A One-Pot Preparation of Aryl- and Heteroarylcycloalkenes: Application to the Total Synthesis of (±)-Laurokamurene B

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Abstract: A general one-pot method has been developed for the preparation of various aryl- and heteroarylcycloalkenes. After lithiation of aryl and heteroaryl bromides followed by transmetalation with $CeCl_3$, the organocerium addition to cycloalkanones proceeds cleanly to provide the intermediate alkoxide. Addition of MsCl or $SOCl_2$ with DBU gave aryl-substituted cycloalkenes in good yields. A short total synthesis of (±)-laurokamurene B making use of this reaction is described.

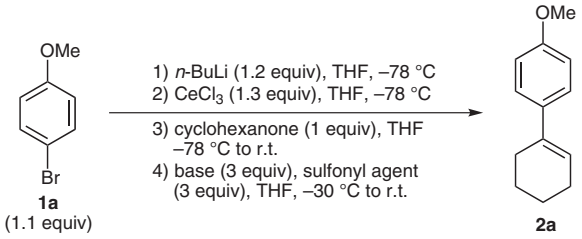
Key words: organocerium reagents, addition reactions, eliminations, arylcycloalkenes, laurokamurene B

Preparation of aryl-substituted cycloalkenes can be carried out most commonly through two approaches. Firstly, amongst the transition-metal-catalyzed reactions, the Heck reaction appears to be the most straightforward method.[1a] However, the coupling of cyclic olefins generates a mixture of double-bond regioisomers.[1b,c] Cross-coupling reactions of cycloalkenyl phosphates,[2] triflates,[3] and halides[4] have been reported with aryl Grignard reagents,[5] arylboronic acids,[6] arylstannanes,[7] and organozinc reagents[8] under Ni(0) and Pd(0) catalysis. Other methods have been developed using iron,[9] cobalt,[10] and copper[11] complexes. While these reactions lead to aryl-substituted cycloalkenes in good yields, each requires the functionalization of ketones into their corresponding vinyl derivatives, and the isolation of an intermediate. The second approach involves classically addition of aryllithium or aryl Grignard reagents to the cyclic ketones,[12] followed by dehydratation of the resulting tertiary alcohols or elimination of the corresponding sulfonate esters.[13] Nevertheless, with this two-step method, addition to ketones with these strongly basic organometallic compounds often leads to unwanted reactions such as enolization, reduction, and pinacol coupling. Recently also, a sequential semipinacol rearrangement–Grob fragmentation of allylic alcohols leading to alkenes was reported.[14]

While investigating a straightforward route to arylcycloalkenes, we reasoned that in order to avoid operating in strongly basic conditions, it might be possible to add neutral organocerium reagents[15] to cycloalkanones, followed by conversion of the intermediate alkoxide to a sulfonate ester, and an E_2 elimination. We report herein that this method is indeed a practical one-pot and synthetically useful preparation of cycloalkenyl arenes.

Initial experiments involved lithiation of 4-bromoanisole (**1a**) with *n*-BuLi, transmetalation with $CeCl_3$, and addition to cyclohexanone providing the intermediate alkoxide which was not quenched (Table 1).

Table 1 Optimization of Reaction Conditions for the One-Pot Preparation of **2a** from 4-Bromoanisole and Cyclohexanone



Entry	Base	Sulfonyl agent	Yield (%)[a]
1	Et_3N	MsCl	73
2	Et_3N	$(F_3CSO_2)_2O$	70
3	DBU	$(F_3CSO_2)_2O$	73
4	DBU	MsCl	87
5	DABCO	MsCl	22
6	pyridine	MsCl	15
7	DIPEA	MsCl	28

[a] Isolated yield.

Addition of Et_3N and MsCl led to the desired cycloalkene **2a** in 73% yield (entry 1). We then investigated the influence of different bases and sulfonyl agents. The use of Et_3N or DBU with $(F_3CSO_2)_2O$ (entries 2 and 3) did not increase the yield whereas DABCO, pyridine, and DIPEA with MsCl (entries 5–7) led to lower yields. Finally, the best result was obtained using DBU and MsCl, thus providing the product **2a** in an improved 87% yield (entry 4). Under these conditions but without addition of cerium(III) chloride, cyclohexene **2a** was isolated in 53% yield.

With these optimized conditions in hand, the scope of this reaction was explored utilizing various aryl- and heteroaryl bromides **1a–d** with cycloalkanones. The desired cycloalkenyl arenes **2a–k** were formed generally in 51–93%

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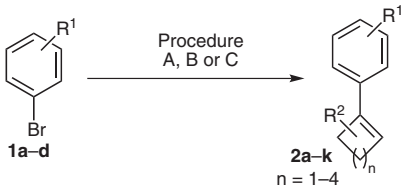
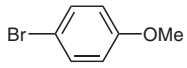
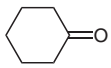
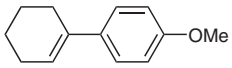
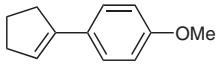
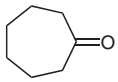
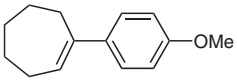
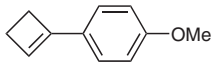
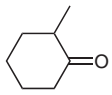
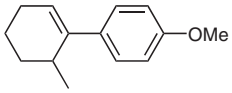
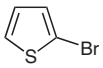
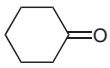
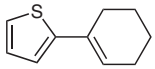
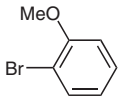
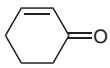
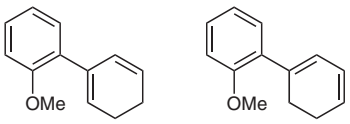
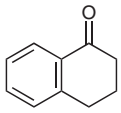
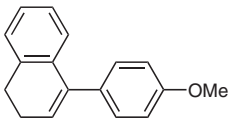
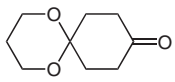
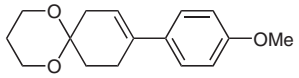
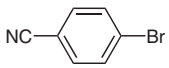
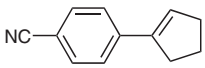
yield (Table 2). Reactions with five-, six- and seven-membered cycloalkanones (entries 1–3) gave the expected cycloalkenes **2a–c** while only the 1-cyclobutenyl-4-methoxybenzene **2d** was obtained in 17% yield (entry 4). This yield was not improved using procedure B or C. With

Table 2 Synthesis of Aryl- and Heteroarylcycloalkenes



Entry	Aryl bromide	Cycloalkanone	Product	Yield (%)[a]	Procedure[b]
1	 **1a**		 **2a**	87	A
2	**1a**		 **2b**	93	A
3	**1a**		 **2c**	73	A
4	**1a**		 **2d**	17	A
5	**1a**		 **2e**	86	A
6	 **1b**		 **2f**	70	A
7	 **1c**		 **2g 2h**	72 **2g/2h** = 70:30[c]	A
8	**1a**		 **2i**	65	A[d]
9	**1a**		 **2j**	51 68	A B
10	 **1d**		 **2k**	0 75	A[e] C[e]

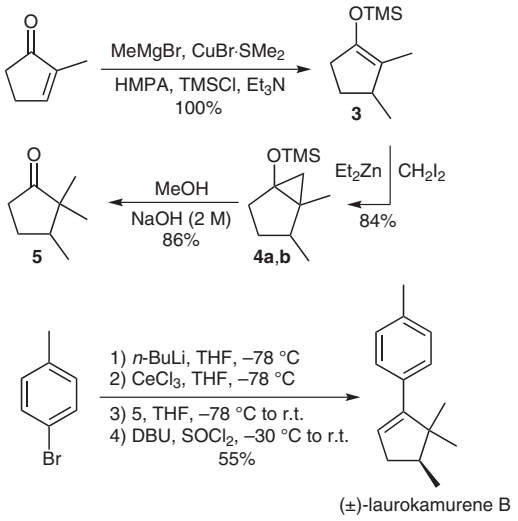
[a] Isolated yield.
[b] Procedure A: 1) *n*-BuLi, **1a–d**, -78 °C, 1 h; 2) $CeCl_3$, THF, –78 °C, 90 min; 3) cycloalkanone, THF, –78 ° to r.t., 3 h; 4) DBU, MsCl, –30 °C to r.t., overnight. Procedure B: see procedure A except that before step 4 THF was evaporated, and toluene was added; then DBU, MsCl at –30 °C and reflux overnight. Procedure C: see procedure A except for step 4: DBU, $SOCl_2$ (3 equiv), –30 °C to r.t., overnight.
[c] Ratio determined by ^1H NMR of the crude mixture.
[d] After addition of DBU and MsCl at –30 °C, the mixture was heated at reflux overnight.
[e] Addition of *n*-BuLi was carried out at –100 °C.

2-methylcyclohexanone (entry 5), the less substituted cycloalkene **2e** was isolated exclusively in 86% yield.

A satisfactory yield was observed with 2-bromothiophene (**1b**, entry 6). In the case of cyclohexenone (entry 7), 1,2-addition of the organocerium reagent proceeded exclusively to give, after esterification and E_2 elimination, the 2-substituted 1,3-diene **2g** and the 1-substituted 1,3-diene **2h** in 72% yield as a 70:30 mixture of regioisomers, respectively, which was separated by column chromatography. With tetralone (entry 8), it was necessary to heat at reflux overnight to afford the product **2i** in 65% yield. However, from 1,4-cyclohexanedione monoethylene ketal and **1a**, using procedure A, the yield dropped to 51% (entry 9). We assumed that this low yield was due to a probable difficulty to achieve antiperiplanarity between the mesyloxy group and the methine proton. A better yield was achieved by slightly modifying the procedure. As such, before the esterification–E_2 elimination step, THF was evaporated and toluene was added, followed by DBU and MsCl. The mixture was refluxed overnight to afford product **2j** in an improved 68% yield. With 4-bromobenzonitrile and cyclopentanone (entry 10), only the corresponding tertiary alcohol was isolated in 43% yield. Using $SOCl_2$ instead of MsCl (procedure C), the desired product **2k** was readily obtained in 75% yield.

The interest of this one-pot preparation of cycloalkenyl arenes was exemplified by a short total synthesis of (±)-laurokamurene B (Scheme 1).[16] Copper-catalyzed 1,4-addition of methylmagnesium bromide to 2-methylcyclopentenone and enolate trapping using trimethylsilyl chloride gave the silyl enol ether **3** in quantitative yield without purification. Cyclopropanation of **3** with CH_2I_2 and Et_2Zn[17] led to trimethylsilyl ethers **4a** and **4b** in 84% yield as a 59:41 mixture of diastereomers, respectively, which could not be separated by column chromatography. After treatment of **4a**,**b** with sodium hydroxide in hydromethanolic solution, 2,2,3-trimethylcyclopentanone **5** was isolated in 86% yield and characterized.[18] Finally, nucleophilic addition of 4-methylphenylcerium reagent to **5** followed by treatment with DBU and $SOCl_2$ gave (±)-laurokamurene B in four steps and 40% overall yield. For this last step, using MsCl instead of $SOCl_2$, the yield dropped to 30%.

In conclusion, we have developed a general one-pot synthesis of aryl- and heteroarylcycloalkenes. This method was applied to the total synthesis of (±)-laurokamurene B.



Scheme 1 Total synthesis of (±)-laurokamurene B

Procedure A for the Preparation of Cyclohexene 2a

Cerium chloride heptahydrate (1.7 g, 4.5 mmol) was quickly ground to a fine powder in a mortar, placed in a two-necked flask and dried at 140 °C for 2 h in vacuo. At r.t., nitrogen gas was introduced, and anhyd THF (25 mL) was added with vigorous stirring. The white suspension was stirred for 90 min at r.t. To a cold (–78 °C) stirred solution of **1a** (720 mg, 3.85 mmol) in anhyd THF (25 mL) was added *n*-BuLi (2.2 M in hexane, 1.9 mL, 4.2 mmol) dropwise. This solution was stirred at –78 °C for 90 min, then added to the cold (–78 °C) suspension of $CeCl_3$ in THF. The resulting solution was stirred at –78 °C for 90 min. Then cyclohexanone (343 mg, 363 μL, 3.5 mmol) dissolved in anhyd THF (5 mL) was added to the corresponding organocerium reagent. The resulting mixture was stirred at –78 °C for 90 min then at r.t. for 90 min. At –30 °C, after dilution with anhyd THF (20 mL), DBU (1.57 mL, 10.5 mmol), then MsCl (815 μL, 10.5 mmol) were added dropwise. The reaction mixture was then allowed to warm to r.t. and stirred overnight. At 0 °C aq 1 M HCl (15 mL) was added, and the solution was stirred for 1 h. The aqueous layer was extracted with Et_2O (3 × 30 mL). The resulting organic layers were washed successively with aq 2 M NaOH (10 mL), H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, and the solvent evaporated. The residue was purified by chromatography on silica gel (pentane–Et_2O = 95:5) to provide the product **2a** in 87% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (2 H, d, *J* = 8.9 Hz), 6.85 (2 H, d, *J* = 8.9 Hz), 6.01–6.06 (1 H, m), 3.81 (3 H, s), 2.41–2.35 (2 H, m), 2.22–2.16 (2 H, m), 1.81–1.73 (2 H, m), 1.70–1.61 (2 H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 135.8, 135.3, 125.9, 123.1, 113.5, 55.2, 27.4, 25.8, 23.1, 22.2 ppm. MS (EI): *m/z* (%) = 188 (100) [M^+], 173 (22), 160 (50), 159 (45), 115 (21), 91 (21). HRMS (EI): *m/z* calcd for $C_{13}H_{16}O$: 188.1201; found: 188.1216.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) Srikrishna et al.[16c] did not succeed to purify the ketone **5** and characterized this one as the corresponding tosylhydrazone.