A facile Zr-mediated multicomponent approach to arylated allylic alcohols and its application to the synthesis of highly substituted indenes and spiroindenes†

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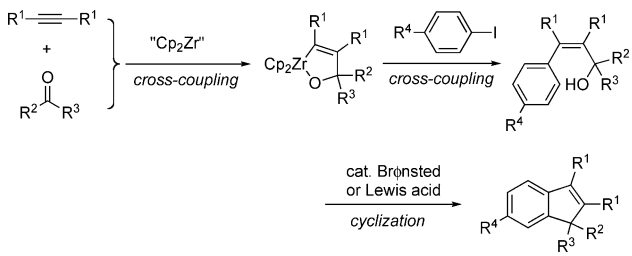
An efficient and one-pot procedure for the synthesis of arylated and stereodefined allylic alcohols has been achieved through zirconium-mediated multicomponent coupling reactions of alkynes, aldehydes (or ketones), and aryl iodides. The subsequent intramolecular Friedel–Crafts reactions of these allylic alcohols catalyzed by Brønsted or Lewis acids afford highly substituted indenes and spiroindenes under extremely mild reaction conditions. This methodology also provided a highly efficient route to the synthesis of spiroindenepiperidines.

Introduction

Substituted indene derivatives including spiroindenes are attractive compounds as they are versatile building blocks for functional materials,[1] biologically active substances,[2] and nonsteroidal anti-inflammatory drugs.[3] They can also be used as ligands by deprotonation for metallocene complexes utilized in the catalysis of olefin polymerization.[4] Despite their wide utility, their synthetic routes are fewer than those for structurally similar heterocycles such as benzofurans and indoles. The most important routes for the construction of indenes include the reduction/dehydration of indanones,[5] the cyclization of phenyl-substituted alkenes[6] or phenyl-substituted allylic alcohols,[7] the ring-expansion of substituted cyclopropenes,[8] metal-catalyzed protcols[9] *etc*. Although these methods are effective for the synthesis of indenes, they have certain drawbacks, more or less, for example, the strong acid medium or a stoichiometric amount of a Lewis acid that is sometimes required, limited methods for the preparation of starting materials, the moderate flexibility for the introduction of different substitutents onto the indene rings. On the other hand, synthetic organic transformations based on a wide variety of zirconacycles have been extensively developed in recent years due to the following advantages of zirconacycles:[10] (i) they are easily prepared by reductive coupling of unsaturated compounds such as alkynes, alkenes, nitriles, or ketones on a zirconocene equivalent, (ii) they are relatively stable under normal conditions, (iii) they have been proved as efficient precursors for a wide range of selective transformation reactions. An elegant synthesis of multi-substituted indenes has been reported by Xi and Takahashi *et al*[11] through hydrolysis of oxazirconacycles derived from the coupling reactions of alkyl alkynes with aryl methyl ketone or through hydrolysis of zirconacyclopentadienes. We recently reported an efficient synthetic approach to stereodefined (*Z*)-enynols *via* zirconium-mediated cross-coupling of alkynes, aldehydes or ketones, and alkynyl bromides in a one-pot procedure.[12] The thus formed (*Z*)-enynols were easily converted to dihydrofurans or furans *via* gold-catalyzed cyclizations.[13] Based on this work, we envisioned that an arylated allylic alcohol with a stereodefined C=C double bond might be formed by the coupling of oxazirconacycles with aryl iodides. These allylic alcohols can be used for the synthesis of highly substituted indenes by a catalytic protocol (Scheme 1). Now we'd like to report the details of these transformations.



Scheme 1

Results and discussion

Alkynes undergo selective intermolecular coupling with aldehydes or ketones using zirconocenes.[14] Recently, we have developed an improved procedure for zirconium-mediated alkyne–aldehyde coupling reactions under the "preactivated" conditions.[12b] The stereodefined allylic alcohols or 3-iodinated allylic alcohols were selectively formed *via* protonolysis or iodonolysis of the corresponding five-membered oxazirconacycles. The methodology has also been successfully applied to the synthesis (*Z*)-enynols through three different component coupling reactions of alkynes, aldehydes and alkynyl bromides in a one-pot procedure. The coupling reaction of aryl halides with organometals represents one of the most powerful methods for C–C bond formation. Although the coupling reactions of aryl iodides with various organozirconocenes such as vinyl zirconocenes, zirconacyclopentenes or

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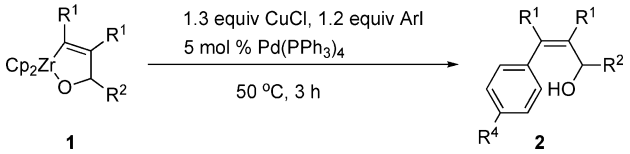
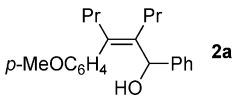
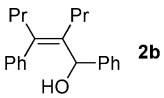
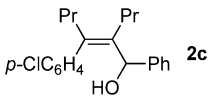
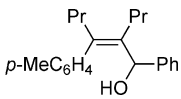
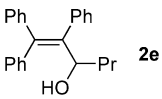
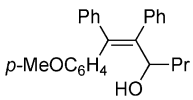
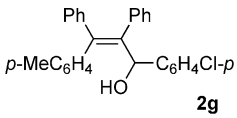
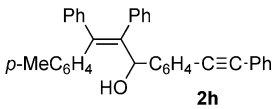
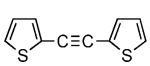
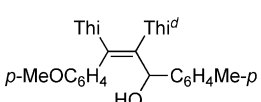
† Electronic supplementary information (ESI) available: Spectroscopic characterization of **2b–i**, **4b–4f**, **5b–j**, **8** and **9**. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/b804888f

zirconacyclopentadienes were known,[15] there is no report for the coupling of aryl iodides with oxazirconacycles. Here we found that treatment of oxazirconacycle **1a** (R^1 = Pr, R^2 = Ph) derived from alkyne–aldehyde coupling with 1.3 equiv of CuCl and 1.2 equiv of *p*-$MeOC_6H_4I$ in the presence of 5 mol% $Pd(PPh_3)_4$ at 50 °C for 3 h afforded arylated product **2a** in 43% yield after hydrolysis (Table 1, entry 1). The use of CuBr (1.3 equiv) afforded a similar yield (44%) of **2a**, however, in the case of CuI, only a low yield of 31% was obtained. It was suggested that the first step of this reaction is transmetalation of a Zr–C(sp^2) bond to a Cu–C(sp^2) bond to form an alkenyl copper species, which is followed by coupling with an arylpalladium intermediate generated from ArI and a Pd(0) catalyst to form the desired arylated products.[15] We next examined the coupling reactions of oxazirconacyclopentenes with various aromatic iodides. As shown in Table 1, alkyl, phenyl, and 2-thienyl-substituted alkynes and alkyl, aryl aldehydes are all compatible with coupling conditions, the corresponding allylic alcohols were formed in 38–70% yields. Aryl iodides bearing electron-donating or electron-withdrawing substituents could be used. For example, the reaction between zirconacycles derived from

Table 1 Synthesis of multi-substituted allylic alcohols through oxazirconacycles



1 **2**

Entry	$R^1C{\equiv}CR^1$	R^2CHO	ArI	Product	Yield (%)[a]
1	PrC≡CPr	PhCHO	*p*-$MeOC_6H_4I$	 **2a**	43
2	PrC≡CPr	PhCHO	PhI	 **2b**	61[b]
3	PrC≡CPr	PhCHO	*p*-$ClCC_6H_4I$	 **2c**	55
4	PrC≡CPr	PhCHO	*p*-MeC_6H_4I	 **2d**	43
5	PhC≡CPh	PrCHO	PhI	 **2e**	62[c]
6	PhC≡CPh	PrCHO	*p*-$MeOC_6H_4I$	 **2f**	70
7	PhC≡CPh	*p*-ClC_6H_4CHO	*p*-MeC_6H_4I	 **2g**	61
8	PhC≡CPh	Ph–C≡C–C_6H_4CHO	*p*-MeC_6H_4I	 **2h**	38
9		*p*-MeC_6H_4CHO	*p*-$MeOC_6H_4I$	 **2i**	68

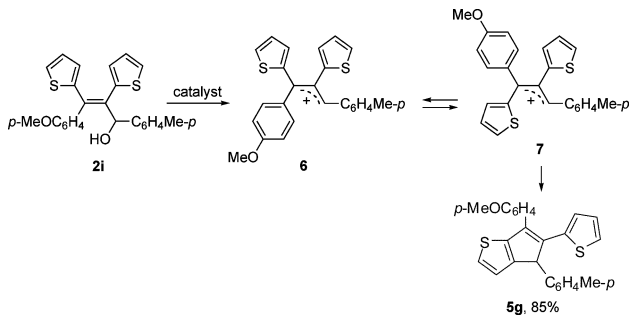
[a] Isolated yields. [b] Containing *ca.* 3% 2*E*-1-phenyl-2-propyl-hex-2-en-1-ol, which could not be separated from the main product. [c] Containing *ca.* 8% 1*E*-1,2-diphenyl-hex-1-en-3-ol, which could not be separated from the main product. [d] Thi is a 2-thienyl group.

bis(2-thienyl)acetylene and *p*-MeC_6H_4CHO with *p*-$MeOC_6H_4I$ resulted in the formation of **2i** in 68% yield (Table 1, entry 9).

Next, we examined the coupling reactions of aryl iodides with oxazirconacyclopentenes **3** derived from alkyne–ketone coupling reactions, which may be used for the preparation of stereodefined and fully substituted allylic alcohols. So far there are few methods for the synthesis of fully substituted allylic alcohols. Initially, we carried out the reaction under the same conditions employed for the coupling of zirconacycles **1** with aryl iodides, however, no expected products were observed. We envisioned that a facile coordination of the magnesium salt produced *in situ* during the exchange reaction of Cp_2ZrCl_2 and EtMgBr with the oxygen moiety might occur, which may further increase the steric hindrance around the reactive metal center. To our delight, it was found that the desired allylic alcohols **4** could be formed through addition of 0.4 mL 1,4-dioxane (to remove the magnesium salt). The representative results are shown in Table 2. As shown in Table 2, cyclic or acyclic ketones are all compatible under the controlled reaction conditions, the corresponding fully substituted allylic alcohols **4a–f** were formed in 23–62% yields. When cyclohexenone was employed, the coupling reaction with iodobenzene proceeded smoothly to afford allylic alcohol **4d** in 49% yield, while the double bond in the cyclic ring was well tolerated during the reaction (Table 2, entry 4).

With multi-substituted allylic alcohols in hand, we were interested in exploring the feasibility of using **2** and **4** in indene formation reactions. We began our investigation with allylic alcohol **2a** through a Friedel–Crafts cyclization. As we know, the main drawback of classical Friedel–Crafts reactions is that a strong acid medium or a stoichiometric amount of a Lewis acid is sometimes required, therefore the method is not compatible with sensitive functional groups. Recently, gold salt has emerged as a useful catalyst for Friedel–Crafts reactions.[16] We have also reported a gold-catalyzed direct amination of allylic alcohols *via* the formation of an allylic cation intermediate.[17] We first examined the reactivity of **2a** in the presence of various gold catalysts. Treatment of **2a** with 5 mol% $AuCl_3$ in CH_2Cl_2 or CH_3CN at room temperature for 1 h afforded the corresponding indene **5a** in 79% and 89% yields, respectively (Table 3, entries 1–2). AuCl or $Sc(OTf)_3$ worked well to generate **5a** in excellent yields of 90% and 91%, respectively (Table 3, entries 4–5). Further studies revealed that a Brønsted acid of $TSOH{\cdot}H_2O$[18] showed excellent catalytic activities to afford 92% yield of the desired product within one hour (Table 3, entry 6).

We chose $TSOH{\cdot}H_2O$ as the catalyst for subsequent experiments. The representative results are summarized in Table 4. The electronic effect of substitution on the aromatic ring at C-3 of allylic alcohols **2** was examined first. It was found that there were no significant differences in the reaction times or the yields between the allylic alcohols bearing an electron-donating group (*p*-MeO, *p*-Me) and those without a substituent on the aromatic ring (Table 4, entries 1–2, 4). However, when **2c** substituted with *p*-ClC_6H_4 was employed, the cyclization reaction was not clean using $TSOH{\cdot}H_2O$ as the catalyst; the desired product **5c** was obtained in 61% yield. The yield can be improved to 80% in the presence of 2 mol% $AuCl_3$ (Table 4, entry 3). The substituent effect on the alcoholic carbon of allylic alcohols was also investigated. Aryl, alkyl-substituted or phenyl, methyl-disubstituted substrates were all compatible with cyclization conditions, and high yields of the corresponding indenes were obtained in each case (Table 4, entries 1–7). It should be noted that in the case of **2i**, a 4*H*-cyclopenta[*b*]thiophene derivative **5g** was selectively obtained. This result indicated that the cyclization can be easily controlled by the electronic effects of the end groups, thus a highly reactive thiophene ring under electrophilic attack would undergo Friedel–Crafts cyclization more preferentially than an aryl ring (Table 4, entry 7 and Scheme 2). Interestingly, this method could also be used for the synthesis of spiroindenes **5h–j** with high yields (Table 4, entries 8–10).

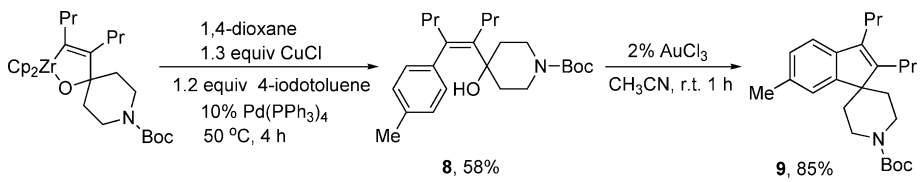


Scheme 2

Compounds containing spiropiperdine backbones have attracted much attention in pharmaceutical research due to their significant biological activities.[19] For example, they can be used as an amine moiety of highly active chemokine CCR2 receptor antagonists.[20] The synthetic routes for these compounds usually involve multistep procedures with low overall yields.[19–20] As shown in Scheme 3, spiroindenepiperidine derivatives could be efficiently prepared using our methods. The precursor **8** for ring-closure could be conveniently constructed through multicomponent coupling of 4-octyne, *tert*-butyl 4-oxopiperidine-1-carboxylate and 4-iodotoluene in 58% yield. Cyclization of **8** to spiropiperdine **9** was achieved in 85% yield using 2% $AuCl_3$ as the catalyst.

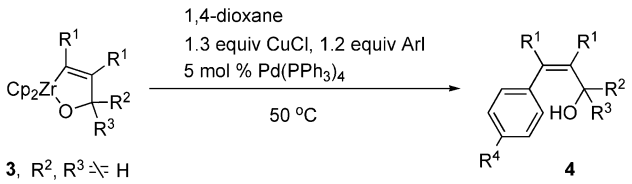
Conclusion

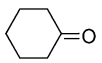
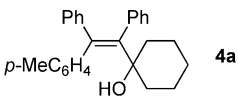
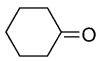
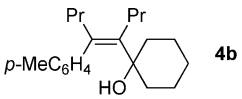
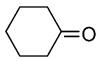
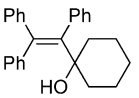
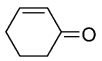
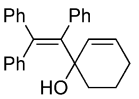
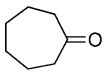
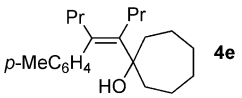
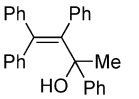
In summary, we have succeeded in developing an efficient, general, and one-pot procedure for the synthesis of arylated and stereodefined allylic alcohols through zirconium-mediated



Scheme 3

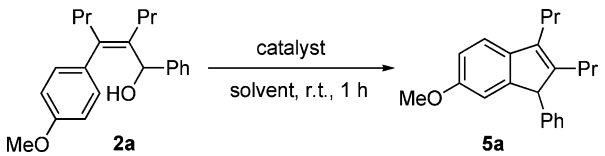
Table 2 Synthesis of fully substituted allylic alcohols through oxazirconacycles



Entry	$R^1C{\equiv}CR^1$	R^2R^3CO	ArI	Product	Yield (%)[a]
1	PhC≡CPh		*p*-MeC_6H_4I	 **4a**	62
2	PrC≡CPr		*p*-MeC_6H_4I	 **4b**	62
3	PhC≡CPh		PhI	 **4c**	61
4	PhC≡CPh		PhI	 **4d**	49
5	PrC≡CPr		*p*-MeC_6H_4I	 **4e**	23
6	PhC≡CPh	PhCOMe	PhI	 **4f**	45

[a] Isolated yields.

Table 3 Optimization studies for the cyclization reaction of **2a**



Entry	Catalyst (mol%)	Solvent	Yield (%)[a]
1	$AuCl_3$ (5%)	CH_2Cl_2	79
2	$AuCl_3$ (5%)	CH_3CN	89
3	$AuCl_3$ (2%)	CH_3CN	90
4	AuCl (5%)	CH_3CN	90
5	$Sc(OTf)_3$ (5%)	$ClCH_2CH_2Cl$	91
6	$TSOH{\cdot}H_2O$ (5%)	CH_3CN	92
7	20% HCl[b]	THF	—[c]

[a] Isolated yield. [b] 20% HCl solution was used. [c] The reaction was not clean, the major products are the mixtures of butadienes derived from dehydration of **2a**.

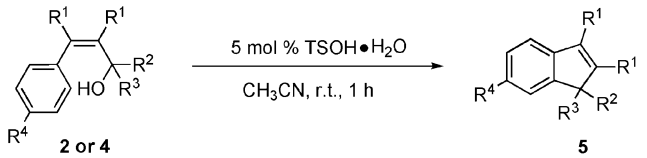
multicomponent coupling reactions of alkynes, aldehydes/ketones, and aryl iodides. The intramolecular Friedel–Crafts reactions of a wide variety of multi-substituted allylic alcohols catalyzed by Brønsted or Lewis acids afford highly substituted indenes and spiroindenes under extremely mild reaction conditions. This methodology also provided a highly efficient route to the synthesis of spiroindenepiperidine derivatives. Further studies to extend the scope of the synthetic utility for indene formations are in progress in our laboratory.

Experimental

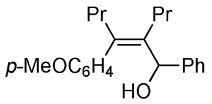
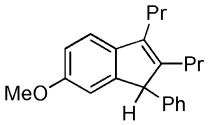
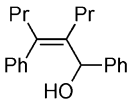
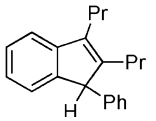
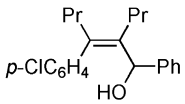
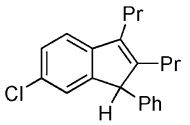
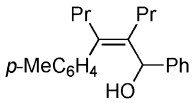
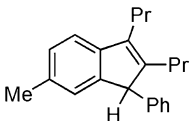
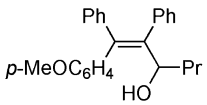
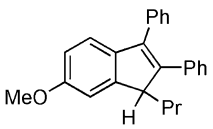
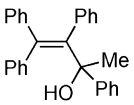
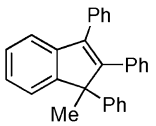
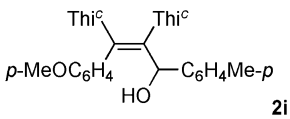
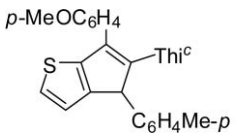
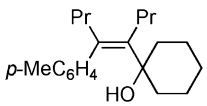
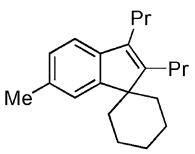
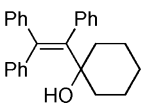
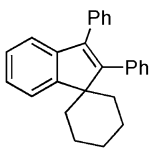
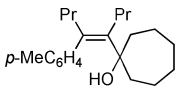
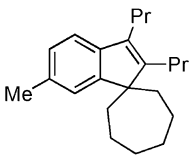
General methods

All reactions using zirconocenes were carried out using standard Schlenk techniques under nitrogen. THF was distilled from sodium–benzophenone. CH_3CN was distilled from CaH_2. Unless noted, all commercial reagents were used without further purification. Zirconocene dichloride, aldehydes, ketones, and alkynes were used as purchased. Benzaldehyde and butyroaldehyde were distilled prior to use. Ethylmagnesium bromide (1.0 M solution in THF) was used as purchased. Oxazirconacycles **1**[12b] and **3**[14f] were prepared according to previously published procedures. ^1H, and ^{13}C NMR spectra were recorded on a Varian XL-300 MHz spectrometer at 300, and 75.4 MHz, respectively, and in $CDCl_3$ (containing 0.03% TMS) solutions. ^1H NMR spectra were recorded with tetramethylsilane ($\delta = 0.00$ ppm) as

Table 4 Synthesis of substituted indenes and spiroindenes *via* the cyclization reaction of **2** or **4**



2 or 4 **5**

Entry	Substrate	Product	Yield (%)[a]
1	 **2a**	 **5a**	92
2	 **2b**	 **5b**	86
3	 **2c**	 **5c**	80[b]
4	 **2d**	 **5d**	99
5	 **2e**	 **5e**	97
6	 **4f**	 **5f**	94
7	 **2i**	 **5g**	85
8	 **4a**	 **5h**	89
9	 **4c**	 **5i**	89
10	 **4e**	 **5j**	85

[a] Isolated yield. [b] $AuCl_3$(2 mol%) was used as catalyst. [c] Thi is a 2-thienyl group.

internal reference; ^{13}C NMR spectra were recorded with $CDCl_3$ ($\delta = 77.00$ ppm) as internal reference. 2D NMR experiments of HMQC, gCOSY and HMBC spectra were recorded in $CDCl_3$ solutions on a Varian XL-300 MHz spectrometer. Mass spectra and high-resolution mass spectra were obtained by using a Waters Micromass GCT mass spectrometer. Elemental analyses were performed on an Italian Carlo-Erba 1106 analyzer.

A general procedure for the preparation of arylated allylic alcohols *via* the palladium-catalyzed coupling reactions of oxazircon-acyclopentenes derived from alkyne–aldehyde coupling with aryl iodides

To a solution of Cp_2ZrCl_2 (0.365 g, 1.25 mmol) in THF (5 mL) was added EtMgBr (1.0 M THF solution, 2.5 mmol) at −50 °C. After stirring for 1 h at the same temperature, alkyne (1 mmol) was added and the reaction mixture was warmed to 0 °C and stirred for 3 h. The thus formed zirconacyclopentene was heated up to 50 °C for a few minutes (*ca.* 5 min), followed by slow addition of the corresponding aldehyde (1.2 mmol) at the same temperature. After stirring for 1 h, CuCl (1.3 mmol), aryl iodide (1.2 mmol), and $Pd(PPh_3)_4$ (5 mol%) were added successively. The reaction mixture was stirred at 50 °C for 3 h, then quenched with 3 N HCl solution (usually, within 2 minutes) and extracted with diethyl ether. The extract was washed with $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica-gel to afford the arylated allylic alcohols **2**.

2*Z*-3-(4-Methoxyphenyl)-1-phenyl-2-propylhex-2-en-1-ol (2a). Column chromatography on silica-gel (petroleum ether–ethyl acetate = 20 : 1–10 : 1) afforded the title product as yellow oil in 43% isolated yield. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.80 (t, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H), 0.92–1.03 (m, 1H), 1.22–1.44 (m, 3H), 1.79 (s, 1H), 1.88–1.98 (m, 1H), 2.03–2.16 (m, 1H), 2.30–2.36 (m, 2H), 3.78 (s, 3H), 5.38 (s, 1H), 6.86 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.17–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.10, 14.82, 21.05, 24.28, 29.78, 36.50, 55.12, 73.71, 113.50, 125.64, 126.57, 127.86, 129.62, 134.54, 137.18, 140.53, 143.14, 158.04. HRMS (EI) calcd for $C_{22}H_{28}O_2$ $[M]^+$: 324.2089, found 324.2086.

A general procedure for the preparation of arylated allylic alcohols *via* the palladium-catalyzed coupling reactions of oxazircon-acyclopentenes derived from alkyne–ketone coupling with aryl iodides

To a solution of Cp_2ZrCl_2 (0.365 g, 1.25 mmol) in THF (5 mL) was added EtMgBr (1.0 M THF solution, 2.5 mmol) at −50 °C. After stirring for 1 h at the same temperature, alkyne (1 mmol) was added and the reaction mixture was warmed to 0 °C and stirred for 3 h. To this reaction mixture containing zirconacyclopentene was added the ketone (1.2 mmol), and then the mixture was warmed to 50 °C. After stirring for 2 h, 1,4-dioxane (0.4 mL), CuCl (1.3 mmol), aromatic iodide (1.2 mmol), and $Pd(PPh_3)_4$ (5 mol%) were added successively. The resulting mixture was stirred at 50 °C until the reaction was completed as monitored by TLC or GC. Then the mixture was quenched with saturated NH_4Cl solution for 20 min and extracted with ether. The extract was washed with $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica-gel to afford the arylated allylic alcohols **4**.

1-(1*Z*-1,2-Diphenyl-2-*p*-tolylvinyl)cyclohexanol (4a). Column chromatography on silica-gel (petroleum ether–ethyl acetate = 20 : 1–15 : 1) afforded the title product as light yellow oil in 62% isolated yield. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.84–0.95 (m, 1H), 1.37–1.56 (m, 8H), 1.82 (d, $J = 8.4$ Hz, 2H), 2.30 (s, 3H), 6.79–7.32 (m, 14H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.08, 21.34, 24.98, 37.82, 75.56, 125.25, 125.85, 126.93, 127.31, 128.25, 128.76, 129.32, 130.84, 136.49, 139.82, 140.15, 140.74, 144.14, 148.35. HRMS (EI) calcd for $C_{27}H_{28}O$ $[M]^+$: 368.2140, found 368.2135.

A general procedure for the preparation of indenes and spiroindenes *via* TSOH·H_2O or $AuCl_3$-catalyzed cyclization of allylic alcohols

A solution of $AuCl_3$ in MeCN (0.05 M) was prepared. The reactions were carried out on a 0.25–0.4 mmol scale. To a 0.1 M solution of allylic alcohol in CH_3CN was added TSOH·H_2O (*p*-toluenesulfonic acid monohydrate, 5 mol%) or $AuCl_3$ (2 mol%) under a nitrogen atmosphere. The resulting solution was stirred at room temperature until the reaction was completed as monitored by TLC (1 h). The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica-gel to afford the indene products.

6-Methoxy-1-phenyl-2,3-dipropyl-1*H*-indene (5a). Column chromatography on silica-gel (petroleum ether–ethyl acetate = 30 : 1) afforded the title product as yellow oil in 92% isolated yield. ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H), 1.30–1.76 (m, 4H), 1.95–2.04 (m, 1H), 2.35–2.45 (m, 1H), 2.57 (t, $J = 7.2$ Hz, 2H), 3.75 (s, 3H), 4.41 (s, 1H), 6.76–6.85 (m, 2H), 7.04 (d, $J = 6.9$ Hz, 2H), 7.20–7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.13, 14.28, 22.20, 23.08, 27.45, 28.68, 55.45, 56.69, 110.39, 111.68, 118.76, 126.47, 128.22, 128.55, 137.14, 138.82, 140.67, 144.85, 150.04, 157.50. HRMS (EI) calcd for $C_{22}H_{26}O$ $[M]^+$: 306.1984, found 306.1980.

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