

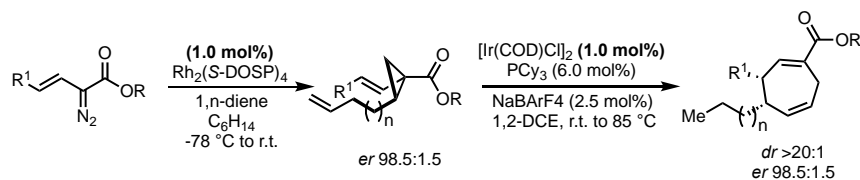
# Iridium-Catalyzed Tandem Chain-Walking/Cope Rearrangement Strategy

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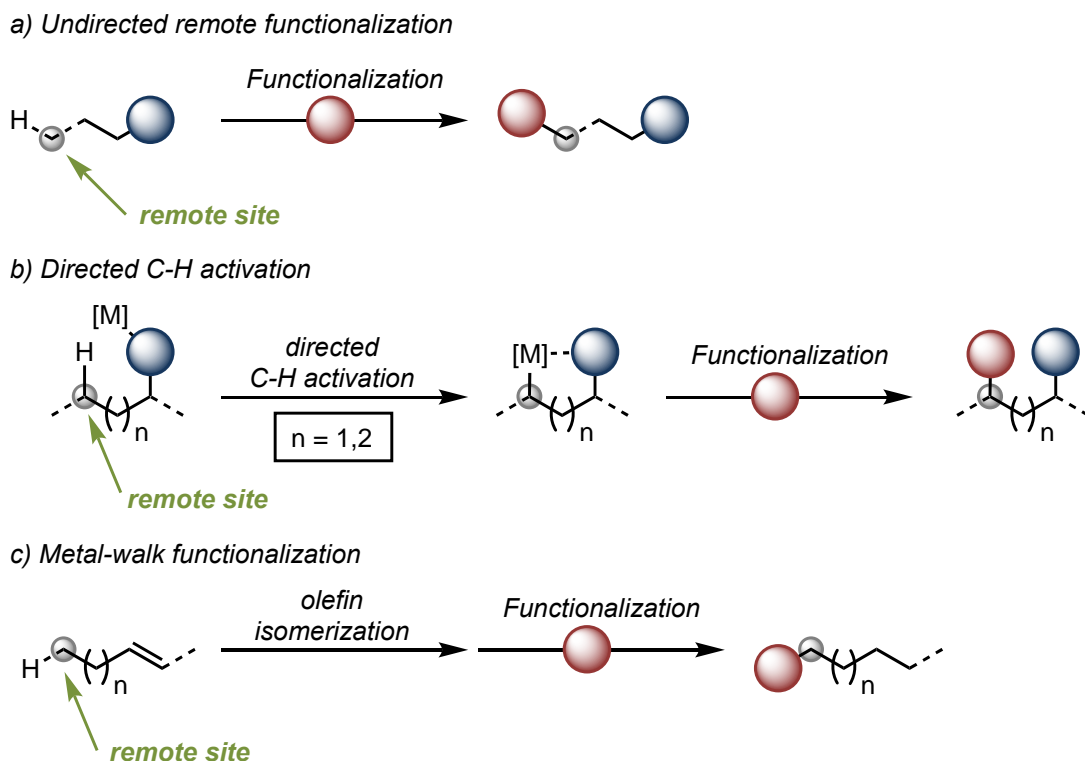
**ABSTRACT** An iridium-catalyzed tandem olefin migration/Cope rearrangement of alkenyl cyclopropanes is reported. By this means, a variety of complex annulenes are obtained as single diastereomers starting from cyclopropyl ester derived from simple 1,3-dienes and alkenyldiazo compounds. Long-range olefin migration over up to 10 positions could be realized and coupled with an efficient Cope rearrangement to yield valuable scaffolds. Various functional groups are well tolerated, giving rise to densely functionalized products. Furthermore, the present methodology could be successfully extended to yield bicyclic cycloheptenones starting from readily available alkenyl cyclopropanols via a Kulinkovich reaction.



**KEYWORDS** chain-walking, remote functionalization, iridium catalysis, Cope rearrangement, alkenyl cyclopropane

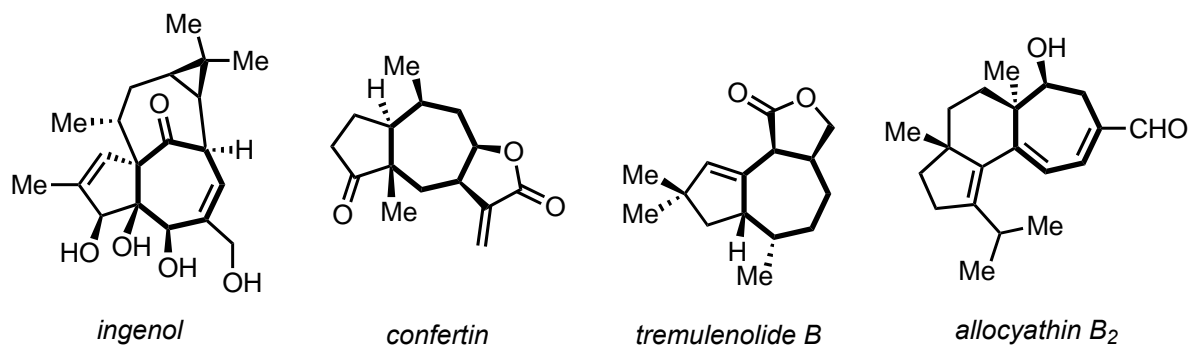
Transition-metal catalyzed C-H activation has received considerable attention in the context of remote functionalization. This methodology has the power to transform abundant starting materials into valuable, functionalized scaffolds at a non-reactive site (Scheme 1a).<sup>1-4</sup> In contrast to directed remote functionalization (Scheme 1b),<sup>5-9</sup> metal-walk functionalization allows for the transformation of positions distal to the initiating site (Scheme 1c).<sup>10-14</sup> From the initial processes utilizing stoichiometric zirconium<sup>15-20</sup>, protocols relying on palladium<sup>13, 21-25</sup>, ruthenium<sup>26-27</sup>, nickel<sup>28-29</sup>, or cobalt<sup>30-31</sup> catalysis have been developed and applied in various C-C and C-X-bond forming processes, respectively.<sup>12-14</sup>

# Metal Ions in Life Sciences



**Scheme 1.** Potential strategies for C-H functionalization

Continuing our efforts to combine transition-metal catalyzed chain-walking processes with subsequent remote functionalization,<sup>13, 19-20, 25</sup> we decided to explore the possibility to intercept an intermediately formed olefin in a rearrangement process. Merging our long-standing interest in cyclopropane chemistry<sup>32-37</sup> with transition-metal catalyzed ‘chain-walking’, the dialkenylcyclopropane rearrangement was deemed as an ideal testing ground. This well-studied process has found countless applications in complex molecule synthesis and developed into a useful tool for the synthesis of (bicyclo)heptadienes.<sup>38-39</sup> This ubiquitous motif forms the core of numerous classes of natural products and has inspired many elegant synthetic approaches (Scheme 2).<sup>40-44</sup>



**Scheme 2.** Cycloheptane-containing annulene natural products

At the outset of our study several challenges had to be met. In order to achieve high diastereoselectivity in the key Cope rearrangement, excellent control over double-bond geometry during the metal-walk had to be ensured. It should be noted that commonly employed catalytic

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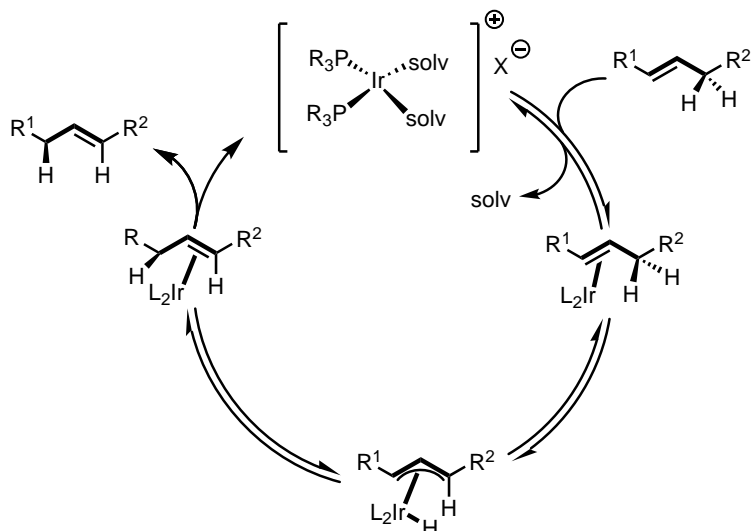
systems for long-range olefin isomerization/remote functionalization generally lack this important attribute. As chain-walking processes can proceed via different mechanisms, control over olefin geometry is determined by the mode of action of the catalyst employed.<sup>45</sup> Due to their simplicity, the majority of utilized catalytic systems follow a sequence of hydrometalation/ $\beta$ -hydride-elimination events to achieve the metal-walk. Typically under these conditions olefin geometry is solely based on kinetic control and fails to provide sufficient levels of selectivity.

To address these shortcomings, studies have focused on the development of catalysts that affect olefin migration via allylic activation (Scheme 3a). Interestingly, only a limited number of examples achieving this goal have been reported solely utilizing zirconium<sup>15-20, 46</sup>, ruthenium<sup>26, 47</sup> or iridium catalysts, respectively.<sup>48-55</sup> Due to their robustness, ease of preparation and functional group tolerance, we decided to study the utility of cationic bis-phosphine iridium complexes. These have been shown to promote medium-range olefin isomerizations of silyl ethers with excellent levels of control of olefin geometry (Scheme 3b).<sup>54</sup> Related iridium complexes have successfully been employed in single-positional isomerization of allylic alcohols into the corresponding carbonyl derivatives which can be directly used in cross-coupling reactions (Scheme 3c),<sup>56-57</sup> and in a one-carbon isomerization followed by a Claisen rearrangement (Scheme 3d).<sup>53</sup> Additionally the resulting high *trans*-selectivity has been exploited in an enantioselective allylboration of aldehydes.<sup>58</sup>

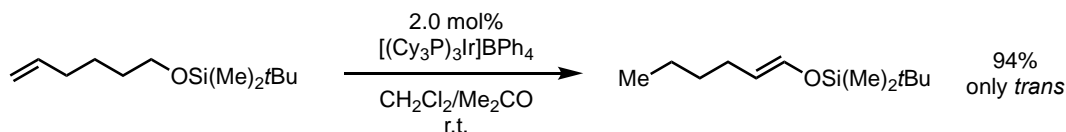
Based on this 1,3-allylic migration mechanism, we envisioned to perform an Ir-catalyzed migration of a remote double bond of various functionalized  $\omega$ -ene alkenylcyclopropanes as an efficient access to stereodefined dialkenylcyclopropanes *en route* to diversely functionalized cycloheptadiene structures (Scheme 3e).

# Metal Ions in Life Sciences

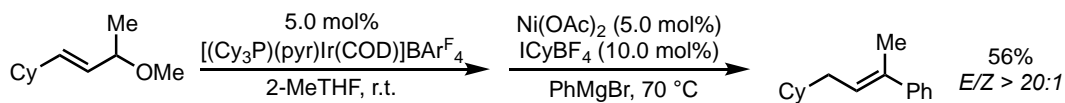
a) Iridium-catalyzed olefin isomerization via allylic activation pathway



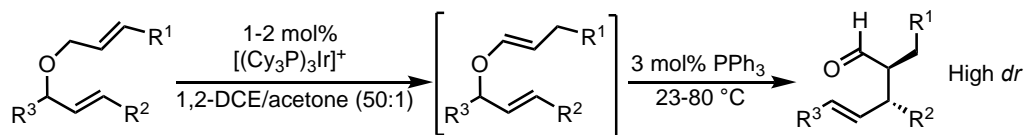
b) RajanBabu and coworkers - olefin migration to form silyl enol ethers (2009)



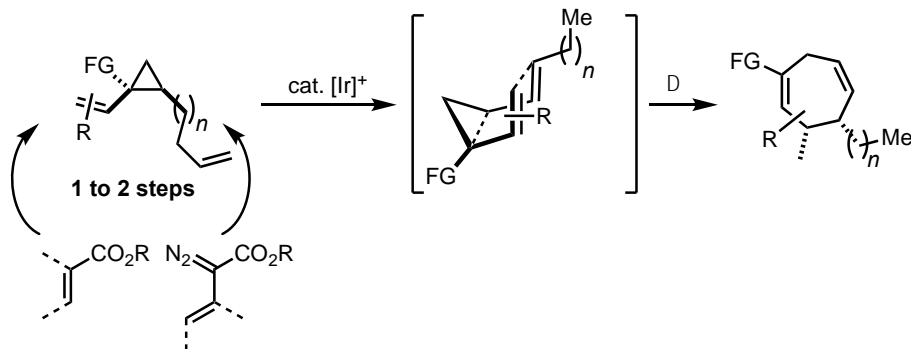
c) Mazet and coworkers - enol ether formation and nickel-catalyzed cross coupling (2018)



d) Nelson and coworkers - One-carbon isomerization followed by a Claisen rearrangement (2003)



e) Our design - tandem iridium-catalyzed olefin migration/Cope rearrangement



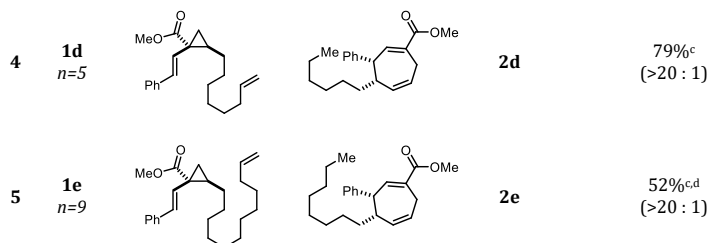
**Scheme 3.** Iridium-catalyzed olefin isomerization and novel application in tandem process

With the goal of developing an experimentally user-friendly protocol, we decided to prepare the catalyst *in situ* by simply mixing commercially available  $[\text{Ir}(\text{COD})\text{Cl}]_2$ ,  $\text{PCy}_3$  and  $\text{NaBAR}^{\text{F}}_4$  without recurring to the semi-hydrogenation reaction of the supporting COD-ligand prior to the catalytic reaction.<sup>59</sup> Under these conditions, the obtained  $[\text{Ir}(\text{PCy}_3)_3]\text{BAR}^{\text{F}}_4$  complex exerted excellent activity even at room temperature. At the outset, we turned our attention towards styrenyl  $\omega$ -ene cyclopropanes, easily accessible through the rhodium-catalyzed decomposition of the respective alkenyl diazoester with various 1, $\omega$ -dienes.<sup>60-61</sup>

To our delight, olefin isomerizations over up to four positions with subsequent Cope rearrangement occurred rapidly upon heating to 85 °C with only 1.0 mol% of Ir-dimer complex (Table 1, entries 1-3). Extending the chain-length required slightly increased catalyst loading (2.5 mol% of Ir-dimer complex) but still furnished the products in moderate to good yields with isomerizations over up to 10 positions (Table 1, entries 4,5).<sup>62</sup> It should be noted that separation of the product from small amounts of remaining internal olefin isomers proved challenging and was only achieved after reduction of the ester functionality (Table 1, entry 5). The relative stereochemistry of **2a** was determined by comparison with reported data.<sup>61</sup>

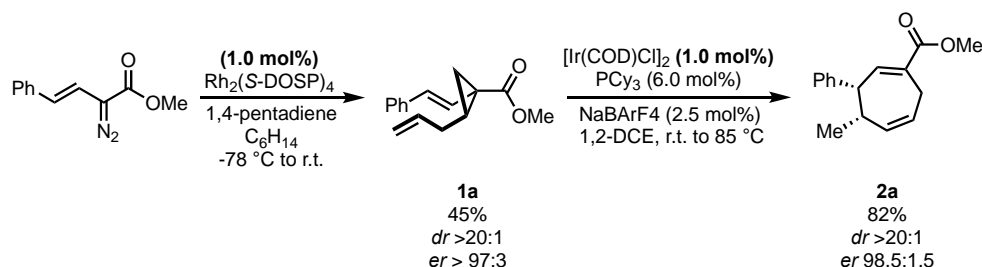
**Table 1.** Iridium-catalyzed olefin migration/Cope rearrangement of  $\omega$ -ene styrenyl cyclopropanes<sup>a</sup>

No	Alkenyl-CP	Product	Yield <sup>b</sup> (dr)
1	<b>1a</b> <i>n</i> =0	<b>2a</b>	82% (>20:1)
2	<b>1b</b> <i>n</i> =1	<b>2b</b>	74% (>20:1)
3	<b>1c</b> <i>n</i> =3	<b>2c</b>	80% (>20:1)



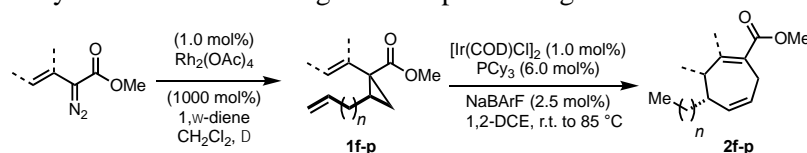
[a] Reaction conditions:  $\omega$ -Ene alkenylcyclopropane (0.5 mmol),  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (1.0 mol%),  $\text{PCy}_3$  (6.0 mol%),  $\text{NaBARF}_4$  (2.5 mol%), 1,2-DCE (1.0 mL), 85 °C. [b] Yield of isolated products after purification by flash chromatography. [c]  $[\text{Ir}(\text{COD})\text{Cl}]_2$  (2.5 mol%),  $\text{PCy}_3$  (15.0 mol%),  $\text{NaBARF}_4$  (6.25 mol%). [d] isolated after DIBAL-H reduction: DIBAL-H (250 mol%), THF (0.1M), -78 °C to room temperature.

It should be highlighted that the present methodology allowed for the synthesis of enantioenriched cycloheptadiene **2a** in only two catalytic steps utilizing only minute amounts of catalyst (Scheme 4).



**Scheme 4.** Efficient enantioselective synthesis of enantioenriched **2a**

Having established a protocol for the long-range olefin isomerization/Cope rearrangement for styrenylcyclopropanes, we examined the scope of various olefinic counterparts with 1,5-hexadiene- and 1,7-octadiene-derived alkenylcyclopropanes (Table 2). To this end, a variety of alkenyldiazo derivatives were synthesized following established procedures and subsequently transformed in the rhodium-catalyzed cyclopropanation reaction (*see supporting information*). Various annulenes were obtained in moderate to good yields with excellent diastereocontrol. Simple cyclopentyl- and cyclohexyl-annelated compounds (Table 2, entries 1-4) could be accessed in good yield with as low as 1.0 mol% of catalyst loading. However, incorporating Lewis-basic groups, i.e., ketones or ethers necessitated the utilization of slightly increased catalyst loading (2.5 mol% of Ir-dimer complex, Table 2, entries 5-11). Nevertheless, the corresponding annulenes were obtained in good yields including benzofuranes (Table 2, entries 7, 8) or cyclic ketones (Table 2, entries 5, 6 and 9). As reported by Davies, upon Cope rearrangement of benzofurane **2l** and **2m**, the dearomatized products were obtained.<sup>63-64</sup> Even quaternary carbon stereocenters could be efficiently installed, giving rise to densely functionalized scaffolds (Table 2, entries 5, 6). Interestingly, without the quaternary carbon center, isomerization of the newly formed olefin into conjugation with the ketone was observed (Table 2, entry 9). It should be noted that in this case only the *syn*-isomer underwent the crucial Cope rearrangement. The corresponding *anti*-isomer merely furnished a mixture of internal olefins, advocating the existence of an iridium-catalyzed olefin equilibration. Finally, challenging sulfonyl-piperidine derived annulenes were obtained in good yield (Table 2, entries 10, 11) after prolonged heating (48 h).

**Table 2.** Scope of different  $\omega$ -ene alkenylcyclopropanes in the iridium-catalyzed tandem olefin migration/Cope rearrangement<sup>a</sup>


No	Alkenyl-CP	Product	Yield [%] <sup>b</sup> (dr)
1	<b>1f</b> <i>n</i> =1 	<b>2f</b> <i>n</i> =1 	70 (>20:1)
2	<b>1g</b> <i>n</i> =3 	<b>2g</b> <i>n</i> =3 	88 (> 20 : 1)
3	<b>1h</b> <i>n</i> =1 	<b>2h</b> <i>n</i> =1 	58 (> 20 : 1)
4	<b>1i</b> <i>n</i> =3 	<b>2i</b> <i>n</i> =3 	52 (>20 : 1)
5	<b>1j</b> <i>n</i> =1 	<b>2j</b> <i>n</i> =1 	87 (>20 : 1) <sup>c</sup>
6	<b>1k</b> <i>n</i> =3 	<b>2k</b> <i>n</i> =3 	55 (>20 : 1) <sup>c</sup>
7	<b>1l</b> <i>n</i> =1 	<b>2l</b> <i>n</i> =1 	73 (> 20 : 1) <sup>c</sup>
8	<b>1m</b> <i>n</i> =3 	<b>2m</b> <i>n</i> =3 	78 (>20 : 1) <sup>c</sup>
9	<b>1n</b> <i>n</i> =3 	<b>2n</b> <i>n</i> =3 	59 <sup>c,d</sup> (>20 : 1)
10	<b>1o</b> <i>n</i> =1 	<b>2o</b> <i>n</i> =1 	51 (>20 : 1) <sup>c,e</sup>
11	<b>1p</b> <i>n</i> =3 	<b>2p</b> <i>n</i> =3 	75 (>20 : 1) <sup>c</sup>

[a] Reaction conditions:  $\omega$ -Ene alkenylcyclopropane (0.25 - 0.5 mmol), [Ir(COD)Cl]<sub>2</sub> (1.0 mol%), PCy<sub>3</sub> (6.0 mol%), NaBARF<sub>4</sub> (2.5 mol%), 1,2-DCE (0.5M), 85 °C. [b] Yield of isolated products after purification by flash chromatography. [c] [Ir(COD)Cl]<sub>2</sub> (2.5 mol%), PCy<sub>3</sub> (15.0 mol%), NaBARF<sub>4</sub> (6.25 mol%). [d] starting material as 60:40 mixture of *syn/anti* isomers, yield based on *syn*-isomer [e] isolated after DIBAL-H reduction: DIBAL-H (250 mol%), THF (0.1M), -78 °C to room temperature.

In order to expand the utility of the methodology, we turned our attention towards the bicyclic synthesis of

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cycloheptenones. As the required starting materials are not accessible by the above presented sequence, a complementary approach was envisioned. The utilization of a Kulinkovich reaction<sup>65-66</sup> would provide a straightforward access to simple alkenyl cyclopropanols which can subsequently be transformed into valuable ketoannulenes.<sup>67</sup> Utilizing a modified Kulinkovich procedure,<sup>68</sup> the thus obtained cyclopropanols were exposed to the optimized reaction conditions after silylation of the hydroxy group (Table 3).

**Table 3.** Iridium-catalyzed olefin migration/Cope rearrangement of alkenyl cyclopropanol ethers<sup>a</sup>

No	Alkenyl-CP	Product	Yield <sup>b</sup> (dr)
1	<b>1q</b> <i>n</i> =1	<b>2q</b> <i>n</i> =1 57 : 43	61 <sup>c</sup> (>20 : 1)
2	<b>1r</b> <i>n</i> =2	<b>2r</b> <i>n</i> =2	63 (>20 : 1)
3	<b>1s</b> <i>n</i> =3	<b>2s</b> <i>n</i> =3	41 (α,β) (>20 : 1)
		<b>2s'</b> <i>n</i> =3	34 (β,γ) (>20 : 1)
4	<b>1t</b> <i>n</i> =3	<b>2t</b> <i>n</i> =3	77 (>20 : 1)

[a] Reaction conditions: ω-Ene alkenylcyclopropanol derivative (0.5 mmol), [Ir(COD)Cl]<sub>2</sub> (1.0 mol%), PCy<sub>3</sub> (6.0 mol%), NaBAR<sup>F</sup><sub>4</sub> (2.5 mol%), 1,2-DCE (1.0 mL), 85 °C. [b] Yield of isolated product after purification by flash chromatography. [c] inseparable mixture of olefin isomers.

Facile cyclic enol ether formation was observed in the presence of only 1.0 mol% of Ir-dimer complex and subsequent mild desilylation delivered the products in good yield (Table 3, entries 1-4). Annulated cycloheptenones comprising cyclohexane and cyclopentane cores with different tether lengths were again well-tolerated. All bicyclic cycloheptenones (**2q-2t**) were again formed as a single diastereomer, advocating the perfect control over the double-bond geometry. Interestingly, during the deprotection step we could observe in two cases (Table 3, entries 1 and 3) partial isomerization of the olefin into the corresponding α,β-unsaturated ketones. The sensitive α'-position at the ring-junction remained unchanged under these conditions.

Herein we report a facile protocol for the synthesis of valuable annulenes starting from simple olefinic precursors obtained in one or two catalytic steps. In the presence of a highly reactive, cationic iridium catalyst, a tandem olefin migration/Cope rearrangement of intermediately formed dialkenyl cyclopropanes could be realized. This functional-group tolerant procedure smoothly delivers bicyclic cycloheptadiene esters and cycloheptenones in moderate to good yield as single stereoisomers. The obtained complex scaffolds comprise quaternary stereocenters, heteroaromatic systems or cyclic amine motifs, present in numerous biologically active compounds. Studies to

extend the scope of this useful tandem sequence and to obtain insights into the mechanistic underlying are ongoing.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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### Supporting Information

This material is available free of charge via the Internet at <http://pubs.acs.org>

Details of experimental procedures, instrumentation used,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all new compounds, HPLC traces of racemic and enantiomerically pure compounds.

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