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Highly Efficient Molybdenum(II)-Catalyzed Intramolecular Allylic Alkylation of Arenes

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Dedicated to Professor Štefan Toma on the occasion of his 70th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The Friedel–Crafts-type intramolecular allylic alkylation of simple arenes is performed in the presence of a catalytic amount of $[Mo(II)(CO)_4Br_2]_2$ (2.5 mol%). The moisture-tolerant protocol provided a mild and direct access to a large library of functionalized 4-vinyl-1,2,3,4-tetrahydronaphthalenes in high yields.

Keywords: allylic alkylation; catalysis; cyclization; Friedel–Crafts reaction

The search for efficient, mild and economically friendly catalytic protocols for the intramolecular alkylation ($Csp^{2<C}$-$>Csp^{3}$ bond-forming process) of simple arenes is a long-sought goal for the whole chemical community.[1] Agrochemicals, pharmaceuticals and "plastic electronics" are among the most important fields that would benefit from synthetic advances in this transformation. Among the plethora of electrophilic precursors employed for the alkylation of aromatic systems, the use of tethered C=C double bonds, bearing a leaving group in the allylic position (allylic alkylation), is of remarkable synthetic interest, providing highly versatile polycylic aromatic compounds.[2,3]

For the present, several catalytic allylic alkylation protocols involving heteroaromatics have been described.[4] In contrast, simple benzene derivatives have received much less attention, because of their intrinsic low nucleophilicity with the consequent requirement for harsh reaction conditions as well as stoichiometric amounts of promoting agents.[5]

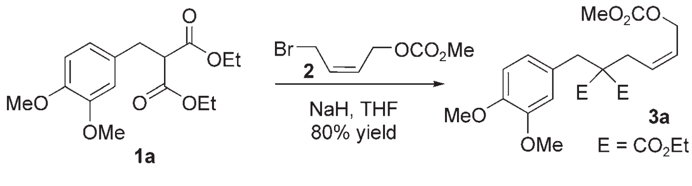
The report by Cook and Hayashi is a breakthrough in this area describing the effectiveness of $InCl_3$ (10–30 mol%), in the presence of molecular sieves, in catalyzing intramolecular Friedel–Crafts (FC)-type alkylation of arenes *via* allyl halide activation.[6]

In conjunction with our current research interest toward the development of catalytic enantioselective intramolecular allylic alkylation of arenes,[4d] we reasoned that the development of new approaches based on electrophilic transition metal complexes would provide opportunities for developing enantioselective variants of the process. Interestingly, although asymmetric allylic alkylation is a well established protocol with countless combinations of allylic derivatives and C-, N- and O-based nucleophiles,[7] the use of simple arenes has been described only by Kočovský and coworkers with electron-rich benzene rings (intermolecular process).[8]

Focusing on operational simplicity, we designed the allyl carbonate **3a** as the model substrate for the catalytic ring-closing process. The synthesis of **3a** was readily accomplished in a gram-scale *via* alkylation of the corresponding diethyl (3,4-dimethoxybenzyl)malonate **1a**[9a] and (*Z*)-bromocarbonate **2**[9b] (yield 80%, Scheme 1).

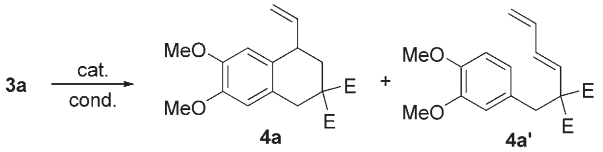
A survey of reaction conditions (i.e., metal salts, solvent, temperature) was then undertaken and a representative collection of results is reported in Table 1.

Palladium-based catalysis, which proved to be effective in the intramolecular allylic alkylation of indoles,[4a] failed in the present cyclization, leading to large amounts of dienyl by-product when combined with



Scheme 1. Synthesis of model carbonate **3a**.

Table 1. Optimization of the reaction conditions for the intramolecular allylic alkylation of **3a**.[a]



Entry	Cat [mol%]	Time [h]	Temp. [°C]	Yield **4a/4a'** [%][b]
1	$[Pd(PPh_3)_4]$ [5]	16	80	-/-[c]
2	$[Pd(PPh_3)_4]$ [5]	16	80	-/78[d]
3	$[PdCl_2(dppf)]$ [5]	16	80	-/-[c]
4	$[Mo(CO)_4Br_2]_2$ [2.5]	16	80	91/-[e]
5	$[Mo(CO)_4Br_2]_2$ [2.5]	16	80	91/-
6	$[Mo(CO)_4Br_2]_2$ [1]	16	80	78/-
7	$[Mo(CO)_4Br_2]_2$/AgOTf [2.5/10]	40	rt	91/-
8	$[Mo(acac)_2Cl_2]$/AgOTf [5/10]	40	rt	26/-[f]

[a] All the reactions were carried in reagent grade $ClCH_2CH_2Cl$ (DCE) without restrictions for air, unless otherwise specified.
[b] Isolated yields after flash chromatography.
[c] Recovery of the starting material > 90%, reaction in THF.
[d] With K_2CO_3 (2 equiv.), reaction in THF.
[e] Under dry conditions.
[f] 70% of the starting material was recovered.

K_2CO_3 (entry 2). On the contrary, the absence of the base led to the recovery of the unaltered starting material with a variety of Pd sources (entries 1 and 3).[10] These results suggest that the relatively poor nucleophilic character of the aromatic rings did not allow the ring-closing process on the η^3-Pd intermediate and, in the presence of a base (i.e., K_2CO_3), the β-H elimination of the Pd-complex became the predominant pathway.

Interestingly, the use of $[Mo(CO)_4Br_2]_2$ (2.5 mol%)[11] led to the desired cyclized compound **4a** regioselectively in 91% isolated yield (**4a**:**4a'** > 50:1, entry 4).

Surprisingly, we discovered that the air-sensitive $[Mo(CO)_4Br_2]_2$ facilitated the ring-closing of **3a** to a comparable extent (yield 91%), even in the presence of air and with reagent-grade dichloroethane (entry 5).[12] The cyclization worked smoothly also in the presence of 1 mol% of catalyst (yield 78%, entry 6), and the possibility to lower the temperature to room temperature was demonstrated by adding 10 mol% of AgOTf, implying that a more active catalyst is generated *in situ* (yield 91%, entry 7).

In contrast, disappointing results in terms of conversion were recorded with a cationic Mo(IV) complex (i.e., $[Mo(acac)_2Cl_2]$/AgOTf), that was previously described as being active in the alkylation of electron-rich arenes with allyl and cinnamyl alcohols (yield 26%, entry 8).[13]

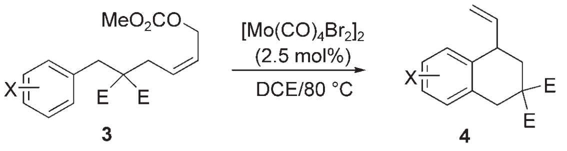
The utility of $[Mo(CO)_4Br_2]_2$ for the synthesis of a variety of substituted tetrahydronaphthalenes was then established and a collection of results is summarized in Table 2.

A wide range of functionalized and unfunctionalized arenes cyclized smoothly under optimal reaction parameters ($[Mo(CO)_4Br_2]_2$ 2.5 mol%, $ClCH_2CH_2Cl$, 80 °C, 16 h) with high yields (48–97%) after flash chromatography. For instance, the cyclization of β-naphthalene-carbonate **3g** proceeded exclusively to the α-position (yield 96%) and *meta*-methoxyacyclic compound **3d** underwent the ring-closing process with a 3:1 regioisomeric ratio. The final chemical outputs did not seem to be markedly affected by the C=C configuration of **3**. In fact, considerably high yields were recorded both with configurationally pure carbonates and with starting materials containing a mixture of diastereoisomers (see entry 2).

Worthy to note is the result obtained with the challenging ferrocenyl carbonate **3l**. It is known, in fact, that catalytic alkylations of ferrocene gave often very poor yields with the need for time-consuming purifications of the crude reaction product.[14] Here, by using 5 mol% of $[Mo(CO)_4Br_2]_2$, the desired cyclized compound **4l** was obtained in 48% yield, as a 72:28 mixture of diastereoisomers, due to the intrinsic *planar chirality*[15] of **4l** (entry 11).

A limitation of the protocol emerged from the use of electron-deficient arenes (i.e., **3m**) that, even under forcing reaction conditions, provided **4m** in poor yield (15%) with the major product being **5m** in 45% yield and a 65:35 diastereomeric ratio (Scheme 2).

Table 2. Mo(II)-catalyzed cyclization of selected substrates.[a]



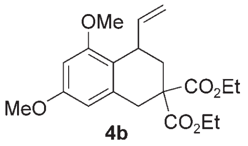
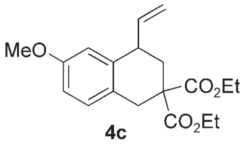
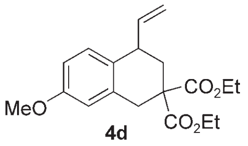
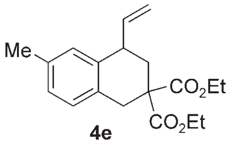
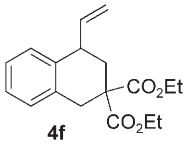
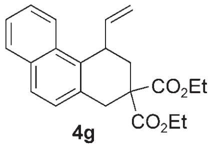
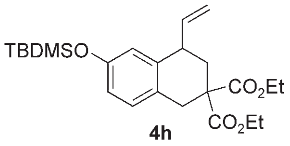
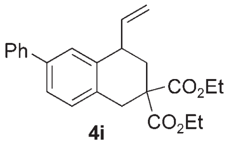
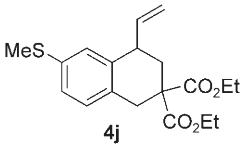
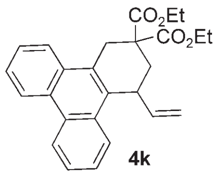
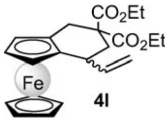
Entry	**3** (Ar) (*Z*:*E*)[b]	Product **4**	Yield of **4** [%][c]
1	**3b** 3,5-$(MeO)_2C_6H_3$ (90:10)	 **4b**	72
2	**3c** 4-MeO-C_6H_4 (75:25)	 **4c**	85
3	**3d** 3-MeO-C_6H_4 (97:3)	 **4d**	81 (3:1)[d]
4	**3e** 4-MeC_6H_4 (> 98:2)	 **4e**	90
5	**3f** C_6H_5 (71:29)	 **4f**	92
6	**3g** β-naphthyl (88:12)	 **4g**	96
7	**3h** 4-TBDMSO-C_6H_4 (> 98:2)	 **4h**	71(97)[e]
8	**3i** 4-Ph-C_6H_4 (97:3)	 **4i**	84
9	**3j** 4-MeS-C_6H_4 (87:13)	 **4j**	70
10	**3k** 9-phenanthrenyl (98:2)	 **4k**	93

Table 2. (Continued)

Entry	**3** (Ar) (*Z*:*E*)[b]	Product **4**	Yield of **4** [%][c]
11	**3l** ferrocenyl (>98:2)	 **4l**	48[f]

[a] All the reactions were carried in reagent grade DCE without restrictions for air.

[b] Determined by H^1-NMR and GC/LC-MS.

[c] After flash chromatography.

[d] The regiochemistry was determined by GC-MS.

[e] 26% of the cyclized product was recovered with a free OH group.

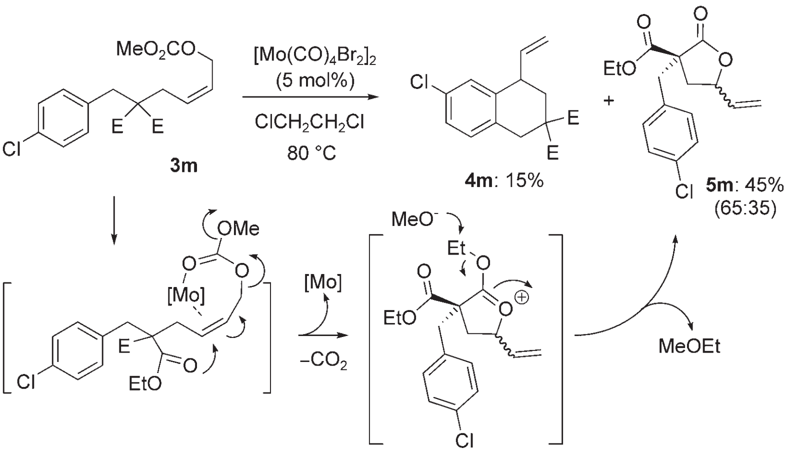
[f] 5 mol% of $[Mo(CO)_4Br_2]_2$ was employed. Diastereomeric ratio: 72:28.

A working reaction mechanism for the formation of **5m** is depicted in Scheme 2. In the presence of deactivated arenes, the expected FC-type alkylation did not take place, but one of the ester moieties underwent the intramolecular nucleophilic attack on the [Mo]-activated allyl carbonate that leads to the final γ-lactone **5m** as a mixture of diastereoisomers.

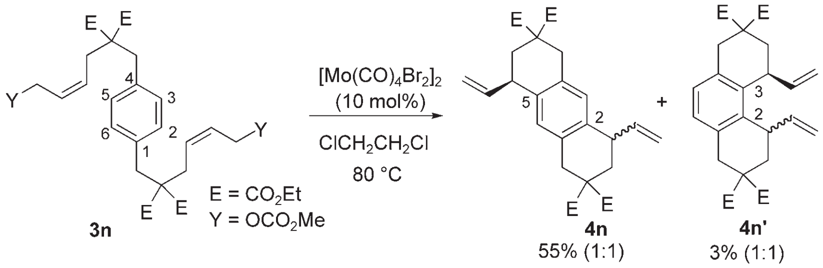
To extend the usefulness of the present [Mo]-catalyzed ring-closing process further, we explored the possibility to perform one-pot multiple C–C bond forming reactions that would lead to functionalized polycyclic aromatic scaffolds.

To this purpose, we synthesized in two steps the aryl biscarbonate **3n** starting from commercially available 1,4-dibromoxylene (see Supporting Information for details). By increasing the loading of catalyst to 10 mol%, complete conversion was obtained within 16 h under reflux (Scheme 3). Employing chromatographic purification it was possible to separate the 2,5-bis-cyclized compounds **4n** (yield 55%, *dr* 1:1) from the corresponding 2,3-bis-cyclized analogues **4n'** obtained as the minor regioisomer (yield 3%, *dr* 1:1).

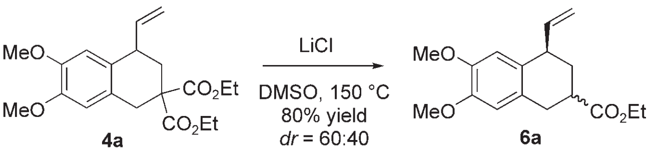
A representative example of effective and selective decarboxyaltion of the benzocarbocycles is described



Scheme 2. Mo-catalyzed ring-closing reaction with arenes bearing electron-withdrawing substituents.



Scheme 3. One-pot double allylic alkylation.



Scheme 4. Representative example of decarboxylation reaction to give the monoester **6a**.

for **4a** (Scheme 4). Following Krapcho-type conditions (LiCl, DMSO wet, 150 °C),[16] the mono-ester **6a** was isolated in 80% yield as a 60:40 mixture of diastereoisomers.

As of today, we do not have sufficient evidence to fully define the operating reaction mechanism. Therefore, neither the presence of a η^3-Mo complex nor allyl-carbocation intermediates[17] can be ruled out *a priori*.

In conclusion, a practical and direct route to 4-vinyl-1,2,3,4-tetrahydronaphthalenes, catalyzed by a Mo(II) salt, is described. The mild reaction conditions (moisture tolerance, low loading of catalyst), combined with the excellent isolated yields recommend the present approach for applications in large-scale production. Mechanistic studies as well as the development of an enantioselective variant of the cyclization are underway in our laboratories.

Experimental Section

Typical Procedure for Mo-Catalyzed Cyclization

In a dry two-necked, round-bottom, 25-mL flask equipped with a condenser, 0.2 mmol of **3** were dissolved in 2 mL of reagent grade 1,2-dichloroethane. Then, 5 μmol (1.9 mg) of $[Mo(CO)_4Br_2]_2$ were added, and the mixture was stirred at 80 °C for 16 h. Then, the volatiles were removed under reduced pressure and the crude material purified by flash chromatography (*c*-hexan:AcOEt 80:20) unless otherwise specified.

4a: White wax; yield: 91%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.2$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.98 (dd, $J_1 = 11.8$ Hz, $J_2 = 13.8$ Hz, 1H), 2.59 (dd, $J_1 = 4.0$ Hz, $J_2 = 11.8$ Hz, 1H), 3.10 (d, $J = 16.0$ Hz, 1H), 3.25 (d, $J = 16.0$ Hz, 1H), 3.45–3.56 (m, 1H), 3.82 (s, 3H), 3.87 (s, 3H), 4.12–4.28 (m, 4H), 5.16–5.26 (m, 2H), 5.67–5.87 (m, 1H), 6.63 (s, 1H), 6.67 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.1$(2C), 34.7, 35.2, 41.4, 53.7, 55.9(2C), 61.4, 61.7, 111.4(2C), 116.3, 125.6, 128.1, 141.7, 147.6, 147.8, 170.8, 171.8; LC-MS: $m/z = 363.0$ (M+1), 747.2 (2M+Na); anal. calcd for $C_{20}H_{26}O_6$: C 66.28, H 7.23; found: C 66.20, H, 7.31%.

Acknowledgements

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[10] Analogous reaction outcomes were recorded with $Pd_2dba_3 \cdot CHCl_3$, $Pd(OAc)_2$ and $[PdCl(C_3H_5)]_2$ as the Pd sources.

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[12] Some control experiments were carried out on the model substrate **3a** in order to rule out the potential roles of Brønsted acidity and hydroxy [Mo] species in the ring-closing process: i) HCl_{Et_2O} (10 mol%), DCE, 80 °C, 16 h = decomposition of the starting material; ii) stirring of $[Mo(CO)_4Br_2]_2$ in reagent grade DCE under air (16 h) then catalysis = **4a′** (75% yield); iii) use of hydrolyzed $[Mo(CO)_4Br_2]_2$ in the cyclization = recovery of unreacted **3a** (91%).

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[17] It is worth mentioning that the use of $InCl_3$ as a Lewis acid failed in promoting the cyclization under our working conditions (yield: <10%).