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A Copper(II) Triflate-Catalyzed Tandem Friedel–Crafts Alkylation/Cyclization Process towards Dihydroindenes

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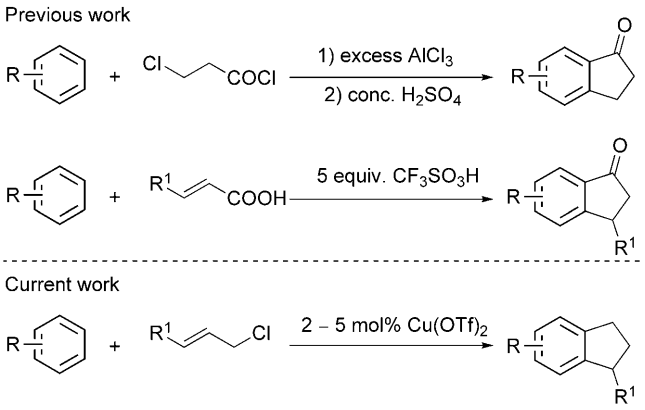
Abstract: A one-pot synthesis of dihydroindenes from substituted benzenes and haloalkenes was developed. The reaction proceeded *via* a copper(II) triflate [$Cu(OTf)_2$]-catalyzed tandem Friedel–Crafts alkylation/cyclization process with high efficiency under relatively mild conditions.

Keywords: dihydroindenes; Friedel–Crafts alkylation; homogeneous catalysis; tandem reactions

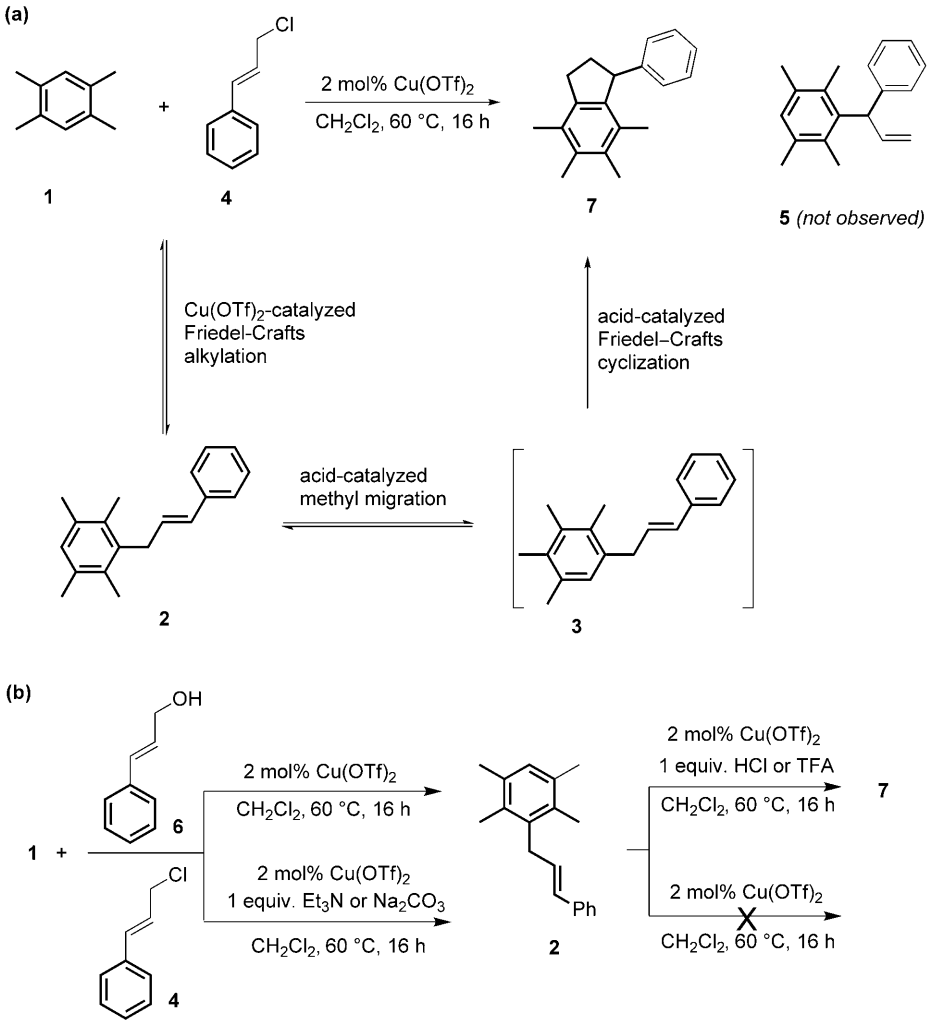


Scheme 1. Bimolecular Friedel–Crafts cyclizations.

Many natural products and synthetic bioactive compounds possess the dihydroindene ring systems.[1,2] As such, the syntheses have been well developed and documented. Some elegant examples include cationic cyclization,[3] organometallic catalytic reactions,[4] cycloaddition/reduction[5] and other miscellaneous routes.[6] However, most of these methods suffered from multiple step synthesis, limited substrate scope, low yields, or tedious processes. The synthesis of such skeletons in a direct and economical matter, while highly desired, remains a challenge. The Friedel–Crafts cyclization reaction is a very important methodology for the synthesis of various useful carbocyclic compounds through carbon-carbon bond formation with aromatic substrates.[7] Bimolecular Friedel–Crafts annulation, in which bifunctional electrophiles react intramolecularly with the same aromatic ring, is inherently more challenging, as competitive intermolecular reactions lead to non-ring products.[8] It is well known that a bifunctional substrate capable of both acylation and alkylation with aromatic compounds is appealing for the formation of important cyclic aromatic ketones.[5,8,9] Excess amounts of Lewis acids, Brønsted acids and/or strong protic acids were typically applied to promote these reactions, as shown in Scheme 1. The cyclic aromatic ketones could then be further reduced to form dihydroindenes.[5] Herein, we report a one-pot $Cu(OTf)_2$-catalyzed sequential alkylation of benzenes with allylic halides and the formation of dihydroindene skeletons through an intramolecular cyclization process.

Allylic halides possess two reactive centers susceptible to Friedel–Crafts alkylation, and the regioselectivity largely depends on the catalyst chosen. For example, it is known that with protic acid catalysts, haloalkenes generally favor the reaction at the double bond,[10,11,12] while reactions at the allylic position can be realized by some ruthenium catalysts.[13]

In this report, the efficiency and the regioselectivity of the Friedel–Crafts alkylations between substituted benzenes and allylic halides with $Cu(OTf)_2$ as catalyst were examined. Experimentally, 1 mmol of 1,2,4,5-tetramethylbenzene **1**, 1.1 mmol of cinnamyl chloride **4** and 2 mol% catalyst were added in 5 mL of CH_2Cl_2 (Scheme 2). The mixture was stirred at 60 °C for 16 h. Instead of observing the Friedel–Crafts alkylation products, 2,3,4,5-tetramethyl-9-phenylindane **7** was isolated in 78% yield. A higher yield of **7** could be achieved when an excess amount of cinnamyl chloride was used (Table 1, entry 1). The structure of **7** was confirmed by an X-ray single crystal diffraction study



Scheme 2. (**a**) Proposed reaction pathway; (**b**) transformation conditions between **1**, **2** and **7**.

(Figure 1).[14] This remarkable reaction proceeds *via* several challenging steps in one-pot with a single catalyst.

In the first step, Friedel–Crafts alkylation of **1** happened at the allylic position to form the intermediate **2**, catalyzed by $Cu(OTf)_2$,[15] [Scheme 2, (**a**)]. Although there was no trace of intermediate **2** in the final reaction mixture, the formation of **2** was confirmed by analysis of a reaction mixture that was quenched at an early stage. Another possible product **5** was not observed either in the final reaction mixture or the quenched reaction mixture. Friedel–Crafts alkylations are usually reversible processes, which require a large excess amount of acids, and for the analogous allylation reactions, a mixture of regiomers is normally obtained. In our case, the catalytic amount of $Cu(OTf)_2$ can efficiently promote the process in a highly regioselective manner to obtain the intermediate **2**. Following the first allylation step, intermediate **2** underwent double methyl migration under acidic conditions to form intermediate **3**. The Lewis acid-

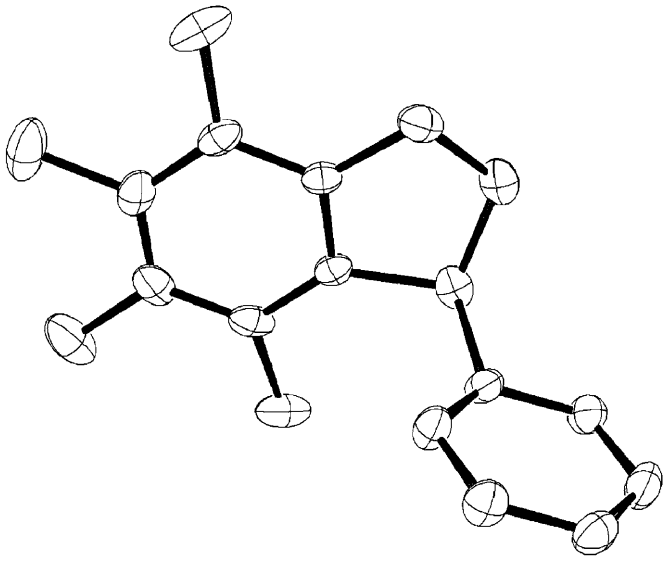
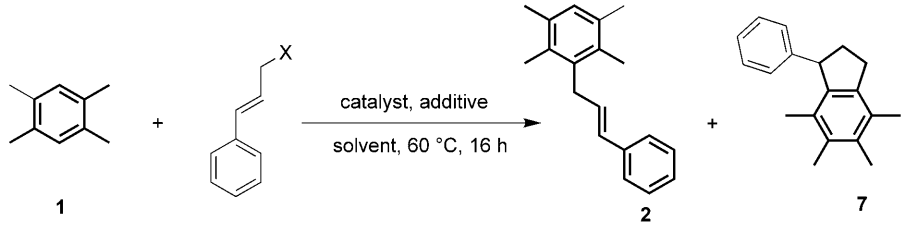


Figure 1. Molecular structure of **7**. Hydrogen atoms have been omitted for clarity.

Table 1. Optimization of the eaction conditions.[a]



Entry	X	Catalyst	Solvent	Additive	Yield [%][a,b] of **7** and (**2**)
1	Cl	$Cu(OTf)_2$	CH_2Cl_2	--	85 (0)
2	Cl	--	CH_2Cl_2	--	0 (0)
3	Cl	$Sc(OTf)_3$	CH_2Cl_2	--	0 (0)[c]
4	Cl	HOTf	CH_2Cl_2	--	0 (0)[c]
5	Cl	$Cu(OTf)_2$	CH_2Cl_2	Et_3N	0 (30)
6	Cl	$Cu(OTf)_2$	CH_2Cl_2	Na_2CO_3	0 (15)
7	Cl	$CuCl_2$	CH_2Cl_2	--	0 (<5)
8	Cl	CuI	CH_2Cl_2	--	0 (0)
9	Cl	$Cu(OTf)_2$	THF	--	0 (<5)
10	Cl	$Cu(OTf)_2$	MeCN	--	0 (<5)
11	Cl	$Cu(OTf)_2$	DMF	--	0 (0)
12	Cl	$Cu(OTf)_2$	toluene	--	0 (0)[c]
13	OH	$Cu(OTf)_2$	CH_2Cl_2	--	0 (30)
14	OH	$Cu(OTf)_2$	CH_2Cl_2	HCl	60 (40)
15	OAc	$Cu(OTf)_2$	CH_2Cl_2	--	20 (10)

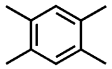
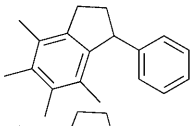
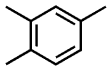
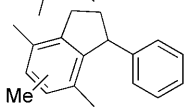
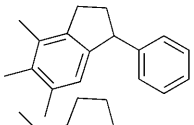
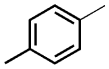
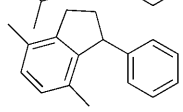
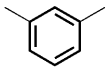
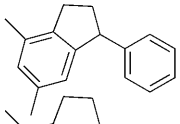
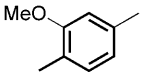
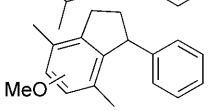
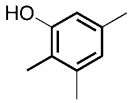
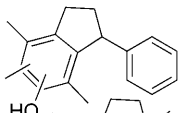
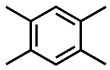
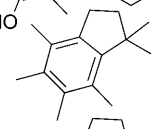
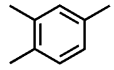
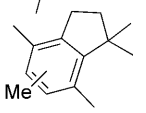
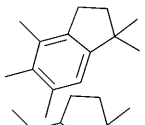
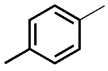
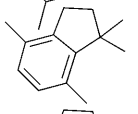
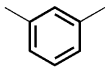
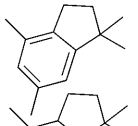
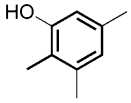
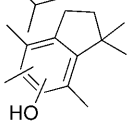
[a] *Reaction conditions:* durene (0.5 mmol), cinnamyl chloride (0.55 mmol), catalyst (5.0 mol%), CH_2Cl_2 (2 mL), 60 °C, 16 h.
[b] Excess amounts of additives (1 mmol) were used.
[c] An unidentified product was observed.

promoted methyl migration reaction itself is well known as a reversible process and the efficiency of this migration is low.[16] Although we were unable to isolate intermediate **3**, it was clearly observed from the final product that this methyl migration process was very efficient in this system. In the final step, intermediate **3** underwent an acid-induced intramolecular alkylation to form cyclized product **7**.[8,17] The preference to form the stable final product **7** may be the major factor in determining the equilibria of the previous two steps, in which the forward reaction was favored, forming the desired intermediates.

In summary, $Cu(OTf)_2$ catalyzed the first allylation step of the reaction and the hydrogen chloride that was generated from the first step played important roles in the methyl migration and the intramolecular alkylation steps, *vide infra*.

Other protic acids or Lewis acids did not promote the reaction to from product **7** (Table 1, entries 3 and 4). When cinnamyl alcohol **6** was used instead of cinnamyl chloride **4**, only **2** was isolated in low yield (Table 1, entry 13). However, when cinnamyl acetate **8** was used as the reactant, both **2** and **7** were produced in a 1:2 ratio (Table 1, entry 15). This is because no strong acids were generated in both systems with cinnamyl alcohol and cinnamyl acetate. Similarly, when an excess amount of a base, such as triethylamine or sodium carbonate, was added to the durene/cinnamyl chloride reaction system, only **2** was observed in low yield (Table 1, entries 5 and 6). Further investigations indicated that **2** can be converted to **7**

Table 2. $Cu(OTf)_2$-catalyzed cycloaddition of arene with haloalkenes.[a]

Entry	Arene	Temp. [°C]	Time [h]	Product	Yield [%][b]
1	 **1**	60	16	 **7**	85 (78)
2		60	16		95[c]
3	 **9**	100	16	 **10**	55
4	 **11**	100	16	 **12**	62
5	 **13**	140	42	 **14**	72
6	 **15**	100	16	 **16**	70
7	 **17**	100	16	 **18**	78
8	 **19**	60	16	 **20**	90
9	 **1**	80	16	 **21**	51
10	 **9**	100	16	 **22**	40
11	 **11**	100	16	 **23**	61
12	 **13**	100	16	 **24**	60
13	 **15**	100	16	 **25**	71
14	 **19**	100	16	 **26**	79

[a] *Reaction conditions:* arene (1 mmol), haloalkene (1.1 mmol), catalyst (5.0 mol%), CH_2Cl_2 or $C_2H_2Cl_4$ (4 mL).
[b] GC yield and isolated yield in parentheses.
[c] 2 mmol of cinnamyl chloride were used.

under standard reaction conditions with stoichiometric amounts of acid additives, such as trifluoroacetic acid, HCl or acid generated *in situ* from the reaction between **1** and cinnamyl chloride [Table 1, entry 14, Scheme 2(**b**)]. If no acid additives were present, **2** could not be converted to **7** in the presence of just $Cu(OTf)_2$ as catalyst.

Solvent effects were also examined, and only dichloromethane gave good results (Table 1, entries 1, 9–12). It was also interesting to note that without any

arenes present in the reaction mixture, cinnamyl chloride alone, in the presence of $Cu(OTf)_2$ catalyst in CH_2Cl_2, generated the cyclicized product (1,2-diphenyl-3-chloromethylcyclopentene). The isolated product was believed to be derived from the intermolecular reaction between two cinnamyl chloride molecules (see Supporting Information). No such cyclic dimer was observed when arenes were present in the reaction mixture.

This reaction protocol was then extended to other substrates. As expected, most of substituted benzenes were active in this reaction to give the corresponding dihydroindenes in moderate to good yields, Table 2. As shown in entries 1–6, bis-, tris- and tetrakis-methyl-substituted benzenes reacted with cinnamyl chloride to form the desired products in good yield. There were no methyl migration steps involved in the reaction of substrates **9**, **11**, **13** and **15**. From the mechanism discussion of substrate **1** we know that the methyl migration step is much slower than final cyclization step. Here reactions of arenes **9**, **11**, **13** and **15** would prefer go through a direct cyclization. Almost no reaction was observed between 1,3,5-trimethylbenzene and cinnamyl chloride under similar conditions. The same reaction was also found to be efficient for substituted phenols, (entries 7 and 8). A very good yield of **20** was obtained when the reaction was carried out with substrate **19**, indicating that the methyl migration step must have occurred. Reactions between 3,3-dimethylallyl bromide and arenes were also examined, and similar cycloaddition products **21**–**26** were obtained (Table 2, entries 9–14).

In conclusion, a one-pot $Cu(OTf)_2$-catalyzed synthesis of dihydroindenes from substituted benzenes and cinnamyl chloride has been developed. The final acid-catalyzed cyclization not only achieved the structurally important dihydroindene skeleton, it was also the key contribution in promoting the preceding aromatic alkylation step and methyl migration step in a smooth manner under the relatively mild condition, both of which were considered to be very challenging by themselves. This efficient method can be applied to the synthesis of a variety of indane skeletons or benzo-fused carbocycles.

Experimental Section

All solvents and chemicals were used as received from commercial suppliers, unless otherwise noted. Dry solvents and a glove box (Argon Innovative Technologies, Inc.) were used for the set-up of reactions. Gas chromatography-mass spectrometry (GC-MS) analyses were performed on a Shimadzu GCMS QP2010 system, while gas chromatography (GC) analyses were conducted on an Agilent GC6890N system. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-400 instrument (400 MHz).

Typical Synthetic Procedure (Table 2, entry 1)

1 mmol of **1** (134 mg), 1.1 mmol of cinnamyl chloride **4** (151 mg) and 0.05 mmol of $Cu(OTf)_2$ (18 mg) were added into a reaction vial with 5 mL CH_2Cl_2 in a glove box. The reaction vial was capped and taken out, heated to 60 °C and kept stirring for 16 h. Then, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL) and water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was dried ($MgSO_4$), and concentrated. The pure product was obtained through flash silica gel column chromatography of the residue using hexane as the eluent.

Acknowledgements

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