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Authors: Masahiro Sai

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Direct Synthesis of Indanes via Iron-Catalyzed Dehydrative Coupling/Friedel–Crafts Cyclization of Two Different Alcohols

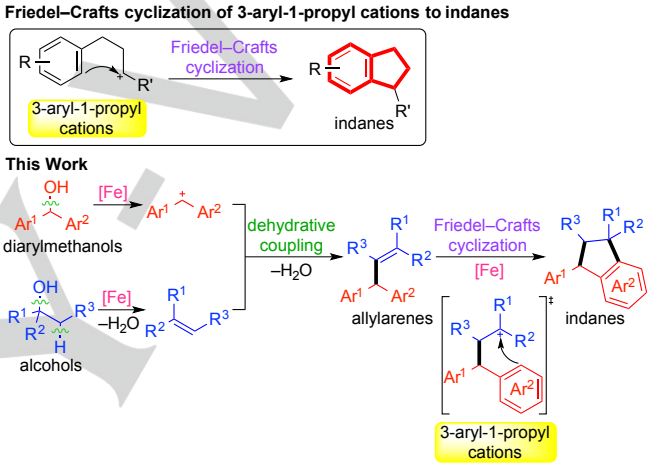
Masahiro Sai*[a]

Abstract: We report herein a novel iron-catalyzed cascade dehydrative coupling/Friedel–Crafts cyclization of two different alcohols, providing a variety of indanes, which are ubiquitous substructures found in natural products, pharmaceuticals, and functional materials. Importantly, the developed approach is highly atom-economic and environmentally benign, as it employs readily available alcohols as substrates and generates water as the only byproduct.

Introduction

In view of the widespread occurrence of the indane scaffold in natural products/pharmaceuticals[1] and functional materials,[2] much effort has been directed at the development of efficient indane synthesis methods.[3] One of such methods relies on the intramolecular Friedel–Crafts[4] cyclization of 3-aryl-1-propyl cations that can be generated by activating the C–O bond of 3-aryl-1-propanols[5] or the C=C bond of allylarenes[6] in acidic conditions. However, the above substrates are not easily accessible, which has inspired the search for alternative approaches such as the in situ generation of 3-aryl-1-propyl cations in the acid-promoted dehydrative coupling of benzylic alcohols with olefins.[7] Although the above protocol provides access to a variety of indanes with different substitution patterns, it generally requires stoichiometric amounts of Lewis acids,[7a–7e] and successful catalytic examples remains scarce.[7f–7h] Furthermore, the preparation of olefins is sometimes problematic, particularly when they are unstable, volatile, or highly elaborated. Thus, it is highly desirable to develop a new catalytic synthesis of indanes from easily available starting materials.

Recently, we have reported new synthetic transformations of unsaturated alcohols involving alcohol C–O bond cleavage by Lewis acids.[8] Based on the results of these studies, we attempted to directly assemble the indane skeleton from two different alcohols, since alcohols are more stable, less volatile, and more readily available than olefins. In order for this approach to be successful, one needs to chemoselectively generate carbocations and olefins from two different alcohols via Lewis acid-catalyzed C–O bond cleavage and then couple these in situ generated partners to provide allylarenes, which subsequently undergo Lewis acid-catalyzed Friedel–Crafts cyclization to indanes (Scheme 1). Accordingly, the dual activation of a hydroxy group and a double bond must be accomplished by a single catalyst even in the presence of excess H_2O, which often deactivates Lewis acids. Herein, we demonstrate the feasibility of this concept by realizing direct iron-catalyzed synthesis of indanes via cascade dehydrative coupling/Friedel–Crafts cyclization of two different alcohols.



Scheme 1. Iron-catalyzed direct synthesis of indanes from two different alcohols.

Results and Discussion

Initially, we aimed to identify the appropriate catalyst and reaction conditions for the synthesis of indane **2a** by the reaction of benzhydrol **1a** with *tert*-butyl alcohol (Table 1) and started by testing a $Ga(OTf)_3/PhCF_3$ system, which was shown to be highly effective for the C–O bond cleavage in our previous study.[8b] Although this system showed high catalytic activity for the initial dehydrative coupling to afford olefins **3** and **4**,[9,10] the desired indane **2a** was obtained in only 10% yield (entry 1). Next, representative Lewis acids were examined. Almost no conversion was observed in the presence of $BF_3{\cdot}Et_2O$ and $AlCl_3$ (entries 2 and 3), while the catalytic activities of $In(OTf)_3$ and $Sc(OTf)_3$ were similar to that of $Ga(OTf)_3$ (entries 4 and 5). To enhance Friedel–Crafts cyclization, soft Lewis acids such as $Cu(OTf)_2$ and AgOTf were employed, but olefin **3** was again obtained as the major product (entries 6 and 7). Further catalyst screening showed that $Fe(OTf)_3$ was particularly effective in promoting indane formation, delivering **2a** in 76% yield (entry 8).[11] The high catalytic activity of $Fe(OTf)_3$ toward indane formation would be attributed to its strong Lewis acidity, which allowed Friedel–Crafts cyclization to occur even in the presence of excess H_2O. We next investigated the effect of solvent and reaction temperature on $Fe(OTf)_3$-catalyzed indane formation,

[a] Dr. M. Sai
Research Foundation ITSUU Laboratory
C1232 Kanagawa Science Park R & D Building, 3-2-1 Sakado,
Takatsu-ku, Kawasaki, Kanagawa 213-0012, Japan
E-mail: msai@itsuu.or.jp
http://itsuu.or.jp

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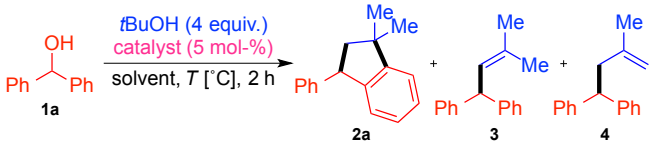
showing that poor yields were observed at 80 °C in $PhCF_3$ and at 85 °C in DCE (entries 9 and 10). Accordingly, high temperature was determined to be of key importance for indane formation, while the yield of **2a** was reduced to 51% when the reaction was carried out in toluene at 115 °C (entry 11).[12] The yield of **2a** was increased to 82% in $PhCF_3$ (with almost complete consumption of **3** and **4**) as the reaction time was extended to 4 h (entry 12). At this point, it should be noted that the previous method[7] of **2a** synthesis involves the use of gaseous and flammable 2-methylpropene instead of *tert*-butyl alcohol and is therefore clearly inferior to the approach described herein.

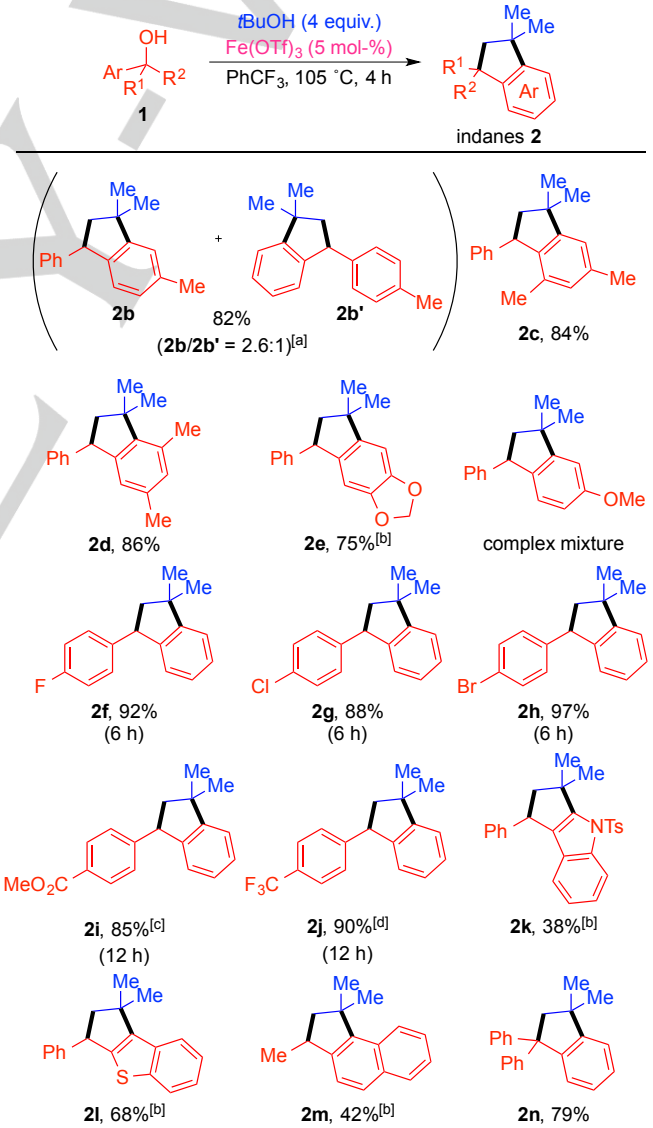
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent[b]	T [°C]	Yield [%][c]			
				1a	**2a**	**3**	**4**
1	$Ga(OTf)_3$	$PhCF_3$	105	0	10	80	6
2	$BF_3{\cdot}Et_2O$	$PhCF_3$	105	95	0	0	0
3	$AlCl_3$	$PhCF_3$	105	93	0	0	0
4	$In(OTf)_3$	$PhCF_3$	105	0	12	75	6
5	$Sc(OTf)_3$	$PhCF_3$	105	0	17	67	5
6	$Cu(OTf)_2$	$PhCF_3$	105	0	11	73	7
7	AgOTf	$PhCF_3$	105	0	7	62	20
8	$Fe(OTf)_3$	$PhCF_3$	105	0	76	11	1
9	$Fe(OTf)_3$	$PhCF_3$	80	0	6	81	7
10	$Fe(OTf)_3$	DCE	85	0	4	88	7
11	$Fe(OTf)_3$	toluene	115	0	51	36	3
12[d]	$Fe(OTf)_3$	$PhCF_3$	105	0	82[e]	4	0

[a] Reaction conditions: **1a** (0.25 mmol), *t*BuOH (1.0 mmol), and catalyst (5 mol-%) in solvent (3 mL) for 2 h. [b] $PhCF_3$ (bp 102 °C), DCE (bp 83 °C), and toluene (bp 111 °C). [c] Determined by ^1H NMR (400 MHz) analysis of the crude reaction mixture. [d] Run for 4 h. [e] Isolated yield.

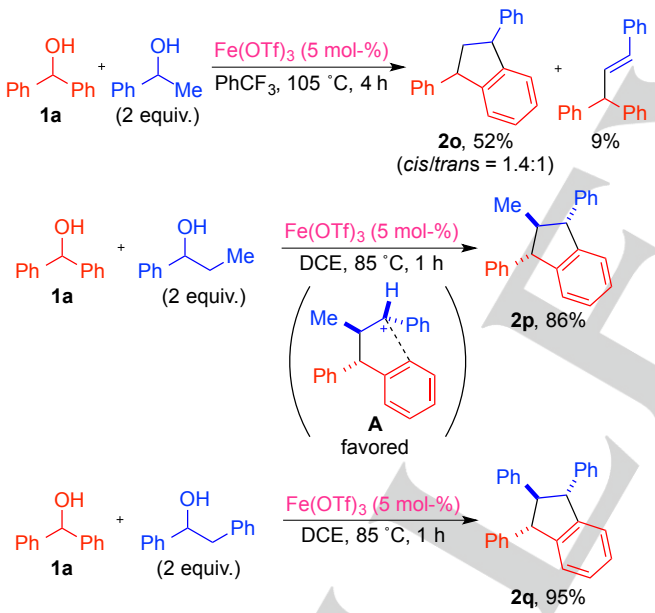
With the optimal conditions in hand, we explored the substrate scope of indane synthesis (Scheme 2), focusing on the use of unsymmetrical diarylmethanols in view of the scarcity of successful examples of regioselective indane synthesis from such compounds.[7d,7e,7h] First, phenyl(4-tolyl)methanol **1b** was reacted with *tert*-butyl alcohol under iron catalysis, resulting in a 2.6:1 mixture of two regioisomers, **2b** and **2b'**. To improve regioselectivity, we examined various unsymmetrical diarylmethanols bearing aryl groups with largely different electron densities and discovered that diarylmethanols with one electron-rich aryl group exclusively generated single regioisomers (**2c**–**2e**). In these cases, direct functionalization of the indane skeleton was achieved because cyclization involved the more electron-rich aromatic ring. In the case of **2e**, cyclization occurred with exclusive regioselectivity at the sterically less hindered *ortho*-position of the more electron-rich aryl ring. Unfortunately, the reactions of diarylmethanols bearing highly electron-rich aryl groups such as anisole and benzofuran residues afforded complex product mixtures. The reaction of diarylmethanols with one electron-deficient aryl group also afforded indanes **2f**–**2j** in high yields with exclusive regioselectivities, although longer reaction times and higher catalyst loadings were required. Heterocyclic compounds showed modest reactivities (**2k** and **2l**), and mono- and triarylmethanols could also be employed (**2m** and **2n**).



Scheme 2. Iron-catalyzed regioselective synthesis of indanes. Reaction conditions: **1** (0.25 mmol), *t*BuOH (1.0 mmol), and $Fe(OTf)_3$ (5 mol-%) in

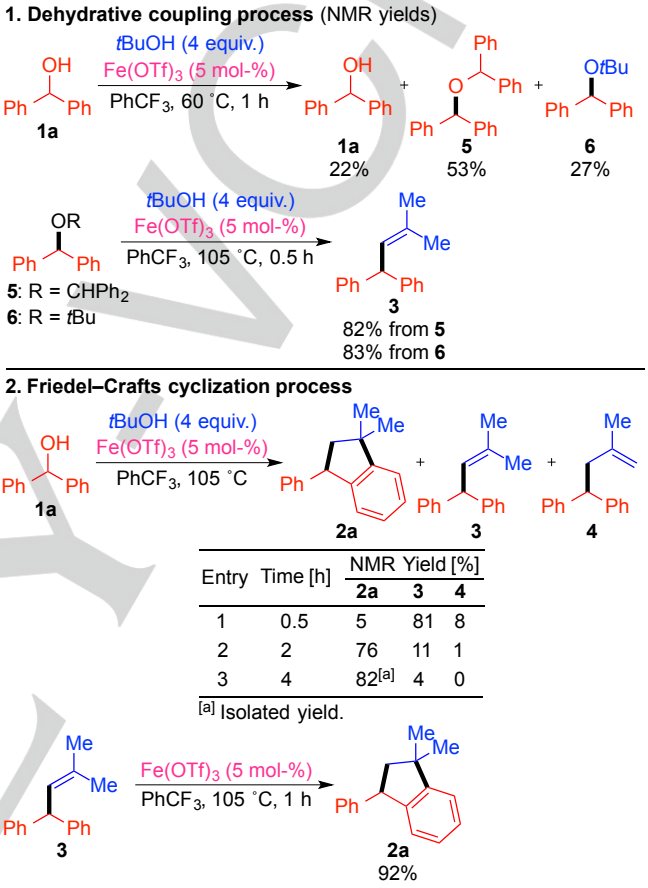
$PhCF_3$ (3 mL) at 105 °C for 4 h. Isolated yield is shown. [a] Determined by ^1H NMR (400 MHz) analysis of the crude reaction mixture. [b] In DCE at 85 °C. [c] With 20 mol-% $Fe(OTf)_3$. [d] With 10 mol-% $Fe(OTf)_3$.

To further demonstrate the utility of the developed method, we tried the diastereoselective synthesis of indanes (Scheme 3). Treatment of **1a** with 1-phenylethanol under standard conditions resulted in a 1.4:1 *cis*/*trans* mixture of 1,3-disubstituted indane **2o**. In contrast, the reaction with 1-phenylpropanol smoothly proceeded in DCE at 85 °C, presumably because of the Thorpe–Ingold effect, providing a single diastereomer of the 1,2,3-trisubstituted indane **2p** in 86% yield.[13] The excellent diastereoselectivity of this reaction was ascribed to the relative stabilities of possible cationic intermediate conformers. Specifically, conformer **A** was more stable than other conformers, as the steric interaction between the methyl group and the phenyl group therein was avoided. Thus, cyclization preferentially involved conformer **A** to diastereoselectively afford **2p**.[14] The reaction with 1,2-diphenylethanol afforded **2q** as a single diastereomer in 95% yield, which highlighted the applicability of our method to the diastereoselective synthesis of 1,2,3-trisubstituted indanes.



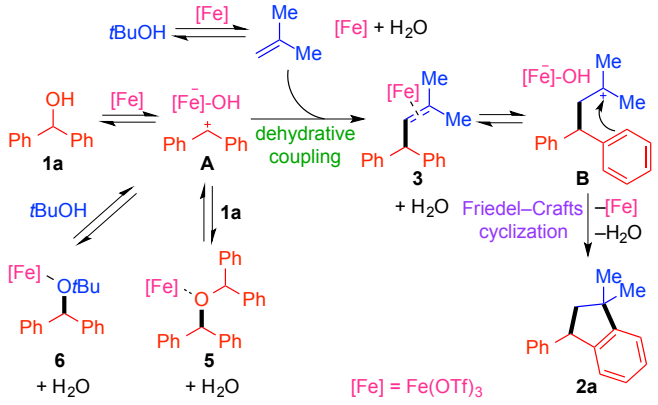
Scheme 3. Diastereoselective synthesis of 1,2,3-trisubstituted indanes.

To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 4). First, iron-catalyzed dehydrative coupling of **1a** with *tert*-butyl alcohol was performed in $PhCF_3$ at 60 °C. In this case, dimer **5** (53% yield) and *tert*-butyl ether **6** (27% yield) were obtained.[15] Exposure of **5** and **6** to standard conditions for 0.5 h furnished olefin **3** in 82 and 83% yields, respectively, which indicated that these ethers are the principal intermediates of dehydrative coupling. Next, we conducted the reaction of **1a** with *tert*-butyl alcohol in $PhCF_3$ at 105 °C and monitored the product distribution at appropriate time intervals. The dehydrative coupling reaction was quite fast, and olefin **3** was obtained in 81% yield after 0.5 h. However, as the reaction proceeded, the yield of **3** significantly decreased, and indane **2a** was obtained as the major product. Moreover, treatment of **3** with $Fe(OTf)_3$ led to the formation of indane **2a** in 92% yield, i.e., **3** was the intermediate leading to the formation of **2a**.



Scheme 4. Control experiments.

On the basis of these results, a plausible indane formation mechanism is illustrated in Scheme 5. Initially, the C–O bond of **1a** is cleaved by $Fe(OTf)_3$ to generate the benzyl cation **A**, while the simultaneous activation of the *tert*-butyl alcohol C–O bond affords 2-methylpropene. Subsequently, **A**, which is in equilibrium with dimer **5** and *tert*-butyl ether **6**, undergoes dehydrative coupling with 2-methylpropene to provide olefin **3**. Under harsh reaction conditions ($PhCF_3$, 105 °C), the double bond of **3** is activated by $Fe(OTf)_3$, and the thus generated tertiary carbocation **B** undergoes intramolecular Friedel–Crafts cyclization to give indane **2a** and regenerate $Fe(OTf)_3$.



Scheme 5. A plausible mechanism.

Conclusions

We have developed a novel regioselective synthesis of functionalized indanes via iron-catalyzed cascade dehydrative coupling/Friedel–Crafts cyclization of two different alcohols, showing that the employed catalytic system is also applicable to the diastereoselective synthesis of 1,2,3-trisubstituted indanes. This method allows using inexpensive, stable, and easily available alcohols as starting materials and generates water as the only byproduct. Thus, the reaction offers a highly atom-economic and environmentally friendly procedure for the synthesis of the indane skeleton.

Experimental Section

General procedure: In a glovebox, $Fe(OTf)_3$ (6.3 mg, 0.0125 mmol) was charged in an oven-dried vial equipped with a stirring bar. Outside the glovebox, to the vial was added a solution of benzylic alcohol **1** (0.25 mmol) and *tert*-butyl alcohol (74.1 mg, 1.0 mmol) in $PhCF_3$ (3 mL). The resulting mixture was stirred in a pre-heated oil bath (105 °C) for 4 h. The reaction mixture was cooled to room temperature, diluted with Et_2O, filtered through a short pad of activated alumina, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc) to give the corresponding product **2**.

Acknowledgements

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Keywords: Alcohols • Iron • C-C coupling • Cyclization • Indanes

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[13] Although the reaction smoothly proceeded in $PhCF_3$ at 105 °C, **2p** was contaminated with an unidentified byproduct.

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[15] For selected examples of acid-catalyzed dehydrative etherification of two different alcohols, see: a) G. V. M. Sharma, A. K. Mahalingam, *J. Org. Chem.* **1999**, *64*, 8943–8944; b) V. V. Namboodiri, R. S. Varma, *Tetrahedron Lett.* **2002**, *43*, 4593–4595; c) B. D. Sherry, A. T. Radosevich, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 6076–6077; d) Y. Liu, R. Hua, H.-B. Sun, X. Qiu, *Organometallics* **2005**, *24*, 2819–2821; e) A. Corma, M. Renz, *Angew. Chem. Int. Ed.* **2007**, *46*, 298–300; *Angew. Chem.* **2007**, *119*, 302–304; f) A. B. Cuenca, G. Mancha, G. Asensio, M. Medio-Simón, *Chem. Eur. J.* **2008**, *14*, 1518–1523; g) J, Kim, D.-H. Lee, N. Kalutharage, C. S. Yi, *ACS Catal.* **2014**, *4*, 3881–3885; h) J. Li, X. Zhang, H. Shen, Q. Liu, J. Pan, W. Hu, Y. Xiong, C. Chen, *Adv. Synth. Catal.* **2015**, *357*, 3115–3120; i) P. K. Sahoo, S. S. Gawali, C. Gunanathan, *ACS Omega* **2018**, *3*, 124–136.

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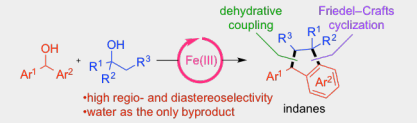
COMMUNICATION

A novel iron-catalyzed cascade dehydrative coupling/Friedel–Crafts cyclization of two different alcohols to indanes has been developed. This approach is highly atom-economic and environmentally benign, as it employs readily available alcohols as substrates and generates only water as byproduct.



Indane Synthesis

*Masahiro Sai**

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Direct Synthesis of Indanes via Iron-Catalyzed Dehydrative Coupling/Friedel–Crafts Cyclization of Two Different Alcohols