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Grignard Reagent/CuI/LiCl-Mediated Stereoselective Cascade Addition/Cyclization of Diynes: A Novel Pathway for the Construction of 1-Methyleneindene Derivatives

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Abstract: Diynes containing a cyclopropane group smoothly undergo a novel intramolecular and stereoselective cascade addition/cyclization reaction to produce the corresponding 1-methyleneindene derivatives in moderate to good yields. This interesting transformation is mediated by Grignard reagent/CuI with LiCl as an additive under mild conditions. The obtained product can easily be further functionalized through cyclopropyl ring opening. A plausible reaction mechanism has also been presented on the basis of deuterium labeling and control experiments.

Keywords: alkenes • alkynes • carbocycles • cyclization • Grignard reaction • small ring systems

Introduction

The indene skeleton, including 1-methyleneindene, has been recognized as a privileged fragment that exists in many natural products as well as drug candidates, and such compounds often have extraordinary biological properties in therapeutic use.[1] Additionally, several applications in the field of material science have also been discovered in recent years.[2] Many synthetic methodologies have been developed to access indene substructures.[3] Moreover, because functionalized indenes can be conveniently obtained from 1-methyleneindene, efficient synthetic approaches to the 1-methyleneindene skeleton has also attracted much attention. Inter/intramolecular strategies have been used with various substrates in the presence of metal catalysts, as well as other nonmetal processes (Figure 1).[4]

Recently, organocopper-mediated cyclization has been used, often with the participation of other metal salts such as Mg or Li, through the formation of ate-complexes to improve the reaction efficiency and chemoselectivity.[5,6] Considering that 1-methyleneindene derivatives have extensive applications and potential value in medicinal and material chemistry, we attempted to explore a new synthetic method with which to construct this kind of pivotal structural motif stereoselectively. Herein, we wish to report an effective and highly stereoselective synthetic method for the construction of the 1-methyleneindene skeleton. Cu^I, Grignard reagents and LiCl were employed as the catalytic system and diynes containing a cyclopropane group were used as substrates.

Results and Discussion

During our ongoing investigation into the preparation of functionalized vinylidenecyclopropanes (VDCPs),[7] we found that using diyne **1aa** as substrate (0.5 mmol, Ms = methanesulfonyl) in the presence of MeMgBr (2.5 mmol, 1.8 mL, 1.4 M in tetrahydrofuran (THF)/toluene = 1:3) with CuI (2.5 mmol) and LiCl (2.5 mmol) as the additives,[8] indene derivative **2aa** was obtained in 27 % yield, and **2aa′** was obtained in 12 % yield in THF at −40 °C within 12 h (Table 1, entry 1). Considering the importance of this indene structure, we decided to optimize the reaction conditions; the results are summarized in Table 1. As can be seen from Table 1, compound **2aa′** was always formed in low yields, but was not observed when **2aa** was obtained in high yields. We assume that **2aa′** was generated as an intermediate during the reaction. Use of LiCl as additive revealed that inclusion of this salt could dramatically increase the yield of **2aa**,[9] giving the desired product in 27 % yield with 56 % conversion at −40 °C (Table 1, entries 1 and 2). Carrying out the reaction at −20 or 0 °C gave **2aa** in 55 % yield (67 % conversion) and 81 % yield (> 99 % conversion), respectively (Table 1, entries 3 and 6). Further increasing the reaction temperature to 25 °C (room temperature) afforded **2aa** in lower yield (Table 1, entry 10). Investigation of other Cu^I or Cu^{II} salts such as CuCl, CuCN, CuBr, $CuCl_2$, and $CuBr_2$ in this reaction at −20, 0, or 25 °C, revealed that 1) no significant improvement was observed; 2) the inclusion of Cu^{II} salts impaired the reaction outcome; and 3) the inclusion of CuI gave the best result for the production of **2aa** (Table 1,

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302191. It contains spectroscopic charts of the compounds shown in Tables 1–3, X-ray crystal data of **2af**, **2c**, and **2g** as well as detailed descriptions of experimental procedures.

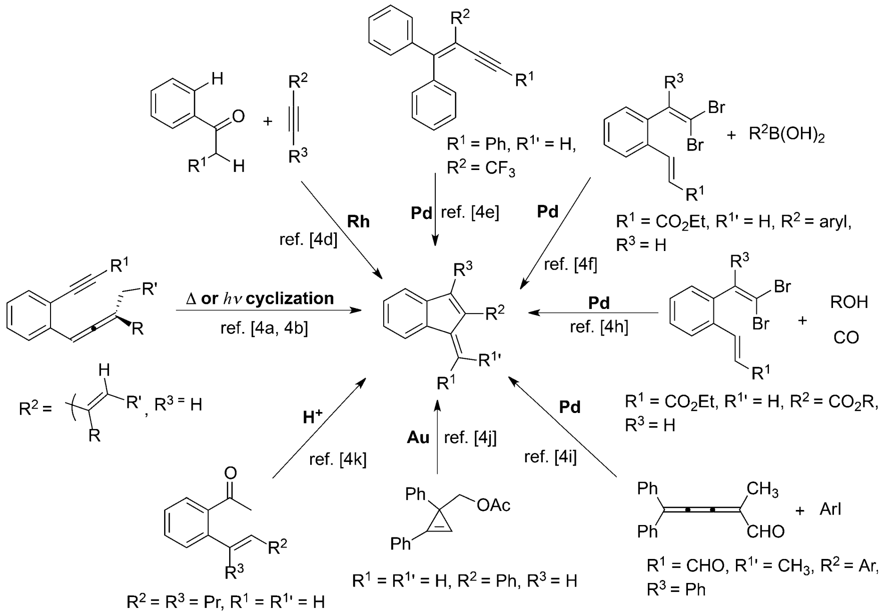
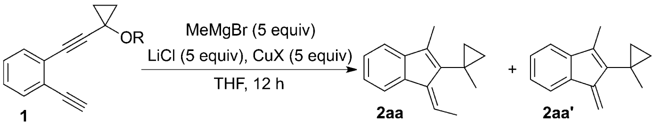


Figure 1. Synthetic approach to the production of 1-methyleneindene derivatives.

Table 1. Optimization of reaction conditions for the Grignard reagent/CuI/LiCl-mediated cascade addition/cyclization reaction of diynes **1**.[a]



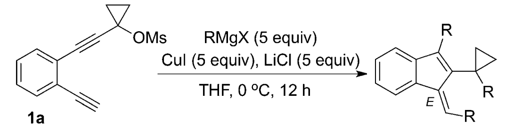
	1	R	CuX	Additive	*T* [°C]	Conv. [%][b]	Yield [%][c] 2aa	Yield [%][c] 2aa′
1	**1aa**	Ms	CuI	LiCl	−40	56	27	12
2	**1aa**	Ms	CuI	–	−40	46	6	13
3	**1aa**	Ms	CuI	LiCl	−20	67	55	–
4	**1aa**	Ms	CuCl	LiCl	−20	78	57	–
5	**1aa**	Ms	CuCN	LiCl	−20	73	31	14
6	**1aa**	Ms	CuI	LiCl	0	>99	81	–
7	**1aa**	Ms	CuCl	LiCl	0	>99	79	–
8	**1aa**	Ms	CuCN	LiCl	0	>99	37	5
9	**1aa**	Ms	CuBr	LiCl	0	>99	44	–
10	**1aa**	Ms	CuI	LiCl	25	>99	47	–
11	**1aa**	Ms	CuCl	LiCl	25	>99	45	–
12[d]	**1aa**	Ms	CuI	LiCl	0	57	8	10
13[e]	**1aa**	Ms	CuI	LiCl	0	66	21	–
14[f]	**1aa**	Ms	CuI	LiCl	0	91	40	–
15	**1aa**	Ms	$CuCl_2$	LiCl	0	90	10	5
16	**1aa**	Ms	$CuBr_2$	LiCl	0	96	14	12
17[g]	**1aa**	Ms	$CuBr_2$	LiCl	0	>99	56	–
18	**1ab**	Ac	CuI	LiCl	0	26	8	–
19	**1ac**	Ts	CuI	LiCl	0	91	43	–
20	**1ad**	H	CuI	LiCl	0	–	–	–

[a] Diyne substrate **1** (0.5 mmol) and the reagents were added to a reaction tube under argon, then the reaction was carried out in THF for 12 h. [b] Conversion was determined on the basis of recovered starting materials. [c] Isolated yield. [d] CuI (0.5 equiv.) was added. [e] CuI (1 equiv.) was added. [f] CuI (3 equiv.) was added. [g] MeMgBr (10 equiv.) was added.

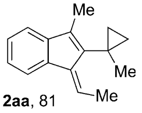
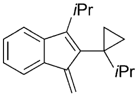
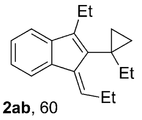
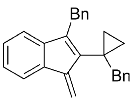
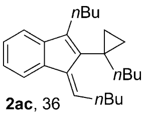
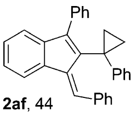
entries 4–5, 7–9, 11 and 15–16). Because it was considered that Cu^{II} salts are probably first reduced to Cu^{I} with the Grignard reagent by SET, we then increased the amount of MeMgBr employed to 10 equiv and found that **2aa** was obtained in higher yield (56%; Table 1, entries 16 and 17). Reducing the CuI loading decreased the yield of **2aa** (Table 1, entries 12–14). Examination of other OR functional groups indicated that when R was an acyl or a tosyl group (**1ab** and **1ac**), **2aa** was formed in lower yield; when OR was a free hydroxyl group (R = H; **1ad**), no reaction occurred under the standard conditions (Table 1, entries 18–20). Thus, we established that by using MeMgBr (5.0 equiv) combined with CuI (5.0 equiv) and LiCl (5.0 equiv) as the additives and carrying out the reaction at 0 °C in THF within 12 h, **2aa** could be obtained in the best yield (Table 1, entry 6).

Having established the optimized reaction conditions, we next examined the use of various Grignard reagents to extend the reaction scope; the results are presented in Table 2. The reactions proceeded smoothly in the presence of alkyl or aryl Grignard reagents to give the corresponding products **2aa**–**ae** and **2af** in 29–81% yields (Table 2, entries 1–6). By using *i*PrMgCl to initiate the reaction, indene derivative **2ad**, bearing a terminal olefin, was formed, presumably due to the steric bulk of the isopropyl Grignard reagent. When BnMgCl was employed in this reaction, a similar result was obtained, perhaps due to the electronic nature

Table 2. Substrate scope of the intramolecular cascade addition/cyclization reaction of diyne **1a** with Grignard reagents.[a]



1a

Entry	RMgX	Yield [%][b]	Entry	RMgX	Yield [%][b]
1	MeMgBr	 **2aa**, 81	4	*i*PrMgCl	 **2ad**, 29
2	EtMgBr	 **2ab**, 60	5	BnMgCl	 **2ae**, 40
3	*n*BuMgBr	 **2ac**, 36	6[c]	PhMgBr	 **2af**, 44

[a] Reaction conditions: Diyne **1a** (0.5 mmol), CuI (2.5 mmol), LiCl (2.5 mmol), THF, 0 °C, 12 h. [b] Isolated yield. [c] The structure of product **2af** was confirmed by X-ray diffraction analysis.

and steric effects of the benzyl group (Table 2, entry 4). Furthermore, the *E*-configuration and exocyclic alkene structure of **2af** was unambiguously determined by X-ray crystallographic analysis, the ORTEP drawing of which is shown in Figure 2 (the CIF data are presented in the Supporting Information). The NOESY-1D and NOESY-2D spectra of **2aa** revealed that the indene derivatives derived from alkyl Grignard reagents also had *E*-configuration (see the Supporting Information for the details).

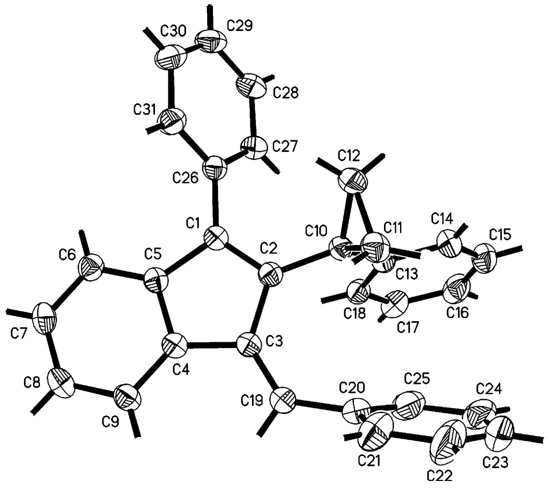


Figure 2. ORTEP drawing of **2af**.

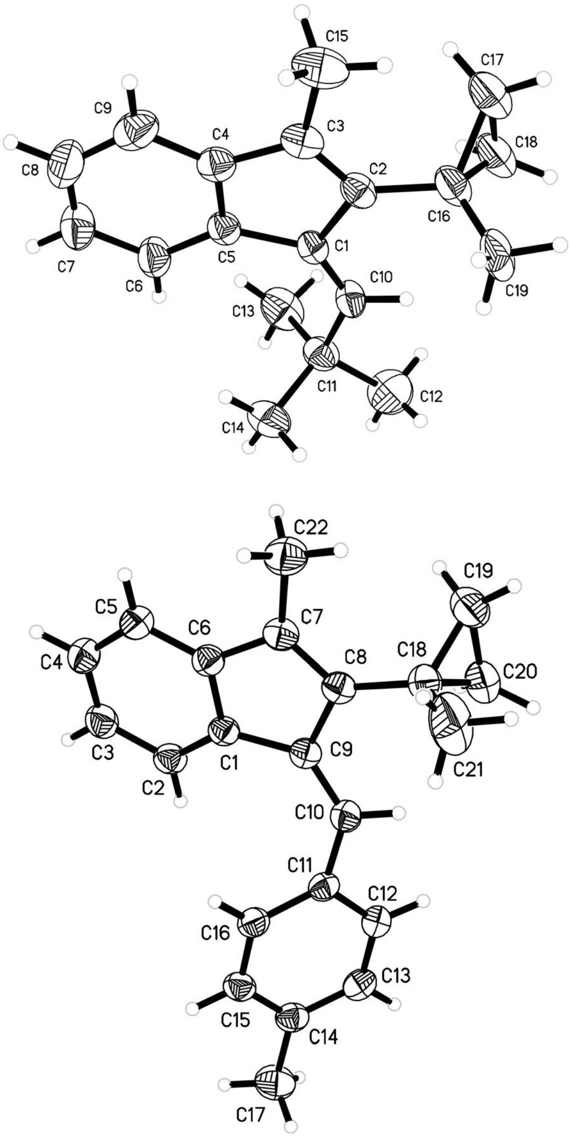
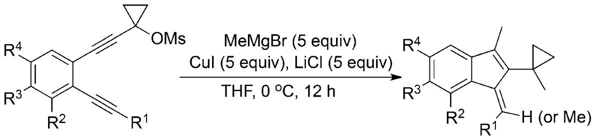


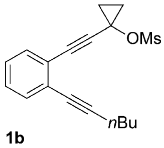
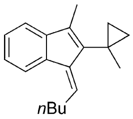
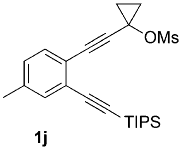
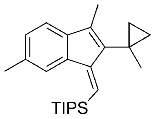
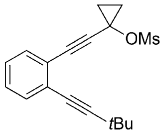
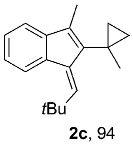
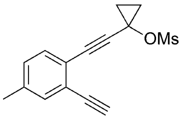
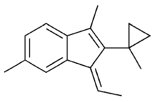
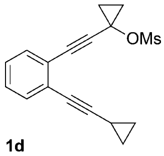
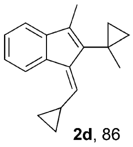
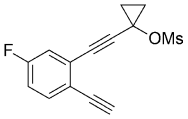
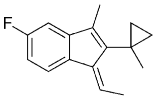
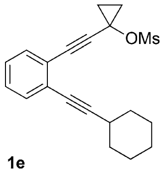
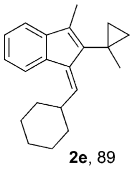
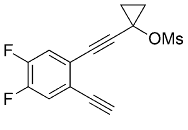
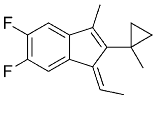
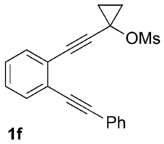
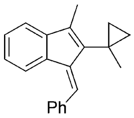
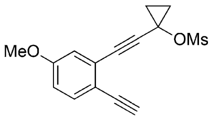
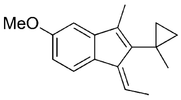
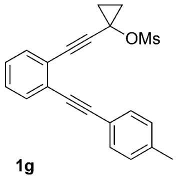
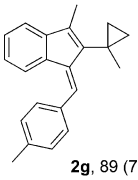
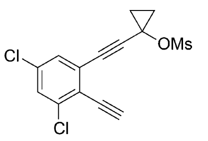
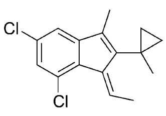
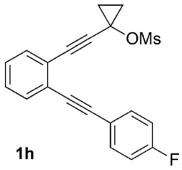
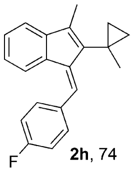
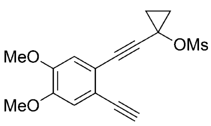
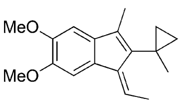
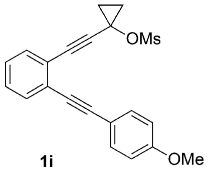
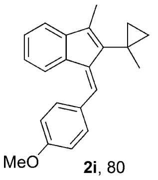
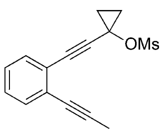
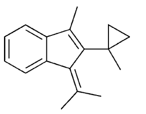
Figure 3. ORTEP drawings of **2c** and **g**.

Under the optimized conditions, the substrate scope was then examined; the results are summarized in Table 3. The reaction conditions were suitable for a variety of diyne substrates **1b–j** and **1q** with a range of functional groups on the terminal alkyne (Table 3, entries 1–9 and 16) and substrates **1j–p**, bearing either an electron-withdrawing or an electron-donating group on the aromatic ring (Table 3, entries 10–15), affording the desired indene derivatives in 70–99% yield. It is noteworthy that this cascade addition and cyclization process is stereospecific. For diyne substrates **1b–j**, having substitution on the terminal alkyne, the corresponding indene products were formed with *Z*-configuration (Table 3, entries 1-9); whereas for diyne substrates **1j–p**, with no substitution on the terminal alkyne, the corresponding indene products were formed with *E*-configuration (Table 3, entries 10–15). The structures of **2c** and **2g** were determined by X-ray crystallographic analysis; their ORTEP drawings are shown in Figure 3 (the related CIF data are presented in the Supporting Information). In the case of diyne substrate **1q**, the desired indene product **2q**, having two substituents on the terminal alkene, was obtained in 82% yield (Table 3, entry 16). It should also be noted that when MeMgBr (4.0 equiv), CuI (4.0 equiv), and LiCl (4.0 equiv) were used in this reaction, the yield of the desired indene product **2** decreased (Table 3, entry 6).

To explore a plausible reaction mechanism, several control experiments and isotope labeling experiments were carried out. As shown in Scheme 1, we found that by using 1-(phenylethynyl)cyclopropyl methanesulfonate as substrate, the corresponding vinylidenecyclopropane could be isolated in 92% yield under the standard conditions, which is consistent with previous reports [Scheme 1, Eq. (1)].[8] Another control experiment using **S10b** as the substrate also gave the corresponding vinylidenecyclopropane **21′** in 24% yield under the standard conditions, presumably due to the special electronic properties of the fluorine atom and the steric bulk of TIPS, suggesting that this novel cascade addition/cyclization reaction might proceed through a vinylidenecyclopropane-like intermediate [Scheme 1, Eq. (2); see the Supporting Information for details]. To verify the possibility of cross-coupling between vinyl and alkyl Grignard reagents, we also conducted a coupling reaction between (*E*)-styrylmagnesium bromide and MeMgBr under the standard conditions. However, the corresponding homo-coupling product was identified in 20% yield rather than the cross-coupling

Table 3. Substrate scope of the intramoleculor cycloaddition reactions of diynes **1** substituted on the terminal alkyne or on the aromatic ring.[a]

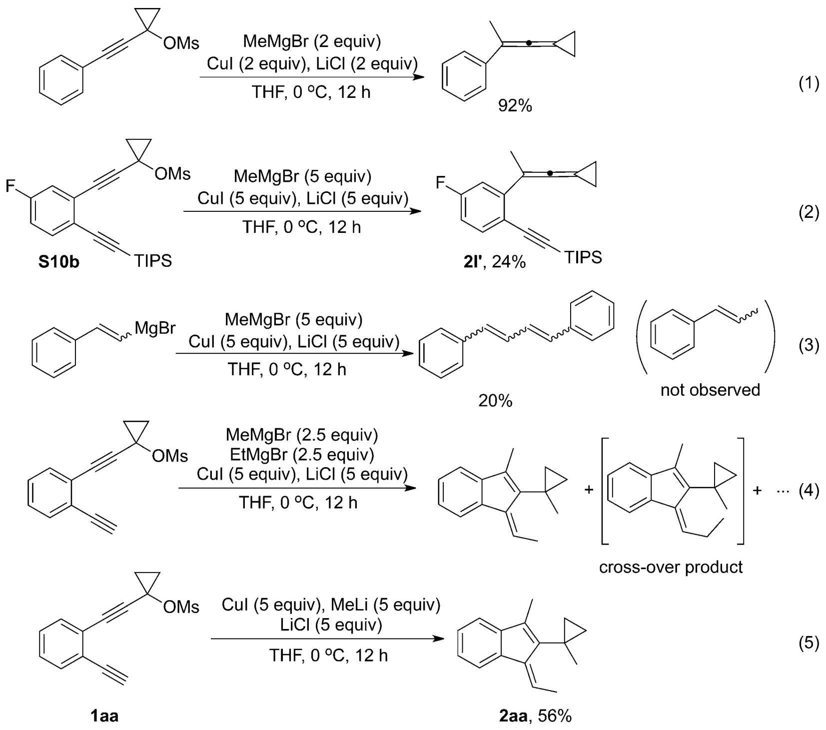


Entry	1	Yield [%][b]	Entry	1	Yield [%][b]
1	 **1b**	 **2b**, 88	9	 **1j**	 **2j**, 92
2[c]	 **1c**	 **2c**, 94	10	 **1k**	 **2k**, 80
3	 **1d**	 **2d**, 86	11	 **1l**	 **2l**, 81
4	 **1e**	 **2e**, 89	12	 **1m**	 **2m**, 81
5	 **1f**	 **2f**, 99	13	 **1n**	 **2n**, 72
6[d]	 **1g**	 **2g**, 89 (75[e])	14	 **1o**	 **2o**, 74
7	 **1h**	 **2h**, 74	15	 **1p**	 **2p**, 70
8	 **1i**	 **2i**, 80	16	 **1q**	 **2q**, 82

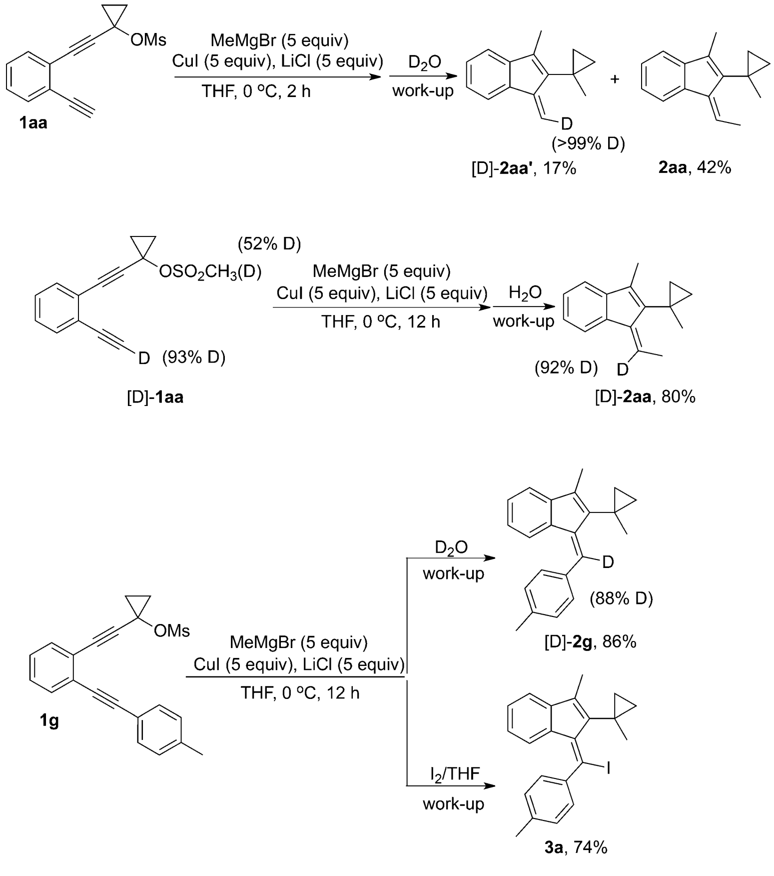
[a] Reaction conditions: Diyne **1** (0.5 mmol), CuI (2.5 mmol), LiCl (2.5 mmol), THF, MeMgBr (2.5 mmol), 0 °C, 12 h. [b] Isolated yield. [c] The structure was confirmed by X-ray diffraction analysis. [d] The structure of product **2g** was confirmed by X-ray diffraction analysis. [e] Isolated yield with CuI (2.0 mmol), LiCl (2.0 mmol) and MeMgBr (2.0 mmol) under the standard conditions.

product [Scheme 1, Eq. (3); see the Supporting Information for details]. Furthermore, when cross-over experiments were conducted with **1a** as substrate and MeMgBr (2.5 equiv) and EtMgBr (2.5 equiv) as reagents under the standard conditions to gain more insights into the coupling process, we found that the cross-over product was indeed formed (GC-MS analysis), suggesting that the cross-coupling process should exist in this particular case during the reaction [Scheme 1, Eq. (4); see the Supporting Information for details and product ratios]. To investigate whether carbomagnesiation or carbocupration was involved during the reaction, a control experiment using a combination of MeLi (5.0 equiv), CuI (5.0 equiv), and LiCl (5.0 equiv) without the use of Grignard reagent, was conducted [Scheme 1, Eq. (5)]. Under these conditions the desired product **2aa** was produced in 56 % yield, suggesting that methyl copper species is involved in the above reaction system.

To gain more mechanistic insights into the reaction, we conducted isotope labeling experiments to further examine the active intermediates in this reaction. First, by using D_2O to quench the reaction after 2 h, deuterated product [D]-**2aa′** (D content > 99 %) was obtained in 17 % yield with *E*-configuration, along product **2aa** in 42 % yield (Scheme 2, see the Supporting Information for details). Second, substrate [D]-**1aa** was prepared and the reaction was conducted under the optimized conditions, affording [D]-**2aa** in 80 % yield without deuterium loss. This finding excludes the possibility of methyl copper species adding to the methylene group of **2aa′** with subsequent elimination of a copper hydride species to form **2aa**. A second isotope labeling experiment, similar to the first, was carried out by using **1g** as the substrate under the standard conditions, producing [D]-**2g** in 86 % yield (D content = 88 %) (Scheme 2, see the Supporting Information for details). We



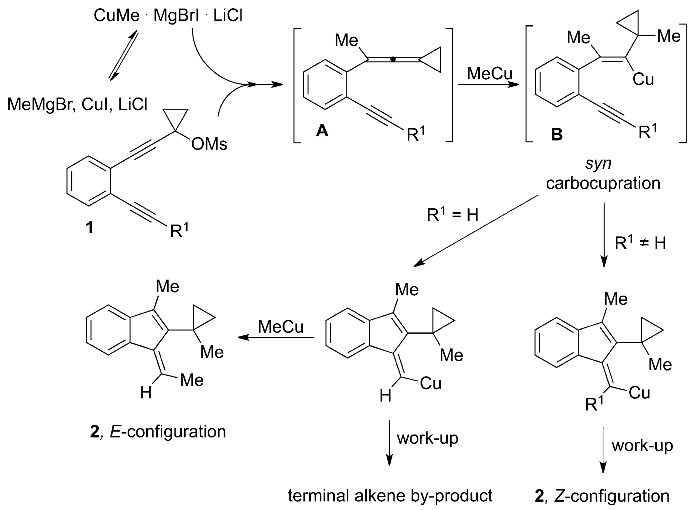
Scheme 1. Control and crossover experiments.



Scheme 2. Isotope/iodine labeling experiments.

also attempted to trap the generated active species in situ by inclusion of another electrophile such as iodine during the quenching process. Under these conditions, the iodinated product **3a** was indeed obtained in 74% yield (Scheme 2, see the Supporting Information for details). Together, these results implied that a vinyl Grignard type intermediate was generated during the reaction. In addition, on the basis of TLC analysis, we observed that during the reaction, **2aa'** could be transformed into **2aa**.

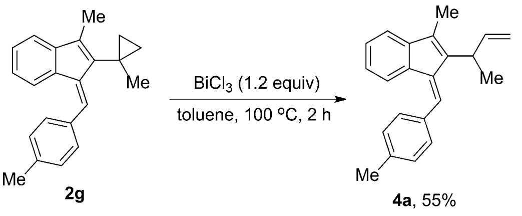
The control and deuterium labeling experiments described above, as well as previous reports,[8] allowed a plausible reaction mechanism for the formation of **2** to be outlined (Scheme 3) with **1** as a reaction model and MeMgBr as the reactant. Initial reaction of ethynylcyclopropyl methanesulfonate **1** with MeCu·MgBrI·LiCl, generated in situ, gives vinylidenecyclopropane (VDCP) intermediate **A**, which undergoes addition with the active copper species (MeCu) generated in situ, to give intermediate **B**. Subsequent intramolecular *syn*-carbocupration takes place to generate the corresponding vinyl copper species. When R^1 is not a hydrogen atom, subsequent addition of vinyl copper to the alkyne moiety gives the corresponding indene derivative **2** with *Z*-configuration after quenching (work-up). When $R^1 = H$, a similar intramolecular *syn*-carbocupration takes place to generate the corresponding vinyl copper species. In this case, the cross-coupling reaction with MeCu might take place to give the desired indene derivative **2** with *E*-configuration. For the copper species generated in situ from sterically bulky Grignard reagent, the cross-coupling reaction might take place with more difficulty,



Scheme 3. A plausible reaction mechanism for the formation of **2**.

thus only affording the terminal alkene indene derivative.[10] When $R^1 \neq H$, the steric bulk of the exocyclic alkene can prevent cross coupling with MeCu under the standard conditions.

Further transformation of indene derivative **2** could be realized through a cyclopropane ring-open reaction upon treatment with $BiCl_3$ at 100 °C in toluene.[11] The newly generated double bond could be used for further application (Scheme 4).



Scheme 4. Further transformation of **2g**.

Conclusion

We have developed a novel Grignard reagent/CuI/LiCl mediated stereoselective cascade addition/cyclization reaction of diynes containing a cyclopropane group that could be used to synthesize a 1-methyleneindene skeleton with a stereospecific exocylic olefin. The strained cyclopropane ring can be used for further transformation through ring opening. A plausible reaction mechanism for the formation of these 1-methyleneindene derivatives has been proposed on the basis of control experiments, deuterium labeling experiments, and previous reports. Further investigations on the mechanistic detail and the application of this novel synthetic method are in progress.

Experimental Section

General procedure for the synthesis of 2: To a flame-dried, argon-purged Schlenk tube, was added LiCl (2.5 mmol), which was heated vigorously, evacuated to dry, and purged with argon three times. CuI (2.5 mmol) was then added into the reaction vessel under argon. The reaction tube was set in an ice-water bath and THF (2 mL) was added to generate a white suspension. Grignard reagent (2.5 mmol) was added and the reaction mixture was stirred for 10 min, then 1-[(2-ethynylphenyl)ethynyl]cyclopropyl methanesulfonate (0.5 mmol) dissolved in THF (5 mL) was added. The reaction was allowed to proceed at 0 °C for 12 h, then quenched by the addition of water (2 mL) and the reaction mixture was extracted with petroleum ether. The organic phase was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography with petroleum ether as eluent.

Compound 2aa: Yield: 84 mg (80 %); yellow-green oil; ^1H NMR ($CDCl_3$, 400 MHz, TMS): $\delta = 0.67–0.88$ (m, 4H; CH_2), 1.35 (s, 3H; CH_3), 2.24 (s, 3H; CH_3), 2.35 (d, $J = 7.6$ Hz, 3H; CH_3), 6.64 (q, $J = 7.6$ Hz, 1H; CH), 7.11–7.22 (m, 3H; Ar), 7.45 ppm (d, $J = 7.6$ Hz, 1H; Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS): $\delta = 11.5$, 13.8, 15.9, 25.3, 29.7, 117.60, 117.63, 124.6, 124.8, 126.5, 137.5, 139.1, 139.3, 139.7, 142.1 ppm; IR (CH_2Cl_2): $\tilde{\nu} =$ 2993, 2951, 2923, 2855, 1640, 1463, 1422, 1477, 1350, 1109, 1046, 1020, 964, 931, 876, 833, 812, 759, 708 cm^{-1}; MS (%): *m/z*: 210 (19.55) $[M]^+$, 195 (70.84), 180 (30.71), 179 (16.59), 178 (15.52), 166 (15.74), 165 (50.06), 43 (100.00); HRMS (EI): *m/z* calcd for $C_{16}H_{18}$: 210.1409; found: 210.1413.

Compound 2aa′: Reacted for 3 h then worked up. Yield: 44 mg (42 %); yellow-green oil; ^1H NMR ($CDCl_3$, 400 MHz, TMS): $\delta = 0.67–0.73$ (m, 4H; CH_2), 1.29 (s, 3H; CH_3), 2.19 (s, 3H; CH_3), 5.90 (s, 1H; $=CH_2$), 5.94 (s, 1H; $=CH_2$), 7.12–7.16 (m, 2H; Ar), 7.22–7.26 (m, 1H; Ar), 7.49–7.51 ppm (m, 1H; Ar); ^{13}C NMR ($CDCl_3$, 100 MHz, TMS): $\delta = 10.9$, 12.4, 12.8, 26.0, 109.6, 117.9, 118.9, 125.0, 127.9, 135.9, 139.1, 139.9, 143.9, 146.5 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3075$, 2995, 2951, 2858, 1605, 1460, 1421, 1387, 1281, 1258, 1108, 933, 898, 761, 730 cm^{-1}; MS (%): *m/z*: 196 (54.72) $[M]^+$, 182 (15.65), 181 (100.00), 179 (14.17), 167 (17.51), 166 (54.49), 165 (67.22), 152 (15.58); HRMS (EI): *m/z* calcd for $C_{15}H_{16}$: 196.1252; found: 196.1253.

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