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RESEARCH ARTICLE

Rhenium-Catalyzed Aryl-Acylcyclization between Enol Lactones and Organomagnesium Halides: Facile Synthesis of Indenones

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Abstract: A set of rhenium-catalyzed aryl-acylcyclization between (hetero)arylmagnesium halides and enol lactones through a cascade Csp^2–Csp^2/Csp^2–Csp^2 bond formation has been developed under mild reaction conditions. Indeed, a wide range of functional groups on both organomagnesium halides and enol lactones are well tolerated by the simple rhenium catalysis, thus furnishing polyfunctionalized indenones in one-pot fashion and with complete control of the regioselectivity. Moreover, this approach also provides a straightforward synthesis to neo-lignan and (*iso*)pauciflorol **F**. Mechanistic studies demonstrated that the reaction involves a sequential of *syn*-carborhenation and intramolecular nucleophilic addition process.

Introduction

Rhenium is a 7 group, six-row transition metal, which possesses versatile reactivity due to its hard and soft Lewis acidity.[1] Since 2000, rhenium complexes have witnessed significant progress in cyclization reactions, nucleophilic additions,[1, 2] as well as challenging inert C–H and C–C bonds functionalizations, [1, 3] thus providing powerful tools for the construction of unique carbon-carbon bonds. However, rhenium-catalyzed cross-coupling with organometallic reagents was rather rare. Organometallics, such as organomagnesium and organozinc reagents, displayed excellent functional groups compatibility and versatile reactivity in transition metal-catalyzed cross-coupling reactions under mild reaction conditions.[4] Generally, most of these advances were achieved with the using of unsaturated halides as the electrophiles. The more environmentally friendly phenol or enol derivatives (halide-free), such as unsaturated pivalates or acetates, have obtained considerable recent attentions and been utilized for transition metal-catalyzed cross-couplings with organometallic reagents using Pd, Rh, Ni, Co, Fe and Cr catalysis, as were reported by Shi,[5] Garg,[6] Fürstner,[7] Ackermann,[8] von Wangelin,[9] Martin,[10] Knochel,[11] and others,[12] thus achieving novel C–C bonds formation in a better mass efficiency fashion (Scheme 1a). However, using enol lactones as the coupling electrophiles for cross-coupling with organometallic nucleophiles has unfortunately thus far proven elusive. In particularly, enol lactones can be easily prepared from ubiquitous phthalic anhydrides with Witting reagents[13] and benzoic acids with alkynes or alkenes.[14] Hence, we became intrigued by developing a transition metal-catalyzed cross-coupling between enol lactones and organometallic reagents.

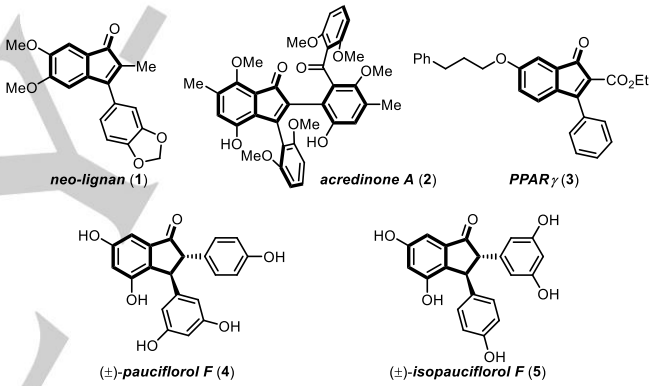

Figure 1. Indenone or indanone-containing natural products and bioactive compounds.

On the other hand, indenones and their indanone derivatives are key important structural motifs for material science applications,[15] as well as of various active natural products and pharmaceuticals with activities of relevance to biology or medicinal chemistry,[16] as found in voltage-gated potassium channel inhibitors against type II diabetes,[17] and peroxisome proliferator-activated receptor γ (PPARγ) agonists (Figure 1).[18] Therefore, there is a continued strong demand for developing efficient and selective synthetic approaches to access these valuable scaffolds. Traditional synthetic methods lack of generality and have limited substrate scope.[19] In recent years, transition metal-catalyzed cyclization with internal alkynes through chelation-assisted C–H activation[20] or multiple cross-couplings[21] has been recognized as an increasingly viable tool for the preparation of indenones (Scheme 1b). Despite these major advances made, the poor regioselectivity using unsymmetrical alkynes as the coupling partners still represent drawbacks. In this context, Dong and coworkers recently reported a palladium/norbornene-catalyzed direct Catellani annulation between unsaturated carboxylic acid anhydrides and aryl iodides, which realized various indenones synthesis with good regioselectivity (Scheme 1b).[22].We herein report a aryl-

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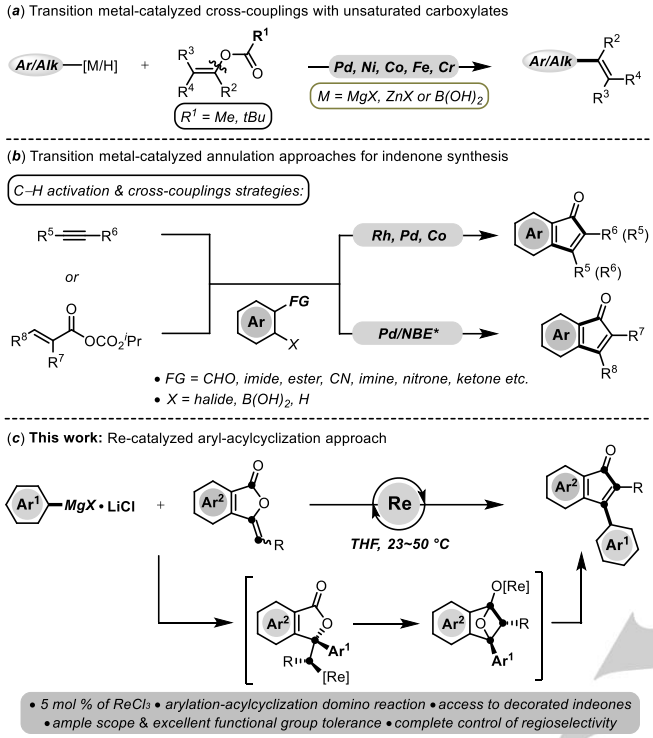
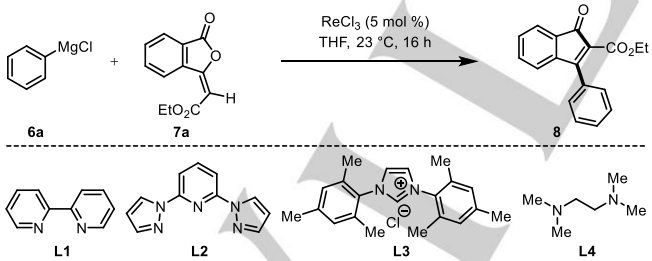
acylcyclization between various organomagnesium halides and readily accessible enol lactones through a rhenium-catalyzed sequential of *syn*-carbometalation and nucleophilic addition process, which provides a straightforward approach to the synthesis of polyfunctionalized indenones in a complete control of regioselective fashion (Scheme 1c).



Scheme 1. *a*) cross-couplings with unsaturated carboxylates, *b*) Indenone synthesis and *c*) rhenium-catalyzed aryl-acylcyclization between organomagnesium halides and enol lactones.

Results and Discussion

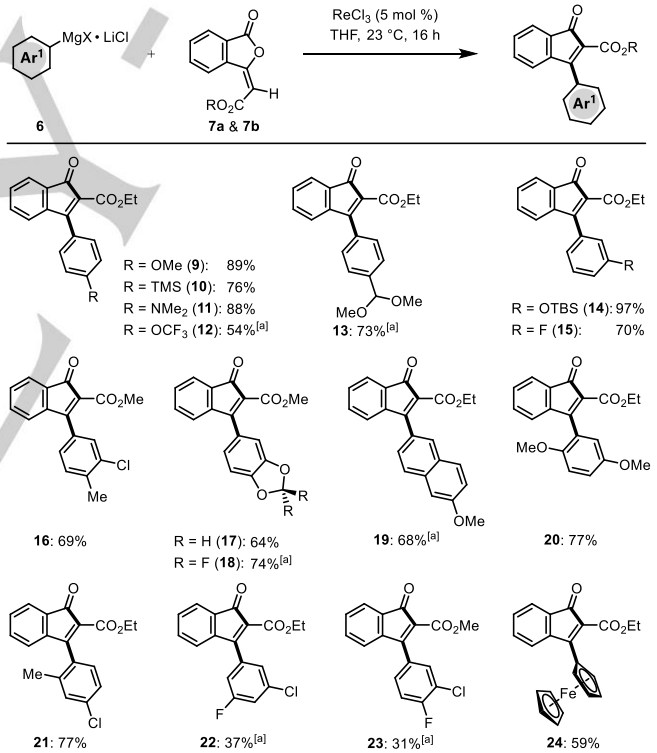
Table 1. Optimization for rhenium-catalyzed arylation/acylcyclization.[a]



Entry	Modified conditions	Yield (%)[b]
1	***None***	***78*** *(75)*[c]
3	**L1** (6 mol %) was used as a ligand	22
3	**L2** (6 mol %) was used as a ligand	35
4	**L3** (6 mol %) was used as a ligand	38
5	**L4** (6 mol %) was used as a ligand	36
6	$CoCl_2$ instead of $ReCl_3$	7
7	$FeCl_2$ instead of $ReCl_3$	14
8	$MnCl_2$ instead of $ReCl_3$	28
9	$Co(acac)_2$ instead of $ReCl_3$	26
10	$FeCl_3$ instead of $ReCl_3$	16
11	Mn(acac)3 instead of $ReCl_3$	37
12	$CuCl_2$ instead of $ReCl_3$	trace
13	--	trace

[a] Reaction conditions: **1a** (0.45 mmol, 1.5 equiv), **2a** (0.3 mmol, 1.0 equiv), $ReCl_3$ (5 mol %), THF (1.0 mL), 23 °C, 16 h. [b] Isolated yields. [c] under 0 °C.

We initiated our studies by optimizing reaction conditions for the envisioned rhenium-catalyzed aryl-acylcyclization between phenylmagnesium chloride (**6a**) and (*E*)-enol lactone (**7a**). A cascade cross-coupling reaction was observed in the presence of 5.0 mol % $ReCl_3$ under room temperature, thus delivering the desired arylated indeone **8** in 78% yield (Table 1, entry 1). A number of representative chelating ligands, such as bipyridine (**L1**), tridentate 2,6-bis(*N*-pyrazolyl)pyridine (**L2**), N-heterocyclic carbene (**L3**) and TMEDA (**L4**), gave significantly decreased yields (entries 2–5). Switching from $ReCl_3$ to other representative transition-metals, such as $CoCl_2$, $Co(acac)_3$, $FeCl_2$, $FeCl_3$, $MnCl_2$, $Mn(acac)_3$, $CuCl_2$, or in the absence of metal catalyst, led to poor yields of the desired product of **8** (entry 6–13).



Scheme 2. Scope of arylmagnesium reagents for rhenium-catalyzed aryl/acylcyclization domino reaction.

Having identified optimized rhenium catalysis in hand, we subsequently explored the substrate scope of various arylmagnesium reagents for the rhenium-catalyzed cascade cross-coupling reaction with (*E*)-enol lactones (**7a**–**7b**) (Scheme 2). A range of arylmagnesium reagents bearing various valuable electrophilic functional groups, such as methyloxyl, trimethylsilyl, dimethylamino, acetal, trifluoromethyl, (*tert*-butyldimethylsilyl)oxyl, fluoro, chloro, methylenedioxyl, difluoromethylene dioxyl substituents, as well as methyloxylnaphthyl magnesium bromide underwent the aryl-acylcyclization with **7a** or **7b** to afford the

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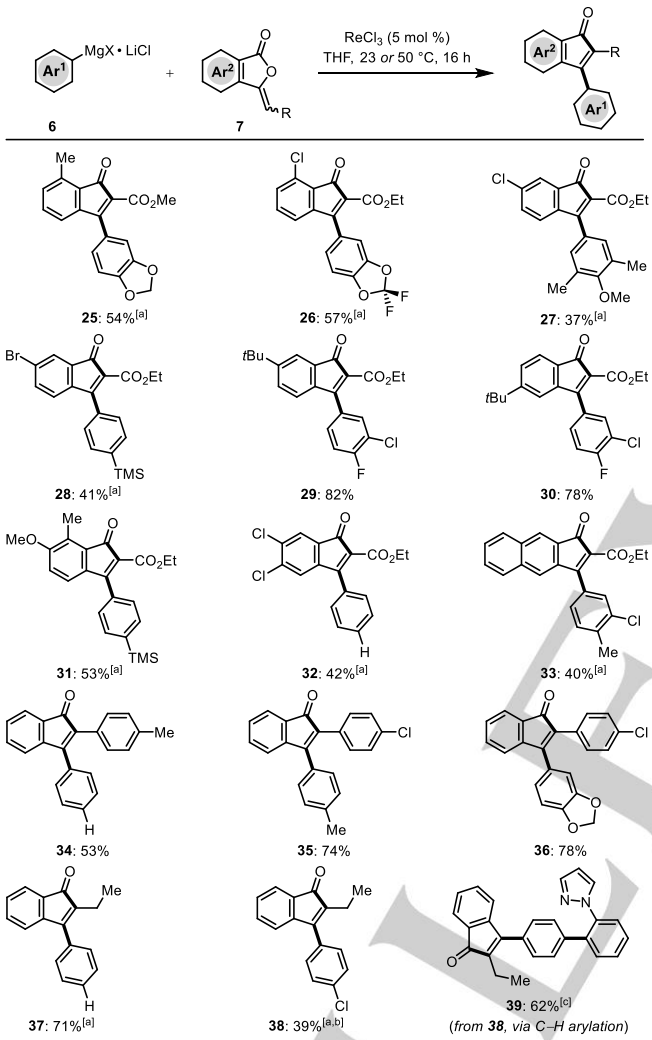
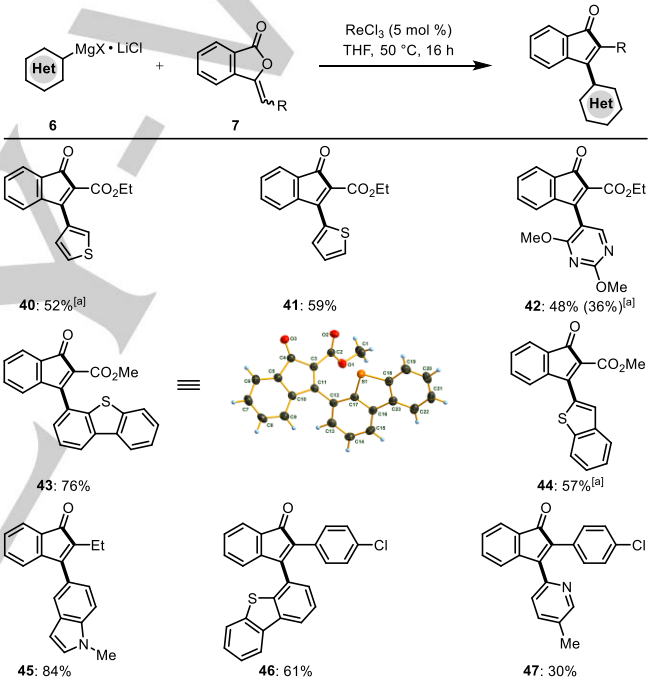
desired products **9**–**19** in 54–97% yields. More sterically hindered *ortho*-substituted aryl Grignard reagents were successfully employed as nucleophiles for the envisioned cascade cross-couplings, thereby providing the corresponding products **20**–**21** in good yields. The arylmagnesium bromides bearing fluoro and chloro substituents were identified to be suitable as well, albeit only delivering the indenones **22**–**23** in modest yields. It is noteworthy that a ferrocenyl magnesium bromide reacted smoothly with (*E*)-alkenyl lactone **7a**, giving the ferrocenylated product **24** in 59% yield.



Scheme 3. Rhenium-catalyzed cascade cross-coupling reaction with unsaturated carboxylates of type **7**. [a] Under 50 °C, 16 h. [b] 5.0 mmol scale. [c] 1-phenyl-1*H*-pyrazole (0.24 mmol), **38** (0.2 mmol), $Ru(MesCO_2)_2(p\text{-cymene})$ (5.0 mmol %), K_2CO_3 (2.0 equiv), PhMe, 120 °C, 20 h.

Subsequently, the versatility of this optimized rhenium catalyst was examined in a range of aryl-acylcyclization reactions with various alkenyl lactones **7** and polyfunctionalized arylmagnesium halides **6** (Scheme 3). As shown, a number of alkenyl lactones bearing methyl, *tert*-butyl, methyloxyl, chloro, bromo, naphthyl groups on the aryl moiety could be successfully employed as coupling partners in this cascade coupling reaction, providing the desired products **25**–**33** in 37–82% yields. Moreover, aryl or alkyl substituted on the alkenyl moiety of the lactones also proved to be viable substrates for the rhenium-catalyzed aryl-acylcyclization, thus leading to the 2,3-unsymmetric diarylated or arylalkylated indenones **34**–**38** in 39–78% yields with complete control of regioselectivity. Notably, both Larock annulation[16a] and C–H activation[20] strategies with unsymmetric internal alkynes remain challenges of the regioselectivity. The late-stage derivatization of the obtained indenone **38** was demonstrated by a subsequent direct ruthenium-catalyzed C–H arylation process.[23]

Cross-couplings with heterocyclic moieties are of special important in pharmaceutical and agrochemical research.[24] Importantly, this rhenium catalysis is not limited to the aromatic Grignard reagents. Indeed, our rhenium catalyst showed comparable levels of catalytic efficacy for the described cascade cross-coupling reactions between various heteroarylmagnesium halides and alkenyl carboxylates, thus yielding the thiophene-, pyrimidine-, (di)benzothiophene-, indole- and pyridine-based indenones **40**–**47** in moderate to high yields (Scheme 4). Among them, the structure of **43** was confirmed by X-ray crystal analysis.[25]



Scheme 4. Substrate ccope of heteroarylmagnesium reagents leading to indenones. [a] Under 23 °C, 16 h.

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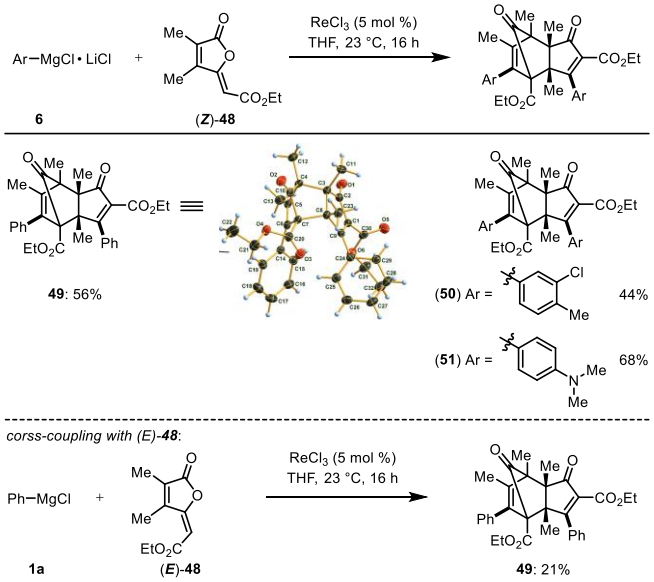
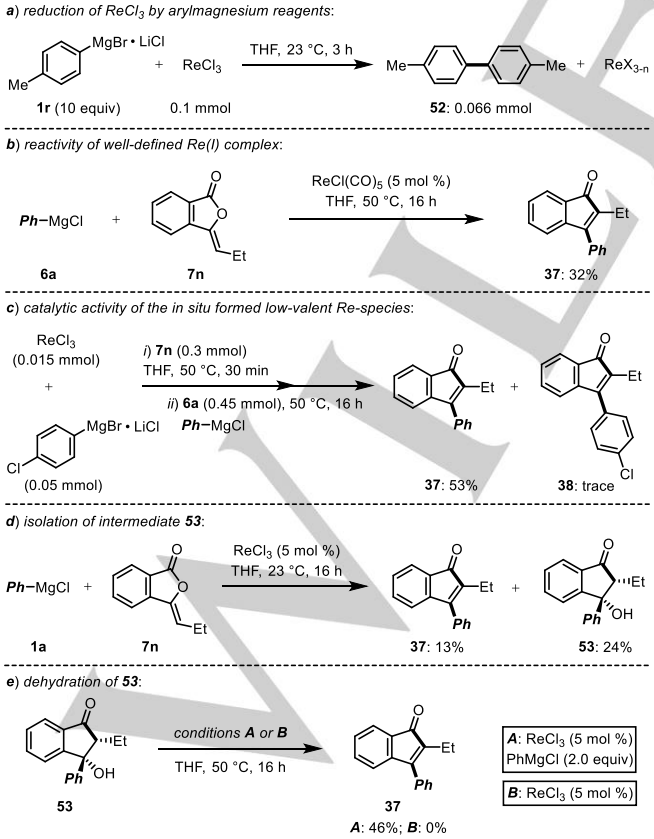


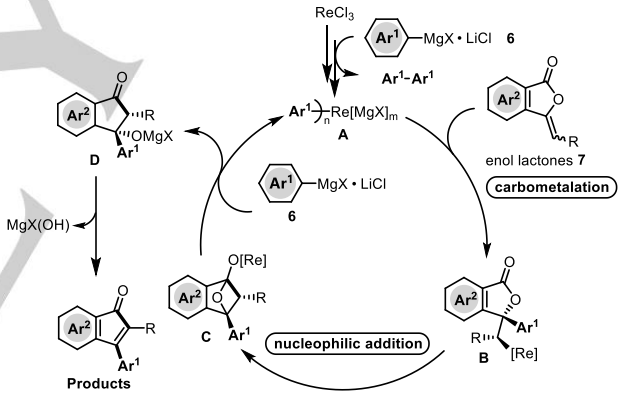
Scheme 5. Rhenium-catalyzed arylation/acylcyclization/Diels-Alder reaction with (*Z*)-enol lactone of type of **48**.

Additionally, we were also pleased to observe that (*Z*)-alkenyl lactone of **48** proved suitable to generate the highly sensitive cyclopentadienone, which subsequently occurred Diels-Alder reaction with another cyclopentadienone under the standard reaction conditions. The corresponding dimers **49**–**51** were obtained in 44–68% yields and the structure of **49** was confirmed by X-ray crystal analysis.[25] In sharp contrast, product **49** was only formed in a poor yield when employing a (*E*)-alkenyl lactone of **48** as the coupling partner (Scheme 5).



Scheme 6. Control experiments.

Intrigued by the remarkable efficacy of this simple rhenium-catalyzed aryl-acylcyclization, a series of preliminarily control experiments were performed (Scheme 6). Firstly, we performed experiments of $ReCl_3$ (1.0 equiv) with excess of *p*-tolylmagnesium chloride under typical reaction conditions for 3 h, which generated the homocoupling product **52** in near 0.66 equiv ratio to that of $ReCl_3$. These findings might suggest the formation of low-valent of Re-species under the standard reaction conditions (scheme 6a). Furthermore, the well-defined rhenium(I) species of $ReCl(CO)_5$ was examined as the catalyst for the envisioned cross-coupling between PhMgCl (**6a**) and enol lactone (**7n**). However, the desired indenone **37** was only delivered in 32% yield (Scheme 6b). An in situ formed low-valent rhenium-species reduced by stoichiometric *p*-ClC_6H_4MgBr could further promote the cross-coupling between PhMgCl (**6a**) and **7n**, thus leading the indenone **37** in 53% yield (Scheme 6c). In order to unravel the catalysts working mode, a carbonyl alcohol **53** (24%) was obtained when performing the reaction at 23 °C (Scheme 6d). This isolated intermediate was then subjected to the catalytic reaction conditions to lead smoothly to the dehydrated indenone **37** in 46% yield. Importantly, dehydration did not occur in the absence of arylmagnesium halide (Scheme 6e). These results demonstrated the cascade aryl-acylcyclization process involved in a sequential of carbometalation and nucleophilic addition process.



Scheme 7. Plausible catalytic cycle.

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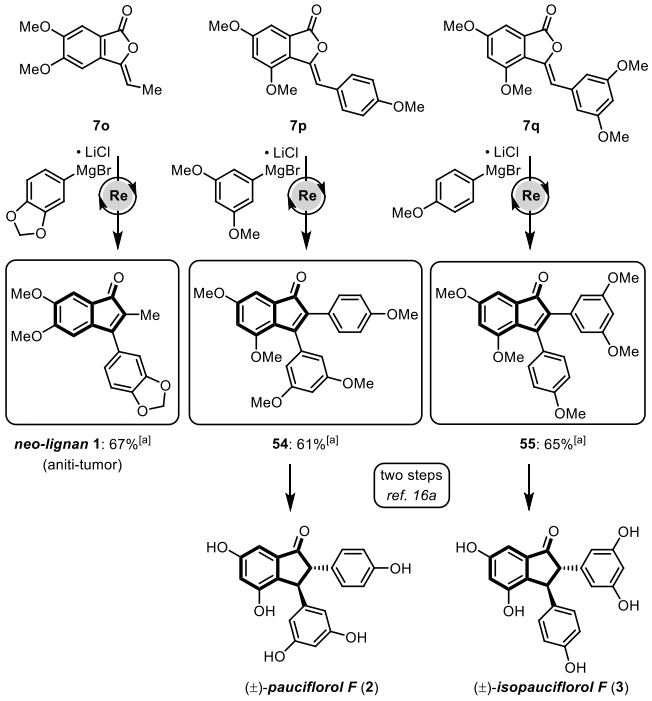

Scheme 8. Formal synthesis of *neo*-lignan, (*iso*)pauciflorol **F** through rhenium-catalyzed aryl-acylcyclization. [a] Reaction conditions: $ReCl_3$ (5 mol %), (*Z*)-enol lactones (0.3 mmol), arylmagnesium halides (1.5 equiv), THF (1.0 mL), 50 °C, 16 h.

Based on these experimental insights, a mechanism for this cascade rhenium-catalyzed aryl-acylcyclization has been proposed as shown in Scheme 7. The reduction and transmetalation of the precatalyst $ReCl_3$ with arylmagnesium halides formed the catalytically active aryl Re/Mg species (**A**), which underwent turnover-limiting *syn*-carborhenation to the enol-lactones (**7**) to generate a carbon-bound Re-enolate (**B**). This intermediate **B** could occur an intramolecular nucleophilic addition to form a diastereoselective key intermediate **C**, then followed by a sequential of transmetalation and C–O bond cleavage with another arylmagnesium halide to regenerate the active Re-aryl catalyst **A** and afford the corresponding indanone **D**. Finally, elimination of MgX(OH) would liberate the desired indanone derivatives.

Finally, the synthetic utilities of this rhenium-promoted cascade aryl-acylcyclization method were illustrated for the synthesis of pharmacologically relevant molecules, such as *neo*-lignan (**1**), (*iso*)pauciflorol **F** (**2**–**3**). In this context, (*E*)-enol lactones **7o**–**7q** were readily prepared according to the Ru- and Rh-catalyzed C–H functionalizations of benzacids (**53** and **57**) with allylacetate[14d] or arylacetylenes,[14b] respectively. Under the standard conditions, 5 mol % of $ReCl_3$ enables cascade arylation-acylation-cyclization of (*E*)-enol lactones (**7o**–**7q**) with arylmagnesium bromides, thus leading to the *neo*-lignan **1** and the corresponding indenones **58**–**59** in 61–67% yields (Scheme 8). Notably, indenones **58**–**59** can be readily transferred to (*iso*)pauciflorol **F** (**2**–**3**), as was reported by Jeffery and Sarpong.[16a] These results show the potential utility of this protocol in medicinal chemistry.

Conclusion

In summary, a simple rhenium-catalyzed aryl-acylcyclization between (hetero)arylmagnesium halides and readily accessible enol lactones has been developed, which provides a simple and expedient route to the synthesis of versatile indenones. This approach proceeds under mild reaction conditions with high efficacy, displays excellent functional group tolerance, features a broad substrate scope of (hetero)arylmagnesium reagents, as well as enol lactones. Mechanistic studies support a in situ formed Re-species enable a sequential of *syn*-carborhenation and intramolecular nucleophilic addition process. Moreover, straightforward synthesis of neo-lignan and (*iso*)pauciflorol **F** shows the potential applications of this protocol for the discovery of novel bioactive molecules.

Acknowledgements

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Keywords: rhenium catalysis • indenone synthesis • aryl-acylcyclization • enol lactones • organomagnesium halides

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[25] The structures of **43** and **49** was determined by X-ray crystallographic analysis. CCDC 2064890 (**43**) and CCDC 2069089 (**49**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data_request/cif.

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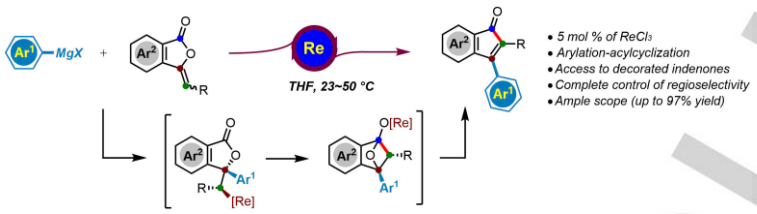

Rhenium-catalyzed aryl-acylcyclization. A range of functionalized organomagnesium halides and enol lactones underwent rhenium-catalyzed sequential aryl-acylcyclization under remarkably mild reaction conditions, thus providing an expedient route to polyfunctionalized indenones with complete control of regioselectivity. This approach features its broad substrate scope, excellent functional group tolerance, and synthetic utility in the straightforward synthesis of biologically relevant molecules.