p** and **1q** having an amino group with 25 mol % TfOH at 25 °C gave the desired indenes **2p** and **2q** in excellent yields (entries 5 and 6). 1,3-Diene **1r** possessing a 4-pyridyl and a 4-methoxyphenyl group was smoothly cyclized to produce **2r** in 90% yield with TfOH (1.3 equiv) at 25 °C (entry 7). The present method was expanded to 1,3-butadiene **1s** possessing a *tert*-butyl and a 4-methoxyphenyl group (entry 8). *Surprisingly, no constitutional isomer was formed in any reactions.*

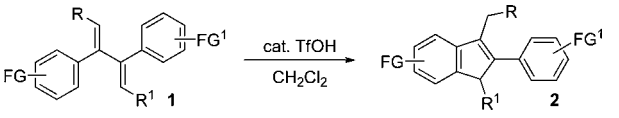
Table 2. TfOH-Catalyzed Cyclization of Symmetric 2,3-Diaryl-1,3-dienes[a]

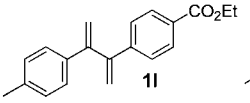
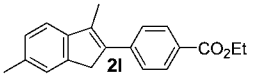
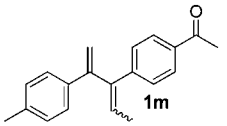
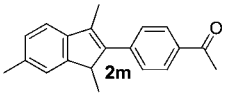
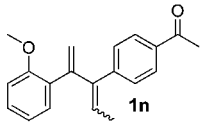
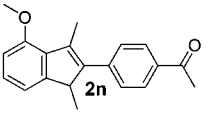
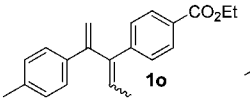
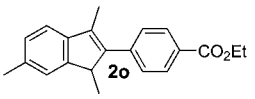
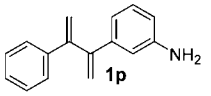
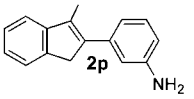
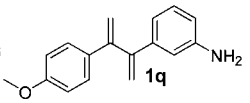
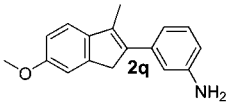
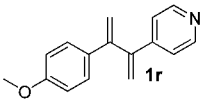
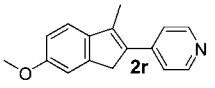
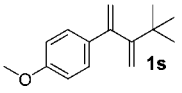
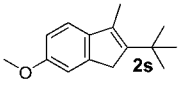


entry	substrate	product	yield (%)
1	 **1b**	 **2b**	88
2	 **1c**	 **2c**	87
3	 **1d**	 **2d**	85 (1:1.4)[b]
4	 **1e**	 **2e**	88
5	 **1f**	 **2f**	80
6	 **1g**	 **2g**	85
7	 **1h**	 **2h**	97[c]
8	 **1i**	 **2i**	95
9	 **1j**	 **2j**	92[d]
10	 **1k**	 **2k**	75[e]

[a] 5 mol % TfOH was used. [b] Ratio of 3,5-dimethyl-2-(3-methylphenyl)indene and 3,7-dimethyl-2-(3-methylphenyl)indene. [c] Reaction was carried out in dichloroethane at 70 °C for 30 min. [d] Reaction was carriedt out with 25 mol % TfOH for 20 min. [e] Reaction was carried out at 70 °C in dichloroethane for 16 h.

Table 3. TfOH-Catalyzed Cyclizationof Unsymmetric Diaryl- and Alkyl Aryl-1,3-butadienes[a]

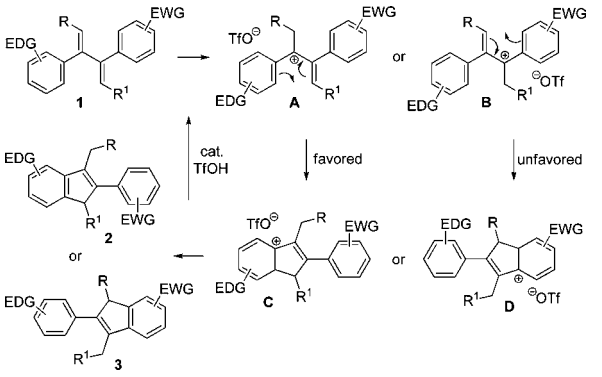


entry	substrate	product	yield (%)
1			97
2			91
3			89[b]
4			98
5			98[c]
6			97[c]
7			90[b,d]
8			99

[a] 5 mol % TfOH was used. [b] Reaction time: 30 min. [c] Reaction was carried out with 25 mol % TfOH at 25 °C. [d] Reaction was carried out with TfOH (1.3 equiv) at 25 °C.

Although the mechanism of the present reaction is not fully established at the present stage, a possible reaction pathway is shown in Scheme 2. Markovnikov addition of a proton to a double bond having a nearby electron-donating group on two phenyl rings of **1** selectively gives the more stable benzylic 3°-carbocation **A** rather than **B**. Then, cationic cyclization of **A** affords an arenium cation **C**. Subsequent deprotonation of **C** produces the indene **2** to release the proton catalyst back into the catalytic cycle. Benzylic 3°-carbocation **B** is assumed to be unstable, mainly due to the electron deficiency of the phenyl group, and thus, indene **3** is not produced.

Scheme 2. Plausible Mechanism for Cyclization of 2,3-Diaryl-1,3-butadiene



In conclusion, we have developed a selective synthetic method of indenes via the Brønsted acid catalyzed cyclization of diaryl- and alkyl aryl-1,3-dienes. Treatment of symmetric or unsymmetric diaryl- and alkyl aryl-1,3-dienes with 5 mol % TfOH gave a variety of indenes in DCM in good-to-excellent yields under very mild conditions. We anticipate that this transformation will be of high value in synthetic and medicinal chemistry.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.