Asymmetric Catalysis

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Palladium-Catalyzed Synthesis of Substituted Cycloheptane-1,4-diones by an Asymmetric Ring-Expanding Allylation (AREA)**

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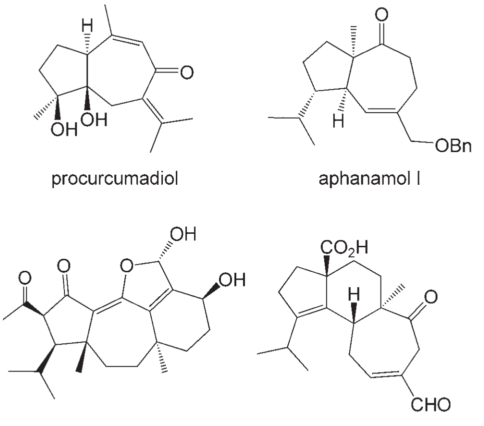
Oxygenated seven-membered carbocycles are a common motif in many natural products, prominent examples being found in the classes of the perhydroazulenes (such as procurcumadiol and (+)-aphanamol I),[1,2] the guanacastepene diterpenes,[3] or the scabronines,[4] a family of cyathane-type diterpenoids (Scheme 1). These molecules have interesting biological and pharmaceutical properties,[5] and thus much effort has been made towards their asymmetric synthesis.[6,7]



Scheme 1. Natural products with oxygenated seven-membered ring systems. Bn = benzyl.

During the course of our research directed towards the asymmetric total synthesis of perhydroazulene-type diterpenes we became interested in the enantioselective synthesis of functionalized seven-membered diketones. The de Mayo reaction constitutes an attractive route to medium-sized carbocycles from 1,3-cyclopentanediones and 1,3-cyclohexanediones.[8] The reaction consists of a sequence of a [2+2] cycloaddition of an enolized 1,3-diketone with an olefin to give a bicyclic cyclobutane which subsequently undergoes a retro-aldol reaction that leads to seven- and eight-membered 1,4- and 1,5-diketones. The potential of this transformation has been demonstrated with the huge number of natural product syntheses that use the de Mayo reaction.[9–11]

The asymmetric transition-metal-catalyzed decarboxylative allylation of ketone or β-ketoester enolates is an extremely valuable tool for the construction of stereocenters adjacent to carbonyl groups.[12,13] The reaction is broadly applicable as they generally proceed with high yields and under very mild reaction conditions. During the course of the de Mayo reaction, a ketone enolate is formed which is normally protonated, and analogously to our previous work we wanted to intercept this protonation reaction by trapping the enolate with a chiral π-allyl palladium complex to give enantioenriched 5-allyl-1,4-cycloheptanediones.[14] In particular we wished to target allylated cycloheptanediones with quaternary stereocenters, the construction of which still remains an elusive goal in organic synthesis.[15] Herein we report on a catalytic asymmetric ring-expanding allylation (AREA) reaction for the synthesis of chiral oxygenated seven- and eight-membered carbocycles.

Early experiments used bicyclo[3.2.0]heptane-2-one derivative (±)-**1** with a methyl group at the bridgehead position (Table 1). Different palladium sources such as [$Pd_2(dba)_3$] (dba = *trans,trans*-dibenzylideneacetone) and [{$Pd(C_3H_5)Cl$}$_2$] were investigated along with a number of chiral ligands **3**–**8** which are commonly used in palladium chemistry (Scheme 2).[16] Furthermore, the influence of the solvent was explored.

We were pleased to see that the AREA reaction of (±)-**1** under various conditions gave the cycloheptane-1,4-dione **2** in good yields and enantioselectivities (Table 1). The reaction times ranged from one hour to three days, depending on both the nature of the chiral ligand and the solvent employed, and were longer compared to a test reaction in which the achiral tetrakis(triphenylphosphine)palladium(0) was used (Table 1, entry 1). All the reactions could be performed with low catalyst loadings at room temperature. The best results were achieved when substrate **1** was treated with 2.5 mol% [$Pd_2(dba)_3$] and 6.5 mol% (*S*)-*t*Bu-phox ((*S*)-**7**)[17] in a 1,4-dioxane/THF (3:1) mixture at 10°C. The product (−)-**2** was isolated in 92% yield and 90% *ee* (Table 1, entry 9a). Only slightly worse results were achieved when [$Pd_2(dba)_3$] and (*S*)-*i*Pr-phox ((*S*)-**6**) were used (Table 1, entry 6). However, throughout our investigations the ligand (*S*)-**7** proved to be superior. In general, the AREA reaction gave enantioselectivities that were somewhat lower than those reported for the allylation of enolates in six-membered ring systems.[13f] We

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Supporting information (experimental procedures and spectroscopic data) for this article is available on the WWW under http://www.angewandte.org or from the author.

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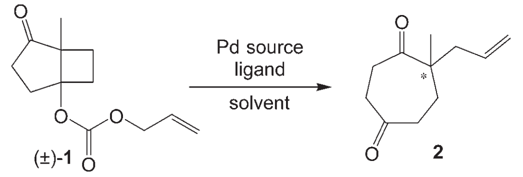
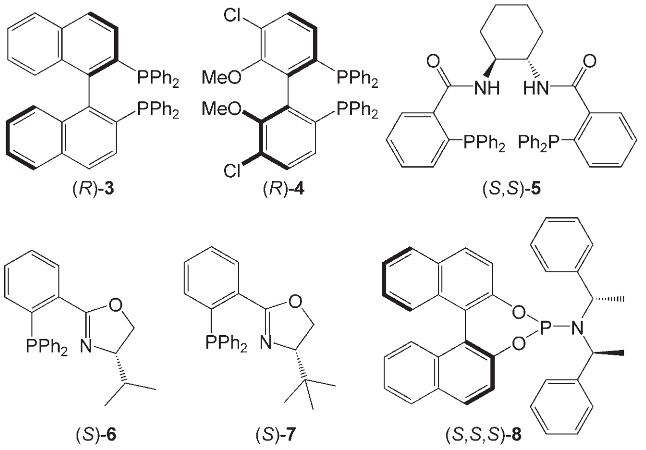
Table 1: Test reactions for the asymmetric ring-expanding allylation (AREA).[a]



Entry	Pd source	Ligand	Solvent	Product	*t*	Yield[b] [%]	*ee*[c] [%]
1	$[Pd(PPh_3)_4]$	–	1,4-dioxane	*rac*-**2**	10 min	92	–
2	$[Pd_2(dba)_3]$	(*R*)-**3**	THF	–	48 h	–	–
3	$[Pd_2(dba)_3]$	(*R*)-**4**	THF	**2**	24 h	57	< 5
4	$[Pd_2(dba)_3]$	(*S*,*S*)-**5**	THF	(*R*)-**2**	24 h	60	63
5	$[Pd_2(dba)_3]$	(*S*,*S*)-**5**	1,4-dioxane	(*R*)-**2**	24 h	85	< 10
6	$[Pd_2(dba)_3]$	(*S*)-**6**	1,4-dioxane	(*S*)-**2**	1 h	91	87
7	$[Pd_2(dba)_3]$	(*S*)-**6**	toluene	(*S*)-**2**	78 h	90	85
8	$[Pd_2(dba)_3]$	(*S*)-**7**	1,4-dioxane	(*S*)-**2**	70 min	90	84
9a	$[Pd_2(dba)_3]$	(*S*)-**7**	1,4-dioxane/THF[d]	(*S*)-**2**	16 h	92	90
9b[e]	$[Pd_2(dba)_3]$	(*S*)-**7**	1,4-dioxane/THF[d]	(*S*)-**2**	16 h	94	89
10	$[Pd_2(dba)_3]$	(*S*,*S*,*S*)-**8**	THF	**2**	78 h	40	< 10
11	$[\{Pd(C_3H_5)Cl\}_2]$	(*S*)-**6**	THF	–	48 h	–	–

[a] The reactions were performed on a 0.29-mmol scale with 5.0 mol% of Pd source and 6.5 mol% ligand at a substrate concentration of 0.033 M at RT (22–25 °C). [b] Yields of isolated product. [c] The *ee* values were determined by GC analysis on a chiral stationary phase (Lipodex E column). The absolute configuration was established by transformation of **2** to the corresponding mono-deoxygenated cycloheptanone and comparison of its optical rotation with the value given in Ref. [13f] (see the Supporting Information). [d] The reaction was performed at 10 °C. [e] The reaction was performed on a 2-mmol scale.



Scheme 2. Chiral ligands for the asymmetric Pd-catalysis.

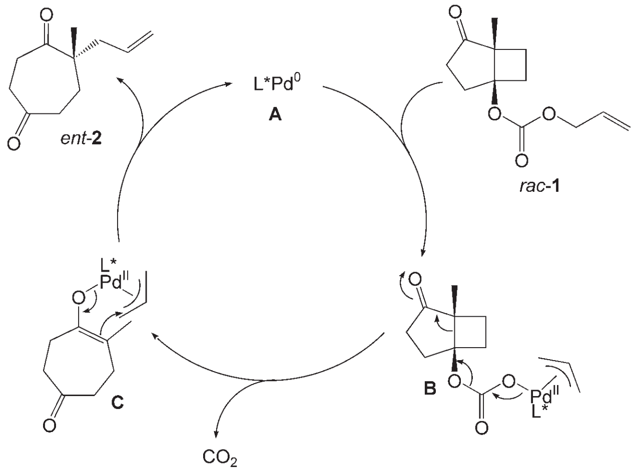
attribute this lower selectivity to the higher conformational flexibility of the seven-membered ring.

We propose the following mechanism for the AREA reaction: The neutral Pd^0 species **A** inserts into the C–O bond of the substrate to give the allyl palladium carbonate **B** (Scheme 3). This undergoes decarboxylative fragmentation and opening of the strained bicycle to give the palladium enolate **C**. Alkylation of this enolate by the chiral π-allyl moiety then gives the product **2** with release of the neutral palladium catalyst **A**. Consequently, this means that the enantioenriched product (−)-**2** is formed in an enantioconvergent fashion from the racemic starting material (±)-**1**.

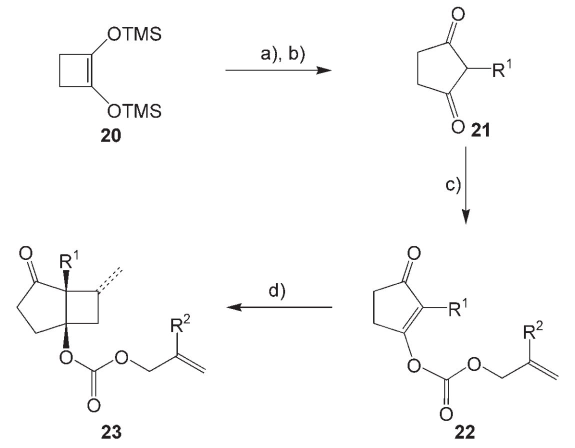
Our preliminary results prompted an investigation into the scope of the AREA reaction. Thus, the substrates **9a**–**19a**, which contained diversity at the α-carbonyl bridge, the allyl carbonate, and the cyclobutane ring, were prepared. Thus, following the method reported by Kuwajima and co-workers,[18] 1,2-bis(trimethylsilyloxy)cyclobutene (**20**)[19] was treated with the corresponding dimethyl acetal in the presence of a Lewis acid (Scheme 4). A subsequent rearrangement mediated by trifluoroacetic acid (TFA) gave the 2-substituted cyclopentane-1,3-diones **21**. This was followed by a selective *O*-alkylation with the desired allyl chloroformate to give the allylic carbonates **22** in excellent yield. A [2+2] cycloaddition reaction with either an excess of ethylene or allene using a mercury vapor lamp gave the substrates **23** for the AREA reaction in reasonable 50–70% yield (Scheme 4).

The subsequent AREA reactions were conducted with a catalyst loading of 2.5 mol% $[Pd_2(dba)_3]$ and 6.5 mol% (*S*)-*t*Bu-phox ((*S*)-**7**) in 1,4-dioxane/THF (3:1) at 10 °C or for slower reacting substrates either at room temperature or at 40 °C. The yields of the isolated products exceeded 80% in each case, which makes this reaction a useful methodology for organic synthesis (Table 2).

Bicyclic substrate **9a**, with an *exo* methylene group was converted into the corresponding seven-membered carbocycle **9b** in 89% yield and 90% *ee* (Table 2, entry 1). Although the intermediately formed enolate could undergo allylation at the α or γ position, it selectively reacted at the α position, thus conserving the *exo* methylene group. Com-



Scheme 3. Postulated mechanism of the decarboxylative ring-expanding allylation.

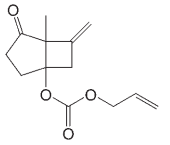
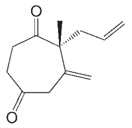
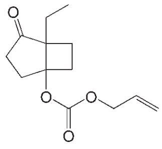
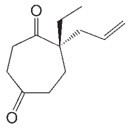
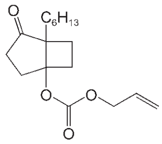
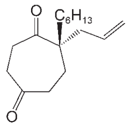
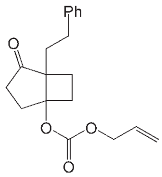
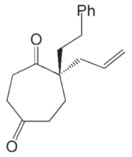
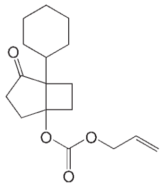
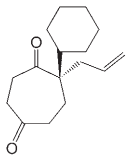
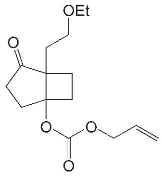
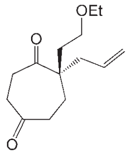
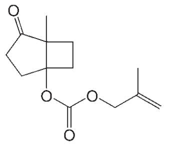
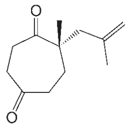


Scheme 4. Reagents and conditions: a) $R^1CH(OMe)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C→RT, 4 h; b) TFA, reflux, 24 h; c) $ClCO_2CH_2CR{=}CH_2$, K_2CO_3, acetone, 0 °C→RT, 3 h; d) ethylene or allene (large excess), CH_2Cl_2, *hν*, 8–20 h. R1, R2: see Table 2 and 3. TMS = trimethylsilyl.

pound **9b** could be further transformed into a synthetically interesting enone when treated with 1,8-diazabicyclo[5.4.0]-7-undecene (see the Supporting Information). This result underlines the versatility of this methodology as both products, **9b** and the corresponding enone, represent valuable intermediates for further synthetic transformations. Use of substrates **10a** and **11a**, which contained an ethyl or a *n*-hexyl group in place of the methyl group in the α position to the carbonyl group, gave a slightly increased selectivity to give the products **10b** and **11b** with enantiomeric excesses of 92 % and 91 %, respectively (Table 2, entries 2 and 3). A further increase in the steric bulk of the alkyl group, however, did not significantly reduce the *ee* (Table 2, entries 4 and 5): The phenethyl- and cyclohexyl-substituted products **12b** and **13b** were isolated in 86 % and 83 % *ee*, respectively. The incorporation of a coordinating oxygen atom in substrate **14a** led to the formation of compound **14b** with a moderate *ee* value (68 %), presumably because the reaction had to be performed at room temperature to obtain a reasonable reaction rate (Table 2, entry 6). Substrate **15a** with a methallyl group afforded the product **15b** in 83 % yield. However, presumably because of the reluctance of the starting methallyl carbonate to react with the sterically encumbered *t*Bu-phox palladium complex, the smaller *i*Pr-phox ligand had to be used and the reaction heated to 40 °C, which resulted in a lower selectivity of 53 % *ee* (Table 2, entry 7).

Some of the products had to be converted into the corresponding methyl ketones to be able to resolve the enantiomers by GC on a chiral stationary phase. This was achieved by means of a Wacker oxidation[20] or—in the case of the methallyl substituted compound **15b**—by ozonolysis. The reactions proceeded cleanly and delivered the methyl ketones that could be used for further elaboration to enone or azulene systems.[21]

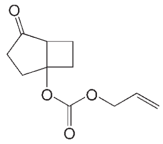
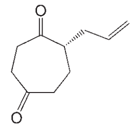
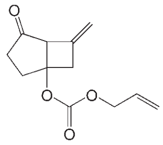
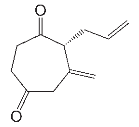
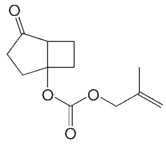
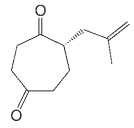
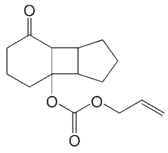
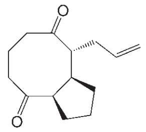
Table 2: Exploration of the substrate scope in the AREA reaction.[a]

Entry	Substrate	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	 **9a**	 **9b**	20	89	90
2	 **10a**	 **10b**	20	93	92[d]
3	 **11a**	 **11b**	20	87	91[d]
4	 **12a**	 **12b**	20	91	86
5	 **13a**	 **13b**	25	82	83[d]
6	 **14a**	 **14b**	3[e]	85	68[e]
7	 **15a**	 **15b**	3[f]	83	53[d]

[a] All reactions were performed on a 0.29-mmol scale with 2.5 mol% $[Pd_2(dba)_3]$ and 6.5 mol% (*S*)-*t*Bu-phox in 1,4-dioxane/THF (3:1) at 10 °C unless otherwise stated. [b] Yields of isolated product. [c] The *ee* values were determined by GC analysis on a chiral stationary phase (Lipodex E column). [d] The *ee* values were determined after conversion of the olefin to the corresponding methyl ketone. [e] The reaction was performed at RT. [f] The reaction was performed with (*S*)-*i*Pr-phox in 1,4-dioxane at 40 °C.

Finally, we investigated the formation of cycloheptane-1,4-diones with tertiary stereocenters (Table 3). Decarboxylative allylations that lead to tertiary stereocenters have been rarely reported.[13b] Most examples used substrates that led to quaternary stereocenters as they cannot epimerize under the reaction conditions. The AREA reactions that led to products with tertiary stereocenters worked best when carried out in 1,2-dimethoxyethane or diethyl ether. Bicycle **16a**, which was

Table 3: AREA reactions that led to products with tertiary stereocenters.[a]

Entry	Substrate	Product	t [h]	Yield[b] [%]	*ee*[c] [%]
1[d]	 **16a**	 **16b**	12	82	73
2	 **17a**	 **17b**	0.7	45, (90)[e]	60
3[f]	 **18a**	 **18b**	4	76	41
4	 **19a**	 **19b**	10	34	48

[a] All reactions were performed on a 0.29-mmol scale with 2.5 mol% $[Pd_2(dba)_3]$ and 6.5 mol% (*S*)-*i*Pr-phox at RT unless otherwise stated. [b] Yields of isolated product. [c] The *ee* values were determined by GC analysis on a chiral stationary phase (Lipodex E column). [d] The reaction was performed using the (*S*)-*t*Bu-phox ligand in 1,2-dimethoxyethane. [e] The yield is based on recovered starting material. [f] The reaction was performed at 40 °C.

accessible in two steps from the commercially available 1,3-cyclopentandione, was converted into the carbocycle **16b** in 82% yield and with a good *ee* value of 73% (Table 3, entry 1). The reactions with substrates **17a**–**19a** were run using the (*S*)-*i*Pr-phox ligand ((*S*)-**6**), because the use of the previously standard (*S*)-*t*Bu-phox ((*S*)-**7**) gave much lower yields and selectivities. The AREA reaction of **17a** was not run to complete conversion as a competing migration of the double bond in **17b** occurred. However, when the reaction was stopped after 40 minutes, the desired product **17b** could be isolated in a high yield of 90% (based on recovered starting material at 50% conversion) with a moderate *ee* value of 60%. Conversion of the methallyl-substituted derivative **18a** required an elevated temperature of 40 °C and gave the product with a modest *ee* value of 41% (Table 3, entry 3). We then focused on the conversion of tricycle **19a** into bicyclo-[6.3.0]undecane-2,6-dione **19b** (Table 3, entry 4). To our surprise, we could detect only one pair of enantiomers from both the asymmetric and the achiral reaction using $[Pd(PPh_3)_4]$. This result seems to indicate an overwhelming dependence of the substrate on the relative stereochemistry of the newly introduced allyl group. Thus, an observed enantiomeric excess of 48% indicates a kinetic resolution of the starting material to give the isolated product in 34% yield.

In conclusion, we have introduced an asymmetric decarboxylative ring-expanding allylation reaction. This method allows for the first time the preparation of enantioenriched substituted cycloheptane-1,4-dione and cyclooctane-1,5-dione derivatives. These compounds are valuable intermediates for the synthesis of functionalized medium-sized carbocycles that can be further elaborated to important natural products. The AREA reaction proceeded under mild conditions in high yield and with reasonable to very good enantioselectivities. The reaction has a broad substrate spectrum to give diketone compounds with both tertiary and quaternary stereocenters.

Experimental Section

General procedure for the AREA reaction: A Schlenk flask (100 mL) was equipped with a magnetic stirrer and flame dried under vacuum. After cooling and flushing the flask with argon, $[Pd_2(dba)_3]$ (45 mg, 2.5 mol%) and (*S*)-*t*Bu-phox (50 mg, 6.5 mol%) were added to the flask in a glovebox. The flask was evacuated for 10 min and then refilled with argon. A dry degassed mixture of 1,4-dioxane/THF (3:1, 60 mL) was then added. The resulting deep red solution was stirred at 25 °C for 30 min until the color of the solution changed orange. The solution then was cooled to 10 °C using a cryostat and the allyl carbonate (2 mmol) was added by syringe in one portion. When the reaction was complete (usually after stirring overnight; monitored by TLC), the reaction mixture was allowed to warm to RT, evaporated under vacuum, and the residue purified by column chromatography (SiO_2, cyclohexane/*tert*-butyl methyl ester 7:1).

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