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Synthesis of Chiral, Fused Tricyclic Molecules by Sequential Metal-Catalyzed Reactions of Simple Substrates

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Abstract: A set of complex tricyclic compounds containing several functional groups and multiple stereogenic centers has been prepared in only two steps with excellent diastereo- and enantioselectivities. The synthesis takes advantage of the highly versatile and enantioselective Pd-catalyzed allylic substitution of simple cyclic allylic acetates or carbonates to form chiral 1,6-, 1,7- and 1,8-enynes, which are then diastereoselectively transformed to the corresponding cyclopentenone- and cyclobutene-based tricyclic compounds.

Keywords: tricarbocycles; metal-catalysis; allylic substitution; Pauson-Khand; cyclizations

Introduction

Currently, the pharmaceutical, agrochemical and fragrance industries depend on the synthesis of complex chiral molecules. Such syntheses, carried out in sustainable and effective ways, remain a challenge for organic chemists.[1] Among the challenging molecules are those containing tricyclic fused skeletons, which are present in natural products. For example, the anti-inflammatory Britanlin A,[2] isolated from *Dichrocephala integrifolia*, and the (−)-Presilphiperfolan-8-ol,[3] isolated from *Eriophyllum staechadifolium* and *Flourensia heterolepis*, have a highly strained structure where 5-membered rings are fused in a 1,2-trans fashion (Figure 1). There are also examples of natural products furnished with fused-cyclobutane tricyclic units. For example, the (+)-Solanascone,[4] a sesquiterpene ketone isolated from *Nicotiana tabacum*, and the Tsugicoline E,[5] another sesquiterpene isolated from fungi *Laurilia Tsugicola* (Figure 1). Molecules with these strained fused skeletons are hard to synthesize, with only few natural products bearing such domains having been synthetized to date in multistep synthetic routes.[3,6]

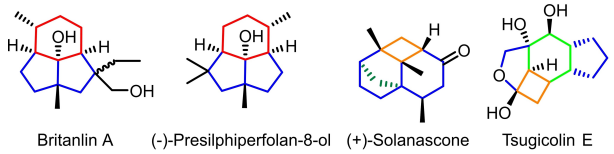
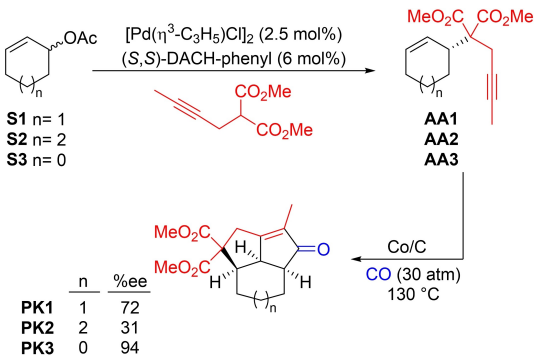


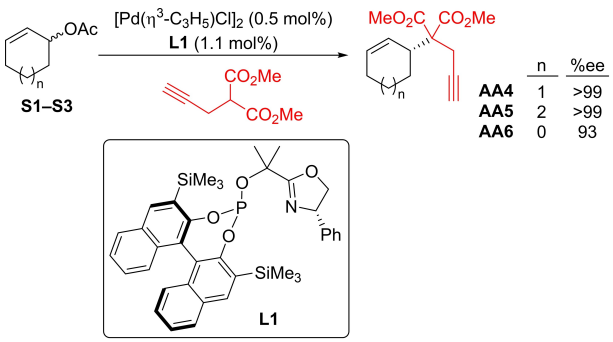
Figure 1. Examples of fused-tricyclic structures found in natural products.

Driven by the progress in enantioselective transition metal catalysis, Chung et al. reported in 2001 the synthesis of three polycarbocycles[7] (Scheme 1) with compact tricyclic skeletons bearing 3 stereocenters, whose structures are found in the synthesis of some natural products.[8] The polycarbocycles were synthesized by a straightforward reaction sequence involving Pd-catalyzed asymmetric allyllic alkylation of three readily available cyclic substrates (compounds **AA1**–**AA3**) followed by a Pauson-Khand enyne cyclization (compounds **PK1**–**PK3**).[7,9]

Enantioselectivity was induced during the allylic alkylation step. Although the authors used the Trost's (*S,S*)-DACH-phenyl ligand, considered as the best



Scheme 1. Synthesis of three polycarbocycle derivatives by Pd-catalyzed allylic alkylation and subsequent Pauson-Khand enyne cyclization.



Scheme 2. The phosphite-oxazoline ligand **L1** and its application in the alkylation of cyclic substrates with propargyl malonate as example.

ligand for the alkylation of cyclic substrates, the enantioselectivity depended on the ring size of the alkylated substrate. Unfortunately, as the ring size increased the enantioselectivity decreased from 94% to 31%, and only the polycarbocycle with 5-membered rings was obtained in high enantioselectivities.

In the last decades, our group has taken advantage of the flexibility of tropos ligands to overcome the substrate specificity and the limited nucleophile scope in Pd-catalyzed allylic substitutions.[10] By introducing flexible biaryl phosphite moieties in heterodonor P,N and P,S ligands, the catalyst has been able to adapt to the demands of each particular substrate, which has significantly broadened the substrate scope.[11] In this aspect, we were recently able to design a family of biaryl phosphite-oxazolines, that turned out to provide high enantioselectivities in the allylic substitution of a wide range of substrates and C-, N- and O-nucleophiles (70 compounds in total).[11a] Particularly, cyclic substrates with different ring sizes (from 5- to 7-membered rings) were successfully alkylated, even with appealing nucleophiles as propargyl malonate (to reach enynes **AA4**–**AA6**, ee's up to 99%), with ligand **L1** bearing an achiral alkyl backbone chain (Scheme 2). Advantageously and in contrast to Chung's report the alkylation of 6- and 7-membered cyclic substrates were reached in yields and enantioselectivities higher as those achieved in the alkylation of the 5-membered cyclic substrate using a low catalyst loading. Moreover, the acceptor capacity of the phosphite group showed a positive effect on activities (TOF's up to 8000 h^{-1}), providing much higher TOF than the most common ligands.[11a]

Continuing the applications of ligand **L1**, in this paper we push forward the synthesis of tricyclic-fused molecules by using simple sequential metal-catalyzed reactions, involving allylic alkylation and subsequent either Pauson-Khand or cycloisomerization reactions.

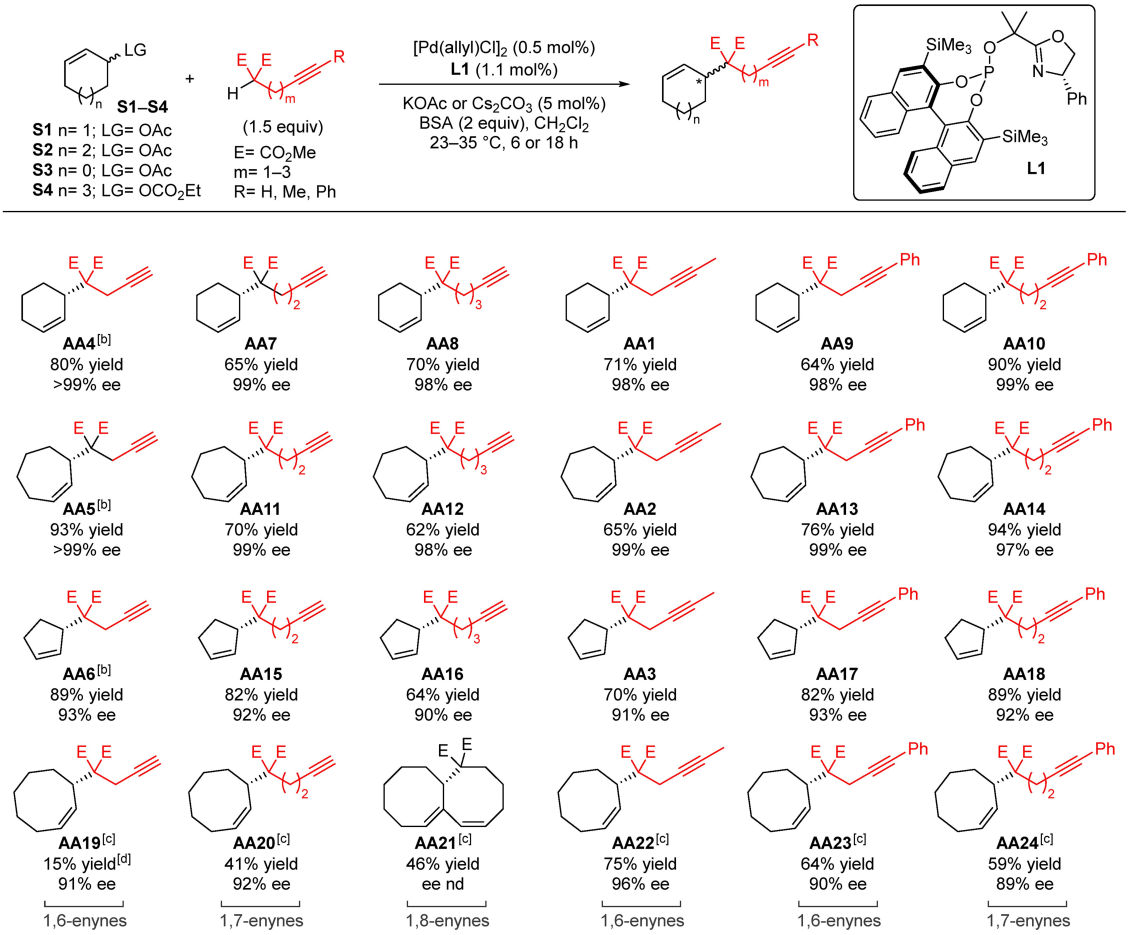
Results and Discussion

Expanding the Scope of the Pd-Catalyzed Asymmetric Allylic Alkylation of Cyclic Substrates. Synthesis of Chiral 1,6-, 1,7- and 1,8-Enynes

To span the range of tricyclic fused molecules to be synthetized, we first explored the use of the phosphite-oxazoline ligand **L1** in the preparation of other chiral enynes different from **AA4**–**AA6** (results are collected in Table 1). To this end, ligand **L1** was tested in the Pd-catalyzed asymmetric alkylation of 5-, 6- and 7-membered ring cyclic substrates with butynyl- and pentynyl-malonates, that have one and two more carbons than the propargyl malonate, respectively (see Table 1, products **AA7**, **AA8**, **AA11**, **AA12**, **AA15** and **AA16** in columns two and three). To study whether the catalytic outcome is maintained with substituted propargyl- and butynyl-malonates, we also studied the allylic alkylation of cyclic substrates **S1**–**S3** using three different substituted malonates containing a phenyl and a methyl group at the terminal position (see Table 1, products **AA1**–**AA3**, **AA9**, **AA10**, **AA13**, **AA14**, **AA17** and **AA18** in columns four to six). Finally, we also extended the study to the alkylation of the 8-membered cyclic substrate **S4** with the six nucleophiles mentioned previously (Table 1, products **AA19**–**AA24**). To the best of our knowledge there are no precedents in the enantioselective allylic alkylation of the 8-membered ring substrate **S4**.[12]

In general, the reactions proceeded smoothly for all combinations of substrates and nucleophiles (Table 1). Positively, 17 new chiral enynes **AA1**–**AA3**, **AA7**–**AA20** and **AA22**–**AA24** were attained in enantioselectivities as high as those previously achieved in the allylic alkylation of substrates **S1**–**S3** with propargyl malonate (compounds **AA4**–**AA6**, Scheme 2). Thus, for the benchmark 6-membered ring substrate **S1** high yields (up to 90%) and excellent enantioselectivities (ee's $>$99%) were furnished regardless of the nucleophile involved (compounds **AA4**, **AA1** and **AA7**–

Table 1. Pd-catalyzed asymmetric allylic alkylation of cyclic substrates **S1**–**S4**.[a]

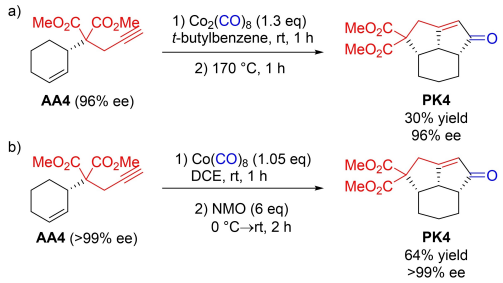


[a] Reactions typically done using 1 mmol of substrate, CH_2Cl_2 (2 mL) and KOAc at 23 °C for 6 h. BSA= Bis(trimethylsilyl)acetamide. Full conversions were attained in all cases except for product **AA19**.[b] Data from ref. [11a]. [c] Reactions performed using Cs_2CO_3 at 35°C for 18 h. [d] 50% conversion.

AA10). High yields and enantioselectivities were also reached in the alkylation of the 7-membered cyclic substrate **S2** (compounds **AA5**, **AA2** and **AA11**–**AA14** in ee's up to 99%). The good performance also extended to the alkylation of the 5-membered cyclic substrate **S3** (compounds **AA6**, **AA3** and **AA15**–**AA18**). Although, as expected, the enantioselectivities were somewhat lower than for substrates **S1** and **S2**, they are remarkable for this challenging substrate and comparable to the best one reported so far for a 5-membered cyclic substrate, for which only enynes **AA3** and **AA6** have been previously reported. Finally, the alkylation of the 8-membered cyclic substrate **S4** also provided the desired 1,6- and 1,7- enynes in enantioselectivities comparable to those achieved with substrate **S3** (ee's ranging from 89% to 96%),[13] except in the addition of the pentynyl malonate that led to the formation of a bicyclic compound **AA21**, resulting from the enyne metathesis,[14] instead of the corresponding 1,8-enyne. The lower conversion achieved in the alkylation of **S4** using propargyl malonate (compound **AA19**) could be attributed to the lower nucleophilicity of the latter combined with the lower electrophilicity of the eight-membered ring allylic system.

Synthesis of Chiral Tricyclic Molecules via Pauson-Khand Reaction

The Pauson-Khand reaction involves the formation of an acetylene-cobalt carbonyl complex which is further decomposed in a [2+2+1] cycloaddition to form α-cyclopentenone containing compounds.[15] In a previous collaboration with Pericàs' group we studied the Pauson-Khand reaction of 1,6-enyne **AA4** through a thermal decomposition by refluxing in a high boiling point solvent such as *tert*-butylbenzene at 170 °C. Although the chiral information of the starting material was kept, the yield was only 30% (Scheme 3a).[11b] Much effort has been devoted to enhance the yield of



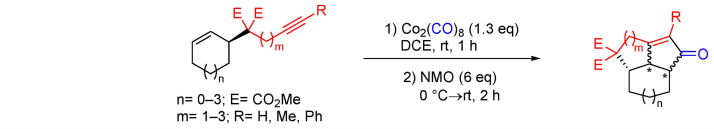
Scheme 3. Pauson-Khand reaction of 1,6-enyne **AA4**: a) under thermal decomposition at 170 °C with *tert*-butylbenzene as solvent, see ref. [11b] and b) using *N*-methylmorpholine-*N*-oxide (NMO).

the reaction by using CO pressure or additives such *N*-oxides that promote the CO elimination leading to a much more reactive cobalt complex. The advantage of using promoters is that the toxic CO is not needed, and reaction conditions can be milder.[16] With the aim to improve the yield we performed the Pauson-Khand reaction of enyne **AA4** with the promoter *N*-methylmorpholine-*N*-oxide (NMO). Under these conditions, the yield increased to 64% with an enantioselectivity that replicated that of the starting material (>99% ee; Scheme 3b).

With the right reaction conditions at hand, we then performed the Pauson-Khand reaction of all the previously synthetized enynes **AA1**–**AA20** and **AA22**–**AA24**. The results are summarized in Table 2. In general, while the reaction of 1,6- and 1,7-enynes proceeded smoothly providing the desired fused-tricyclic cyclopentenones without loss of enantioselectivity, the reaction of 1,8-enynes did not proceed at all,[17] recovering the unreacted starting enynes after reaction.[18]

Concerning the effect of the size of the starting enyne cycle, we found that the Pauson-Khand reaction of 5-, 6- and 7-membered cyclic 1,6- and 1,7-enynes yielded the corresponding tricyclic products regardless of the presence of different substituents (H, Me and Ph) at the α-position, in excellent diastereoselectivities and maintaining the enantioselectivities induced during the Pd-AAA step (Table 2, products **PK1**–**PK14**). The only exception was the seven-membered ring 1,7-enyne **AA14** with a Ph substituent at the α position, which did not react using either NMO or thermal conditions. The use of the related six-membered ring 1,7-enyne **AA10** with a Ph substituent at the α position

Table 2. Preparation of chiral fused-tricyclic cyclopentenones **PK1**–**PK17** by Pauson-Khand reaction.[a]



PK4 64% yield >99% ee	**PK7** 76% yield[b] 99% ee	**PK1** 64% yield 98% ee	**PK8** 55% yield 98% ee	**PK9** 76% yield[c] 3:1 dr 98% ee (major); 99% ee (minor)
PK5 70% yield 99% ee	**PK10** 89% yield[b] 99% ee	**PK2** 87% yield 98% ee	**PK11** 83% yield 99% ee	Not formed
PK6 75% yield 93% ee	**PK12** 54% yield[b] 91% ee	**PK3** 67% yield 91% ee	**PK13** 87% yield 92% ee	**PK14** 55% yield 92% ee
PK15 77% yield 91% ee	Not formed	**PK16** 76% yield 95% ee	**PK17** 67% yield 90% ee	Not formed

[a] Full conversions were attained in all cases, except for the 3 examples in which the Pauson-Khand compound was not formed for which the starting enyne was recovered. [b] The second step of the reaction was carried out for 17 h. [c] Reaction carried out from –20 °C→rt for 24 h.

resulted in the formation of two diastereoisomers, albeit in high ratio (3:1) and both diastereoisomers were attained in excellent enantioselectivities (ee's up to 99%).

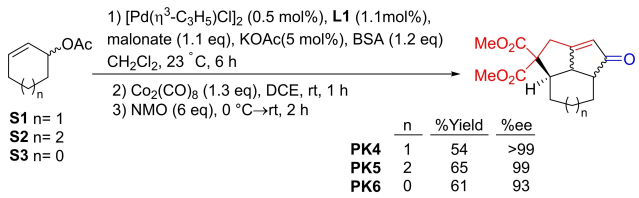
When 8-membered ring enynes were used only the 1,6-enynes **AA19**, **AA22** and **AA23**, with different substituents at the α-position provided the desired tricyclic compounds (**PK15**–**PK17**) in good yields, as a single diastereoisomer with ee's up to 95%, being both 1,7-enynes unreactive (Table 2).

Based on the successful results described above, we also studied the tandem one pot reaction involving as example the asymmetric allylic substitution of substrates **S1**–**S3** using propargyl malonate as nucleophile followed by the Pauson-Khand (Scheme 4). Positively, in all cases the reactions afforded the desired tricyclic compounds **PK4**–**PK6** in excellent enantioselectivities, albeit the yields were somewhat lower (54, 65 and 61% yield, respectively).

Synthesis of Chiral Tricyclic Molecules Via Metal-Catalyzed Cycloisomerization

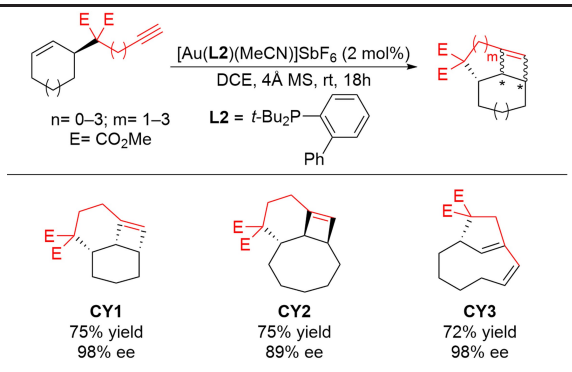
To obtain a larger variety of tricyclic structures we also submitted the appropriate chiral enynes of Table 1 to [2+2] cycloisomerization reactions. In particular, we focused on the synthesis of chiral tricyclic molecules containing a highly strained cyclobutene ring. To achieve the maximum diversity, we explored the use of the complementary approaches developed by Echavarren's and Fürstner's groups using achiral enynes. Whereas the Echavarren's methodology makes use of Au-catalysts to synthesize the desired tricyclic compounds from achiral unsubstituted 1,7-enynes,[19] the Fürstner's approach uses $PtCl_2$ under reductive conditions and achiral 1,6-enynes with the requirement of having a substituent at the α-position.[20]

We first studied Echavarren's approach on unsubstituted chiral 1,7 enynes **AA7**, **AA11**, **AA15** and **AA20**. Whereas the reaction of the 6- and 8-membered ring enynes **AA7** and **AA20** afforded the desired tricylic products **CY1** and **CY2** as single diastereoisomers in good yields and ee's up to 98% (Table 3), the reaction of the 5-membered ring enyne **AA15** provided a complex mixture of unidentified products and the reaction of the 7-membered ring enyne **AA11** did not proceed. We also evaluated the related



Scheme 4. One pot synthesis of **PK4**–**PK6**.

Table 3. Au-catalyzed cyclization of unsubstituted chiral 1,7-enynes **AA7** and **AA20** and 1,6-enyne **AA5**.[a]



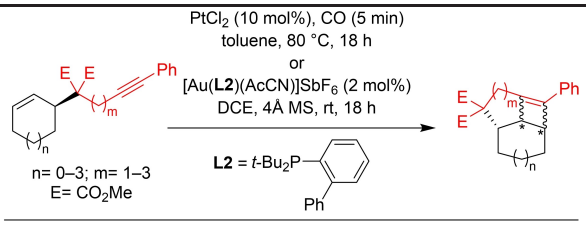
[a] Full conversions were attained in all cases.

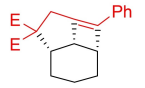
unsubstituted 1,6- and 1,8- enynes of Table 1 but no reaction was observed, recovering the unreacted starting enynes, except for 1,6-enyne **AA5**, with a 7-membered ring, that led to the formation of the bicyclic compound **CY3**. The formation of the latter most likely proceeds via a single cleavage rearrangement rather than from the conrotatory ring opening of the corresponding cyclobutene ring.[21]

We then applied the Fürstner's methodology with phenyl substituted 1,6-enynes **AA9**, **AA13**, **AA17** and **AA23**. We found that 1,6-enynes **AA9** and **AA13**, containing a 6- and 7-membered ring, gave the corresponding fused tricylic compounds **CY4** and **CY5** in good yields (up to 90%) as a single diastereoisomer and excellent enantioselectivities (ee's up to 99%; Table 4). However, the reaction of enynes **AA17** and **AA23**, with a 5- and 8-membered rings, gave a complex mixture of unidentified compounds. Interestingly, we also found that the 1,7-enyne **AA10** is prone to undergo [2+2] cycloaddition yielding **CY6** in 55% yield as a single diastereoisomer and 98% ee (Table 4). For the rest of substituted 1,7-enynes complex mixtures of unidentified compounds were reached.

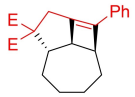
Finally, we also investigated whether Echavarren's approach can be applied to enynes substituted with an aromatic group at the α-position. We found that 1,7-enynes **AA10** and **AA24** with a 6- and 8-membered cycles, undergo [2+2] cycloaddition to yield the corresponding fused tricylic compounds **CY6** and **CY7** in good yield (up to 85%) as a single diastereoisomer and excellent enantioselectivities (ee's up to 98%; Table 4). These results represent an improvement compared to those obtained with the Fürstner methodology, for which product **CY6** was obtained in lower yield and product **CY7** could not be reached. When related 1,7-enynes **AA14** and **AA18** with a 5- and a 7-membered ring were used complex mixtures of unidentified compounds were reached. As expected, the Au-catalyzed cyclization of methyl and phenyl α-

Table 4. Metal-catalyzed cyclization of phenyl substituted 1,6- and 1,7-enynes.[a]

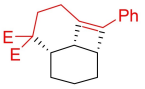




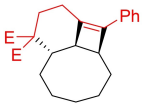
CY4	Yield	ee
Pt cat.	90%	97%
Au cat.	nr	–



CY5	Yield	ee
Pt cat.	74%	99%
Au cat.	nr	–



CY6	Yield	ee
Pt cat.	55%	98%
Au cat.	85%	98%



CY7	Yield	ee
Pt cat.	ni	–
Au cat.	80%	89%

[a] Full conversions were attained in all cases. nr= No reaction. ni= not isolated (complex mixture of products).

substituted 1,6-enynes did not work recovering the starting materials.

Conclusion

A set of complex tricyclic compounds containing several functional groups and multiple stereogenic centers has been prepared in only two steps with excellent diastereo- and enantioselectivities. For this purpose, we have taken advantage of the broad scope of the allylic alkylation with the Pd/**L1** catalytic system to prepare chiral 1,6- 1,7- and 1,8-enynes from 5- to 8-membered cyclic acetates or carbonates. 1,6- and 1,7-enynes were diastereoselectively transformed to the corresponding cyclopentenone-containing tricyclic compounds in good yields and excellent control of the two new stereocentres formed (typically only one diastereoisomer is formed with ee's up to >99%). Positively, the sequential allylic substitution/Pauson-Khand reaction could also be performed in one pot. The formation of the cyclobutene-containing tricyclic analogues was also attained via Pt- and Au-catalyzed cycloisomerization reactions. Nevertheless, these later processes showed to be dependent on the length, the substituents and the ring size of the enyne. Thus, for instance, it was not possible to achieve any of the cyclobutene-based tricycles from enynes containing a 5-membered ring. Despite this, a diverse set of cyclobutenes were attained in good yields as single diastereoisomers with high enantiocontrol.

Experimental Section

General Considerations

All reactions were carried out using standard Schlenk techniques under an argon atmosphere unless otherwise noted. Solvents were purified and dried by standard procedures. Substrates **S1**–**S4** were prepared following the reported procedures.[22] ^{1}H and ^{13}C NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of NMR solvent.

General Procedure for the Asymmetric Allylic Alkylation of Substrates S1–S3

A solution of **L1** (7.3 mg, 0.011 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was stirred. After 30 min a solution of substrate (1 mmol) in CH_2Cl_2 (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (730 µL, 3 mmol) and KOAc (3 mg, 0.03 mmol) were subsequently added. After 6 h, the reaction mixture was diluted with Et_2O (5 mL). Saturated NH_4Cl (aq) (25 mL) was then added and the mixture was extracted with Et_2O (3 × 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR and ees were calculated by HPLC or GC. The residue was purified by flash chromatography (petroleum ether/ethyl acetate) to give the desired enynes.

General Procedure for the Asymmetric Allylic Alkylation of Substrate S4

A solution of **L1** (7.3 mg, 0.011 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) was stirred. After 30 min a solution of **S4** (198 mg, 1 mmol) in CH_2Cl_2 (1.5 mL), nucleophile (3 mmol), *N,O*-bis(trimethylsilyl)-acetamide (730 µL, 3 mmol) and Cs_2CO_3 (10 mg, 0.031 mmol) were subsequently added. The reaction was then stirred at 35 °C. After 18 h, the reaction mixture was diluted with Et_2O (5 mL). Saturated NH_4Cl (aq) (25 mL) was then added and the mixture was extracted with Et_2O (3 × 10 mL) and the extract dried over $MgSO_4$. Conversions were measured by ^{1}H NMR and ees were calculated by HPLC. The residue was purified by flash chromatography (petroleum ether/ethyl acetate) to give the desired enynes.

General Procedure for the Pauson-Khand Reaction

A solution of the enyne (0.5 mmol) and $Co_2(CO)_8$ (180 mg, 0.52 mmol) in CH_2Cl_2 (8 mL) was stirred at room temperature for 1 h (TLC monitoring indicated full conversion). *N*-methylmorpholine-*N*-oxide (352 mg, 3 mmol) was then added portion wise at 0 °C. Stirring was continued at room temperature until TLC monitoring showed complete consumption of the cobalt-alkyne complex (see Table 2 for details). The solvent was then evaporated under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate) to give the desired tricyclic cyclopentenones.

General Procedure for the Au-Catalyzed Cyclization

To a solution of the corresponding enyne (0.2 mmol) in dichloromethane (1 mL), [Au(JohnPhos)(CH_3CN)]SbF_6 complex (3.1 mg, 4 μmol) and 4 Å MS (20 mg) were added. The resulting suspension was stirred at rt. After 18 h, the solvent was then evaporated under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate) to obtain the corresponding products.

General Procedure for the Pt-Catalyzed Cyclization

To a solution containing the corresponding enyne (0.2 mmol) and $PtCl_2$ (5.3 mg, 0.02 mmol) in toluene (1 mL), CO was bubbled for 5 min. Then, the flask was closed and stirred at 80 °C for 18 h. Then, the solvent was then evaporated under reduced pressure, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate) to obtain the corresponding products.

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