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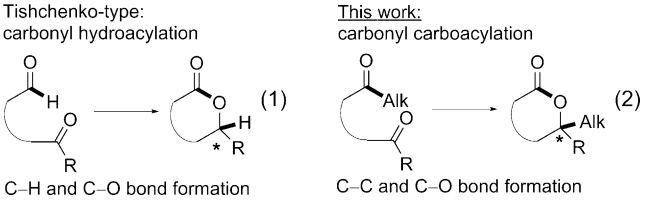
Synthetic Methods

Highly Enantioselective Rhodium(I)-Catalyzed Carbonyl Carboacylations Initiated by C–C Bond Activation**

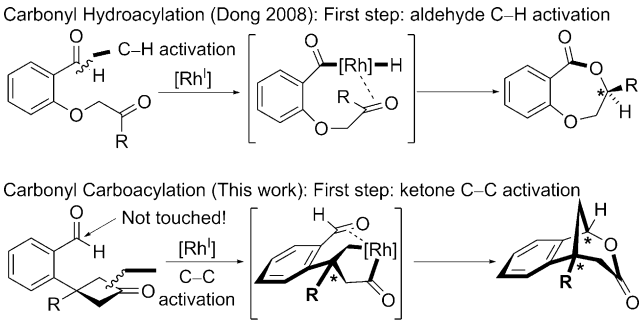
*Laetitia Souillart and Nicolai Cramer**

Abstract: *The lactone motif is ubiquitous in natural products and pharmaceuticals. The Tishchenko disproportionation of two aldehydes, a carbonyl hydroacylation, is an efficient and atom-economic access to lactones. However, these reaction types are limited to the transfer of a hydride to the accepting carbonyl group. The transfer of alkyl groups enabling the formation of C–C bonds during the ester formation would be of significant interest. Reported herein is such asymmetric carbonyl carboacylation of aldehydes and ketones, thus affording complex bicyclic lactones in excellent enantioselectivities. The rhodium(I)-catalyzed transformation is induced by an enantiotopic C–C bond activation of a cyclobutanone and the formed rhodacyclic intermediate reacts with aldehyde or ketone groups to give highly functionalized lactones.*

Lactones are ubiquitous and very important structural motifs in natural products and pharmaceuticals.[1] Despite numerous lactonization methods,[1,2] efficient processes to access lactones from uncommon precursors are highly desirable. Many methods involve either the stoichiometric activation of the hydroxy or the carboxy group. An atom-economic strategy is a crossed intramolecular Tishchenko reaction, thereby disproportionating two aldehyde moieties into a lactone.[3] The same overall transformation can be achieved by carbonyl hydroacylations operating by a different mechanism.[4] All the processes are strictly limited to the transfer of a hydride to the accepting carbonyl group [Eq. (1)]. However, the transfer of carbon chains is highly desirable, thus enabling the formation of valuable C–C bonds during the lactonization event [Eq. (2)].



Herein, we disclose such an asymmetric carbonyl carboacylation which provides bicyclic lactones induced by a highly enantioselective C–C bond activation of cyclobutanones (Scheme 1). The selective catalytic C–C bond activation by transition-metal catalysts is an intriguing strategy to access organometallic species for uncommon disconnections.[5] The development of enantioselective variants lags behind and most reports focus on asymmetric β-carbon-elimination processes.[6,7] Insertions of rhodium(I) complexes into the acyl–carbon bond of ketones are mechanistically different, and strained ketones are a versatile substrate class.[8] Rhodium(I)-catalyzed carboacylations of olefins and alkynes for conversion of a ketone substrate into a structurally more complex product ketone have been reported,[9] including recently published enantioselective variants.[10] These reactions involve a C–H or C–C bond-forming step by reductive elimination, which is well established with rhodium catalysts. In contrast, related C–O bond formations are less common for rhodium,[4b–f,11] and to the best of our knowledge rhodium-catalyzed carbonyl carboacylations are elusive. Dong et al. reported intramolecular asymmetric carbonyl hydroacylations providing Tishchenko-type lactone products.[4d–f] In this case the reaction is initiated by an oxidative insertion of the rhodium(I) catalyst into the acyl C–H bonds, with subsequent addition across the ketone carbonyl group (Scheme 1). In contrast, our envisioned carbonyl carboacylation process requires the opposite reaction order. First, an activation of the acyl–carbon bond of the ketone moiety must proceed, thus leaving the acyl–hydrogen bond of the aldehyde group untouched. We hypothesized that the superior reactivity of the cyclobutanone would enable such reactivity reversal, and overrule the common C–H versus C–C activation propensity.[12] Moreover, this oxidative insertion reaction must proceed in an enantioselective manner, thus setting the



Scheme 1. Asymmetric carbonyl carboacylation strategy to provide bicyclic lactones.

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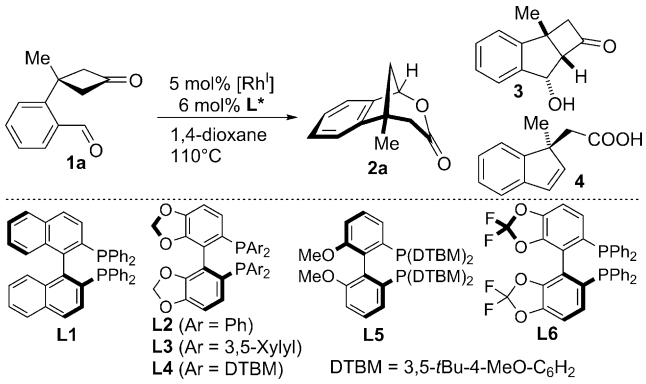
quaternary stereogenic center of the products. The transient rhoda(III)cyclopentanone will then add across the carbonyl group to give, after reductive elimination, the desired lactone.

The investigation of the reaction was performed on the model cyclobutanone **1a**. Submitting **1a** to [{Rh(cod)Cl}$_2$] as a rhodium(I) source in the presence of binap (**L1**) in 1,4-dioxane at 110 °C gave the desired lactone **2a** in a promising enantiomeric ratio of 93.2:6.8, albeit with poor conversion and yield (Table 1, entry 1). Segphos-type ligands (**L2**–**L4**) improved both the yield and enantioselectivity (entries 2–4). DTBM-Segphos (**L4**) is the most efficient, thus affording the lactone **2a** in 94% yield with an excellent enantiomeric ratio of 99.4:0.6 (entry 4). The reaction stalls at 70% conversion with the related DTBM-MeOBiphep (**L5**; entry 5). Difluorphos (**L6**) provides outstanding enantioselectivities but low yields (entry 6). Notably, the reaction is highly sensitive to the counterion. For instance, other rhodium(I) precursors such as [{Rh(cod)(OH)}$_2$] or cationic [Rh(cod)$_2$]BF$_4$ do not give competent catalysts (entries 7 and 8). Intriguingly, the use of the iodide complex [{Rh(cod)I}$_2$][13,14] totally changed the reaction pathway, thus inducing formation of the aldol product **3**[15] rather than engaging in C–C bond cleavage (entry 10). The optimal temperature window for the process is rather narrow. Lowering the temperature by 20 °C decreased the yield to 25% (entry 11) and an increase of 20 °C gave the indenyl acetic acid **4** in high yields (entry 12). This elimination was not observed in catalytic reactions at 110 °C. The bicyclic lactones **2** were found to eliminate cleanly by simply heating above 130 °C in 1,4-dioxane.

Next, we explored the generality of the process with the optimized reaction conditions. We first evaluated the influence of cyclobutanone substitution. Different aliphatic chains, and aromatic and functional groups such as esters and ethers are well tolerated, and the lactones **2** are obtained in good yields and excellent enantioselectivities (Table 2, entries 1–5). Electronic modifications of the aryl moiety, which influence the electrophilicity of the aldehyde group, had no impact on

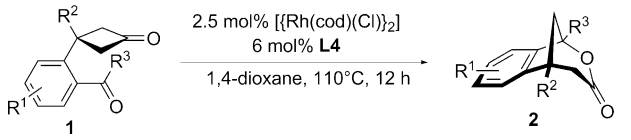
Table 1: Optimization of the asymmetric carbonyl carboacylation.[a]



Entry	[Rh^I]	L*	Changes to conditions	Yield [%][b]	e.r.[c]
1	[{Rh(cod)Cl}$_2$]	**L1**	–	8	93.2:6.8
2	[{Rh(cod)Cl}$_2$]	**L2**	–	30	99.2:0.8
3	[{Rh(cod)Cl}$_2$]	**L3**	–	45	99.5:0.5
4	**[{Rh(cod)Cl}$_2$]**	**L4**	**–**	**94 (89)[d]**	**99.4:0.6**
5	[{Rh(cod)Cl}$_2$]	**L5**	–	65	99.5:0.5
6	[{Rh(cod)Cl}$_2$]	**L6**	–	15	99.8:0.2
7	[Rh(cod)(OH)]$_2$	**L4**	–	0	n.d.
8	[Rh(cod)$_2$]BF$_4$	**L4**	–	25	n.d.
10	[{Rh(cod)I}$_2$]	**L4**	–	81 (**3**)[d]	0
11	[{Rh(cod)Cl}$_2$]	**L4**	at 90 °C	25	n.d.
12	[{Rh(cod)Cl}$_2$]	**L4**	at 130 °C	90 (**4**)[d]	n.d.

[a] Reaction conditions: 0.05 mmol **1a**, 2.50 μmol [Rh^I], 3.00 μmol L*, 0.25 M in 1,4-dioxane at 110 °C for 12 h. [b] Yield of **2a** determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC with a chiral stationary phase. [d] Yield of isolated product. cod = 1,5-cyclooctadiene, n.d. = not determined.

Table 2: Scope of enantioselective C–C activation of aldehydes **1**.[a]



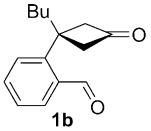
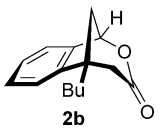
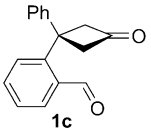
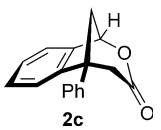
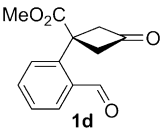
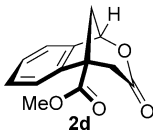
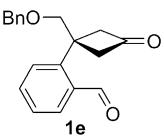
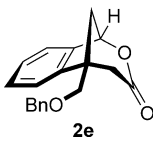
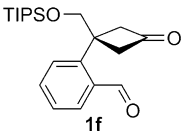
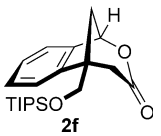
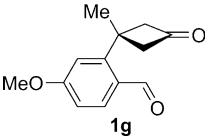
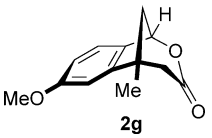
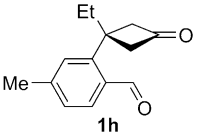
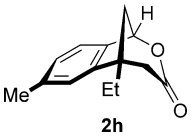
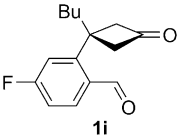
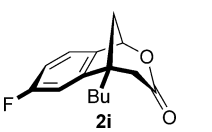
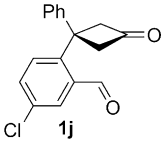
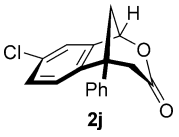
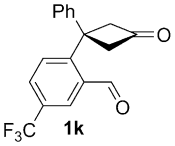
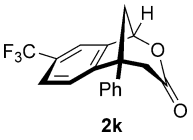
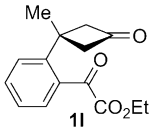
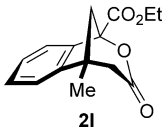
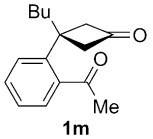
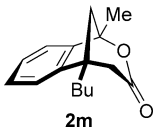
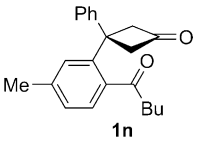
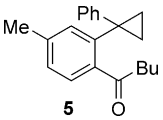
Entry	1	2	Yield [%][b]	e.r.[c]
1[d]	 **1b**	 **2b**	76	99.3:0.7
2	 **1c**	 **2c**	80	99.4:0.6
3	 **1d**	 **2d**	78	99.7:0.3
4[d]	 **1e**	 **2e**	89	98.9:1.1
5[d]	 **1f**	 **2f**	64	97.2:2.8
6[d]	 **1g**	 **2g**	83	99.6:0.4
7	 **1h**	 **2h**	83	99.5:0.5
8[d]	 **1i**	 **2i**	69	99.4:0.6

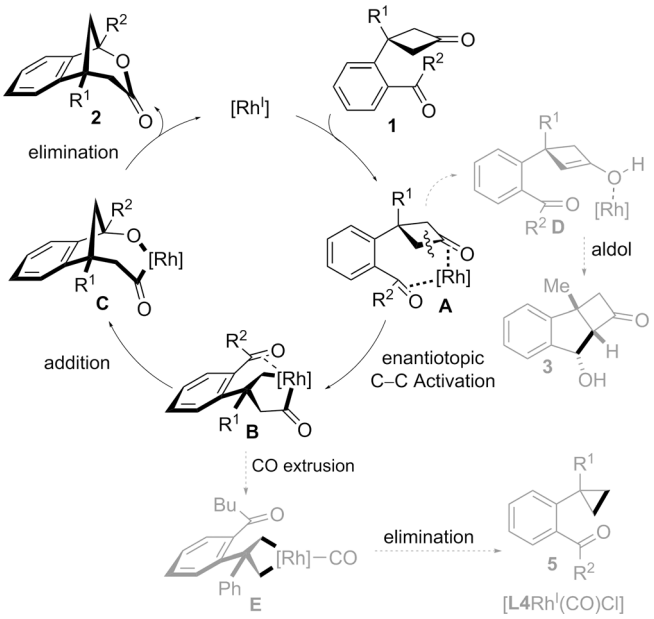
Table 2: (Continued)

Entry	1	2	Yield [%][b]	e.r.[c]
9	 **1j**	 **2j**	86	99.5:0.5
10	 **1k**	 **2k**	85	99.3:0.7
11	 **1l**	 **2l**	80	99.7:0.3
12[e]	 **1m**	 **2m**	81	99.8:0.2
13[e]	 **1n**	 **5**	10	–

[a] Reaction conditions: 0.10 mmol **1**, 2.50 μmol [{Rh(cod)Cl}$_2$], 6.00 μmol **L4**, 0.25 M in 1,4-dioxane at 110 °C for 12 h. [b] Yield of isolated product. [c] Determined by HPLC with a chiral stationary phase. [d] 2.50 μmol [{Rh(cod)Cl}$_2$], 6.0 μmol **L4**, 0.25 M in 1,4-dioxane at 110 °C for 24 h. [e] 5.00 μmol [{Rh(cod)Cl}$_2$], 12.0 μmol **L4**, 0.25 M in 1,4-dioxane at 110 °C for 48 h.

the reaction outcome (entries 6–10). We then aimed at replacing the aldehyde with less reactive and more hindered ketones. In this respect, activated ketones, such as the α-ketoester **1l** gave **2l**, having two quaternary stereogenic centers at the bridgehead positions, with similar enantiomeric ratio (entry 11). Unbiased ketones such as the methyl ketone **1m** are slightly less reactive and require increased catalyst loading and prolonged reaction times to provide **2m** in good yield and excellent enantioselectivity (entry 12). In contrast, the bulkier butyl ketone **1n** is not a suitable substrate. While the C–C activation is still proceeding, the addition across the carbonyl group fails. As a consequence, decarbonylation occurs to form the cyclopropane **5** (entry 13).[8b,16] As the concomitantly formed rhodium(I) carbonyl complex is catalytically not competent, a single turnover is observed.

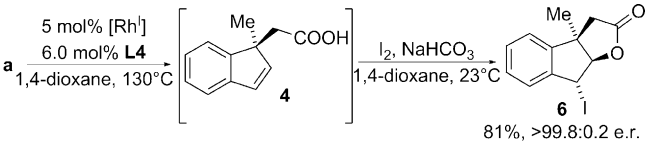
Mechanistically, the carbonyl carboacylation is induced by a coordination of the rhodium(I) catalyst to the cyclobutanone **1** (Scheme 2). At this stage, too strong of a Lewis-acidic metal could induce enolization and subsequent intramolecular aldol addition, thus giving compound **3** as observed with the [{Rh(cod)I}$_2$] complex. A suitable rhodium complex oxidatively adds selectively in one of the two enantiotopic acyl–carbon bonds of the cyclobutanone to give the rhodacyclopentanone **B**. Depending on the sterics and the electrophilicity of the appended carbonyl group, two pathways are



Scheme 2. Mechanistic model for the rhodium-catalyzed asymmetric carbonyl carboacylation and observed side-reactions.

possible. Reluctant substrates cause extrusion of carbon monoxide, giving **E**. Reductive elimination provides cyclopropane and an inactive Vaska-type complex.[16] In contrast, competent substrates undergo insertion of the carbonyl group into the rhodium(III)–alkyl bond to give the rhodabicycle **C**. Reductive elimination forms the ester linkage leading to the desired lactone **2** and closure of the catalytic cycle.

To illustrate further the complexity-generating potential of the carbonyl carboacylation, the indenyl acetic acid **4**, formed at higher reaction temperature, was directly exposed to iodine/sodium bicarbonate at ambient temperature (Scheme 3). This one-pot iodolactonization provided the



Scheme 3. One-pot carboacylation/elimination/iodo lactonization for the synthesis of **6**.

lactone **6** in 81 % yield as a single diastereomer and excellent enantioselectivity. Moreover, X-ray crystallography established its absolute configuration.[17] In addition to the X-ray structure of **2j**,[17] it provides evidence for a constant enantiotopicity of the insertion into the acyl C–C bond of cyclobutanones.

In summary, we demonstrated a rhodium-catalyzed carbonyl carboacylation process providing efficient access to the benzo[*c*]oxepinone scaffold. The transformation is initiated by a highly enantioselective C–C bond activation, and tolerates a broad range of substituents. The reaction is well-suited for one-pot, complexity-generating downstream reactions. Ongoing research is focused on the exploitation of

additional C–C bond activation processes to enable novel and versatile transformations.

Experimental Section

Cyclobutanone (**1a**; 18.6 mg, 0.100 mmol), [{Rh(cod)(Cl)}$_2$] (1.14 mg, 2.50 μmol), and (*R*)-DTBM-Segphos (7.08 mg, 6.00 μmol) were weighted into an oven-dried vial equipped with a magnetic stir bar, capped with a septum and purged with nitrogen. Dry 1,4-dioxane (0.1 mL) was added and the mixture was degassed with three freeze-pump-thaw cycles. The mixture was stirred for 20 min at 23 °C and subsequently heated at 110 °C. After 12 h, the reaction mixture was cooled to 23 °C and purified by silica gel column chromatography eluting with pentanes/ethyl acetate (10:1). Lactone **2a** was isolated colorless oil in 94 % yield (17.5 mg) and 99.7:0.3 e.r.

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