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Carbon–Carbon Bond Formation via the Electrophilic Addition of Carbocations to Allenes

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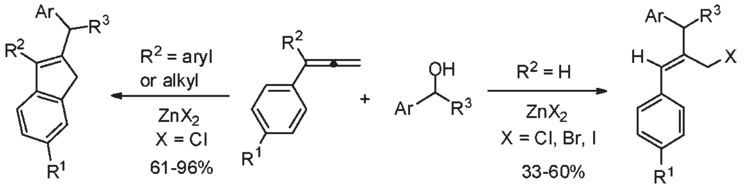
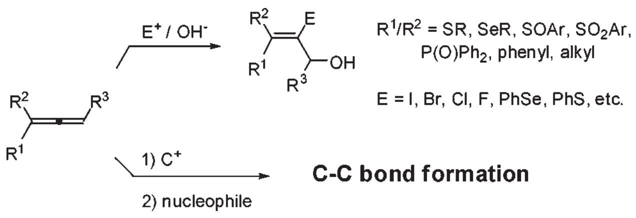
ABSTRACT



A novel electrophilic addition of aryl-substituted allenes and carbocations forming a carbon–carbon bond is described. Stereodefined allylic halides and indenes were furnished with excellent regio- and stereoselectivity depending on the structure of allenes.

Electrophilic addition reactions of allenes have become increasingly attractive in organic synthesis as two functionalities may be introduced within one synthetic operation in high regio- and stereoselectivity.[1,2] In our previous reports, a variety of functional groups, such as sulfide, selenide, sulfoxide, sulfone, phosphine oxide, carboxylate, and butenolide, etc., have been introduced into allenes to control the regio- and stereochemistry (Scheme 1).[3] In these reactions, the electrophilic moiety (I, Br, Cl, F, PhSe, PhS, etc.) is added to the central carbon atom of the allene moiety, and in most of these reactions, the hydroxyl group acts as the nucleophile due to the presence of even a trace of water in the solvent. We envisioned that a carbocation may also act as the electrophile in such transformations to form a C–C bond directly. In this paper, we wish to report the realization of such a concept with the observation that the halogen anion and aromatic substituents participated in the reaction as the nucleophiles to afford stereodefined allylic halides or indenes (Scheme 1).

Scheme 1



Initially, we began by trying to react propa-1,2-dienylbenzene **1a** with a 1,3-diphenyl allyl cation generated from the treatment of 1,3-diphenylprop-2-en-1-ol **2a** in toluene with ZnI_2.[4] Interestingly (1*Z*,4*E*)-(1,3,5-triphenyl)-2-(iodomethyl)penta-1,4-diene *Z,E*-**3a** was formed in 46% yield, indicating that the iodine anion was acting as the nucleophile.[5] However, the stereochemistry is opposite from our previous reports on such chlorinations,[5] as determined by an NOE study of **3c** (Figure 1). In addition, it should be noted that the reaction with Selectfluor and NBS afforded the 2-halo-2-propenol as the only or major product,[6] indicating the influence of the electrophile on the

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(1) For a review, see: Ma, S. *Ionic Addition to Allenes. In Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

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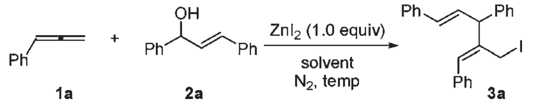
reactivity of the in situ formed allylic intermediate. Efforts were then made to optimize the reaction conditions (Table 1). Of the solvents screened, CH_2Cl_2 was the better choice to afford **3a** in 66% yield (Table 1, entry 5). The yield of **3a** was further improved to 73% when the reaction was carried out at 0 °C (Table 1, entry 8). However, the reaction at −40 °C gave **3a** only in 54% yield (Table 1, entry 9).

Table 1. Optimization of Conditions for the ZnI_2-Mediated Electrophilic Carbochlorination of 1,3-Diphenylprop-2-en-1-ol **2a** with Propa-1,2-dienylbenzene **1a**[a]



entry	solvent	temp	time (h)[b]	yield of **3a** (%)[c]
1	Toluene	rt	26	46
2	EtOAc	rt	48	NR
3	THF	rt	21	trace
4	MeCN	rt	18	0
5	CH_2Cl_2	rt	9	66
6	$CHCl_3$	rt	12	62
7	$ClCH_2CH_2Cl$	rt	16	14
8	**CH_2Cl_2**	**0 °C**	**15**	**73**
9	CH_2Cl_2	−40 °C	48	54

[a] The reactions were conducted using 0.2 mmol of **1a**, 0.2 mmol of **2a**, and 0.2 mmol of ZnI_2 in 2 mL of solvent under a nitrogen atmosphere in a Schlenk tube. [b] The reaction was monitored by TLC. [c] Determined by ^1H NMR of crude product.

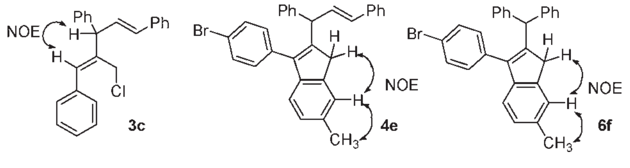
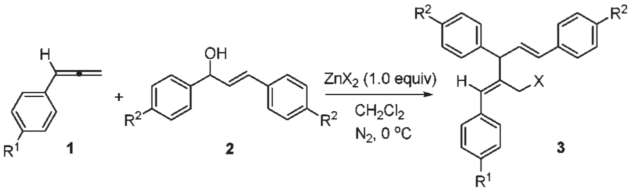


Figure 1. NOE study of **3c**, **4e**, and **6f**.

By utilizing different ZnX_2, different halogen atoms (I, Br, Cl) could be smoothly introduced into corresponding **3a**−**c** in 36−60% yields (Table 2, entries 1−3). Reactions employing other aryl-substituted propadienes **1b** and **1c** were also carried out successfully to furnish **3d**−**f** in 33−53% yield (Table 2, entries 4−6). 1,3-Diarylallyl alcohol **2b** could also be utilized to construct allylic iodides **3g** in 53% yield, respectively (Table 2, entry 7). It should be noted that such stereodefined allylic halides are not easy to make and ZnI_2 provided the highest yields.[7]

Further exploration on the $ZnCl_2$-promoted reaction of 1,1-diphenylpropa-1,2-diene **1d** and 1,3-diphenylprop-2-en-1-ol **2a** surprisingly led to the observation that, instead of 1,4-pentadiene product **3i**, indene product **4a** was observed in 88% yield (Table 3, entry 1). It should be noted that indenes are important core structures in organic chemistry, which serve as building blocks for ligands in metallocene-based olefin polymeriztion catalysts,[8] functional materials,[9] and bioactive pharmaceutical compounds.[10] This indicates that the formed allylic cationic intermediate may undergo a Friedel−Craft-type reaction with one of the two phenyl rings, indicating the dramatic influence of the initial electrophile on the reactivity of the formed intermediate via the intermolecular addition with the allenes.[3,6] Then we focused on optimizing the conditions (Table 3). Besides $ZnCl_2$, ZnI_2 was also tested in this reaction to yield **4a** in a lower yield (76% vs 88%, compare Table 3, entries 2 and 1). When the reaction was conducted at rt, the yield of **4a** was improved to 97% (Table 3, entry 3). The reaction under reflux did not give better results (Table 3, entry 4); other solvents were tested with CH_2Cl_2 being most suitable (Table 3, entries 5−10). When the amount of $ZnCl_2$ was reduced to 0.5 equiv, the yield of **4a** dropped to 80% (Table 3, entry 11).

Table 2. Reaction of Arylpropa-1,2-dienes **1** and 1,3-Diarylprop-2-en-1-ol **2** for the Synthesis of 1,4-Pentadiene Derivatives **3**[a]



	1	**2**			
entry	R^1	R^2	X	time (h)[b]	yield of **3** (%)[c]
1	H (**1a**)	H (**2a**)	I	15	60 (**3a**)
2	**1a**	**2a**	Br	15	40 (**3b**)
3	**1a**	**2a**	Cl	20	36 (**3c**)
4	Me (**1b**)	**2a**	I	13	53 (**3d**)
5	**1b**	**2a**	Cl	19	33 (**3e**)
6	Cl (**1c**)	**2a**	I	40	50 (**3f**)
7	**1a**	Cl (**2b**)	I	6	53 (**3g**)

[a] The reactions were carried out using 1.0 equiv of **1**, 1.0 equiv of **2**, and 1.0 equiv of ZnX_2 in CH_2Cl_2 under a nitrogen atmosphere at 0 °C. [b] The reaction was monitored by TLC. [c] Isolated yields.

With these optimized reaction conditions (Table 3, entry 3), the scope of the $ZnCl_2$-mediated reaction of

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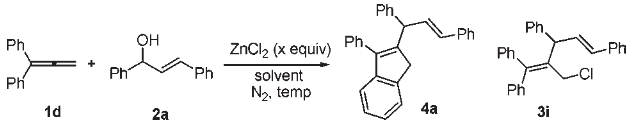
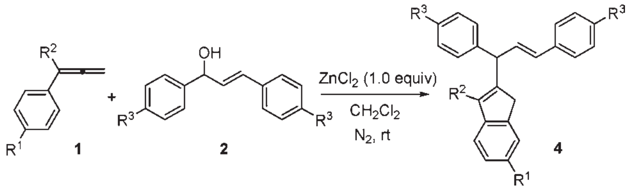
Table 3. Optimization of Conditions for the Electrophilic Addition of 1,3-Diphenylprop-2-en-1-ol **2a** with 1,1-Diphenylpropadiene **1d**[a]



entry	solvent	temp	x	time[b]	yield of **4a** (%)[c]
1	CH_2Cl_2	0 °C	1.0	2 h	88
2[d]	CH_2Cl_2	0 °C	1.0	2 h 30 min	76
3	$\mathbf{CH_2Cl_2}$	**rt**	**1.0**	**40 min**	**97**
4	CH_2Cl_2	reflux	1.0	30 min	83
5	$CHCl_3$	rt	1.0	45 min	46
6	$ClCH_2CH_2Cl$	rt	1.0	1 h 20 min	73
7	toluene	rt	1.0	3 h	36
8	THF	rt	1.0	50 min	69
9	EtOAc	rt	1.0	45 min	40
10	MeCN	rt	1.0	35 min	31
11	CH_2Cl_2	rt	0.5	3 h 45 min	80

[a] Unless otherwise specified, the reactions were conducted using 0.2 mmol of **1d**, 0.2 mmol of **2a**, and 0.2 mmol of $ZnCl_2$ in 2 mL of solvent under a nitrogen atmosphere in a Schlenk tube. [b] The reaction was monitored by TLC. [c] Determined by ^1H NMR of crude product. [d] The reaction was conducted utilizing 1.0 equiv of ZnI_2.

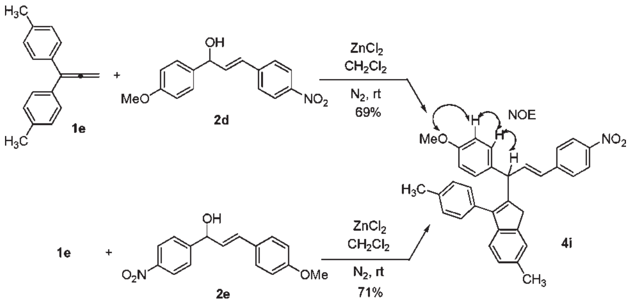
Table 4. Reaction of Allenes **1** and 1,3-Diarylprop-2-en-1-ols **2** for the Synthesis of Indene Derivatives **4**[a]



	1		**2**		
entry	R^1	R^2	R^3	time[b]	yield of **4** (%)[c]
1	H	Ph (**1d**)	H (**2a**)	40 min	89 (**4a**)
2	Me	p-$CH_3C_6H_4$ (**1e**)	**2a**	35 min	77 (**4b**)
3	Cl	p-ClC_6H_4 (**1f**)	**2a**	5 h 50 min	81,[d] 85[e] (**4c**)
4	Me	p-ClC_6H_4 (**1g**)	**2a**	1 h	90 (**4d**)
5	Me	p-BrC_6H_4 (**1h**)	**2a**	1 h 5 min	86 (**4e**)
6	H	C_2H_5 (**1i**)	**2a**	25 min	61 (**4f**)
7	H	Ph (**1d**)	Cl (**2b**)	45 min	89 (**4g**)
8	H	Ph (**1d**)	OMe (**2c**)	1 h 30 min	64 (**4h**)

[a] Unless otherwise specified, the reactions were carried out using 1.0 equiv of **1**, 1.0 equiv of **2**, and 1.0 equiv of $ZnCl_2$ in CH_2Cl_2 under a nitrogen atmosphere at rt. [b] The reaction was monitored by TLC. [c] Isolated yields. [d] The reaction was conducted at rt for 5 h and 50 min. [e] The reaction was conducted under reflux for 35 min.

Scheme 2

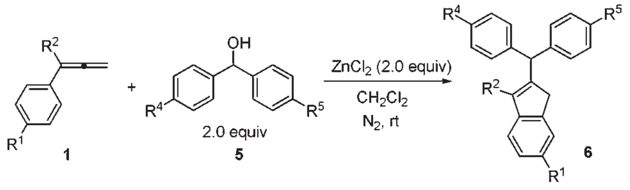


different terminal arylallenes **1** and 1,3-diarylprop-2-en-1-ols **2** was then studied. As demonstrated in Table 4, symmetric 1,1-diarylallenes **1d**–**f** afforded the corresponding indene derivatives **4a**–**c** in good to excellent yields (Table 4, entries 1–3). To our delight, the reaction showed excellent regioselectivity with nonsymmetric allenes **1g** and **1h**, which was established by the NOE study of **4e** (Table 4, entries 4 and 5; Figure 1): cyclization occurred on the aryl ring bearing an electron-donating group exclusively, furnishing **4d** and **4e** as the sole product in 90% and 86% yields, respectively. Allene **1i** bearing an alkyl group reacted smoothly to produce corresponding indene derivative **4f** in 61% yield (Table 4, entry 6). In addition, other 1,3-diarylallyl alcohols bearing a para-electron-withdrawing or -donating group **2b** and **2c** were also examined to give corresponding products **4g** and **4h** smoothly (Table 4, entries 7 and 8).

Notably, the reaction utilizing nonsymmetric alcohol **2d** also gave the product **4i** exclusively in 69% yield (Scheme 2). The regiochemistry of this reaction was established by the NOE study of **4i**. Interestingly, employment of nonsymmetric alcohol **2e** led to the same product **4i** in 71% yield.

Furthermore, we observed that diaryl methols may also be used as the source for the in situ generated carbocation. After a series of trials, it was demonstrated that diphenylmethanol **5a** afforded 2-diphenylmethyl-6-methyl-3-p-tolyl-1H-indene **6a** in high yield (Table 5, entry 1) when the amounts of both **5a** and $ZnCl_2$ were raised to 2.0 equiv. The scope of the electrophilic addition of allenes **1** and diarylmethanols **5** was then examined (Table 5). Substituted diarylmethanol **5b** and **5c** were smoothly utilized; **5c**, bearing a p-Cl group on the aryl ring, gave product with a higher yield than **5b** with a p-OMe group (96% vs 82%, Table 5, enties 2 and 3). Nonsymmetric alcohol **5d** was applied smoothly to generate **6d** in 87% yield (Table 5, entry 4). Nonsymmetric diaryl allenes **1g** and **1h** were also introduced successfully: corresponding products **6e** and **6f** were furnished in 89% and 79% yields, showing excellent regioselectivity with the cyclization occurring on the aryl ring with an electron-donating group (Table 5, entries 5 and 6). The regiochemistry of this reaction was established by the NOE study of **6f** (Figure 1). Allene **1i** bearing an alkyl group was also successfully utilized to generate corresponding indene derivative **6g** in 76% yield (Table 5, entry 7). The reaction may be easily conducted on a scale of 5 mmol of **1e** (1.100 g) in a slightly higher yield (Table 5, entry 8).

Table 5. Reaction of Allenes **1** and Diarylmethanols **5** for the Synthesis of Indene Derivatives **6**[a]



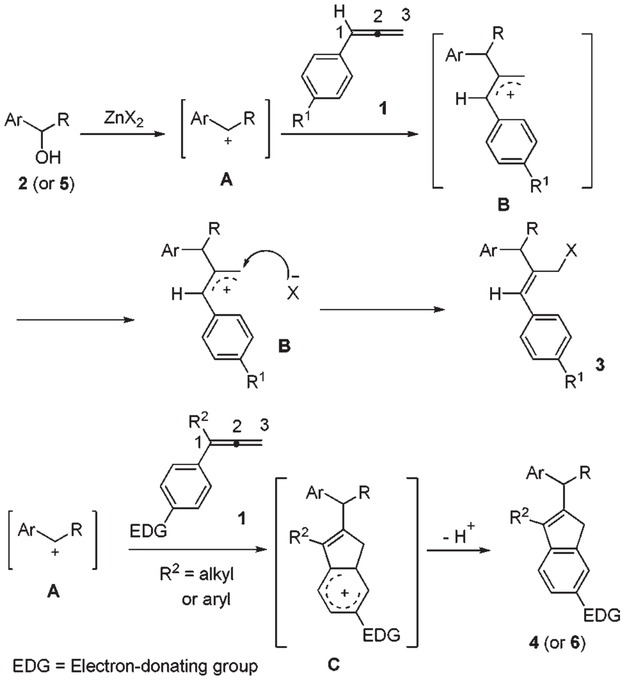
	1		5			
entry	R^1	R^2	R^4	R^5	time[b]	yield of **6** (%)[c]
1	Me	*p*-$CH_3C_6H_4$ (**1e**)	H	H (**5a**)	1 h	88 (**6a**)
2	**1e**		OMe	OMe (**5b**)	1 h 30 min	82 (**6b**)
3	**1e**		Cl	Cl (**5c**)	1 h 35 min	96 (**6c**)
4	**1e**		H	Cl (**5d**)	40 min	87 (**6d**)
5	Me	*p*-ClC_6H_4 (**1g**)	**5d**		45 min	89 (**6e**)
6	Me	*p*-BrC_6H_4 (**1h**)	**5a**		1 h	79 (**6f**)
7	H	C_2H_5 (**1i**)	**5a**		45 min	76 (**6g**)
8[d]	**1e**		**5b**		2 h	84 (**6b**)

[a] The reactions were carried out using 1.0 equiv of **1**, 2.0 equiv of **5**, and 2.0 equiv of $ZnCl_2$ in CH_2Cl_2 under a nitrogen atmosphere at rt. [b] The reaction was monitored by TLC. [c] Isolated yields. [d] The reaction was conducted with a 5 mmol (1.100 g) scale of **1e**.

A rationale for this transformation is shown in Scheme 3. Initially, carbocation **A** would be formed via the interaction of ZnX_2 with an alcohol.[4] Electrophilic addition of the in situ generated cations with allene **1** at the central carbon atom from the opposite side of the R^1-aryl group generates the stereodefined allylic carbocation intermediate **B**. Cationic intermediate **B** is captured by the halogen anion to form allylic halide **3**. In contrast, when alkyl or aryl groups are introduced as the R^2 group, a concerted process of cation interaction with the moiety and the Friedel–Crafts-type of attack of the electron-rich aryl ring would afford intermediate **C**. Elimination of H^+ forms the final product **4** or **6**.

In conclusion, we have disclosed the highly regio- and stereoselective electrophilic addition of carbocations with aryl-substituted allenes. When monosubstituted allenes are employed, the halogen anion acts as the nucleophile and attacks the allenes to generate stereodefined allylic halides. By utilization of 1,1-disubstituted allenes, a Friedel–Crafts cyclization reaction occurs to form indene derivatives. For the first time, the sp^3 carbocation adds directly to allenes forming a carbon–carbon bond with excellent regio- and stereoselectivity, providing a novel and efficient strategy to construct stereodefined allylic halides or substituted indene derivatives depending on the nature of the allenylic substituents. Due to the potential of the products, easy availability of the starting materials, and the high selectivity, this methodology may be of high interest for organic and pharmaceutical chemists.

Scheme 3. A Proposed Mechanism



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Supporting Information Available. Typical procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.