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Enantioselective Synthesis of Polycyclic Carbocycles via an Alkynylation–Allylation–Cyclization Strategy

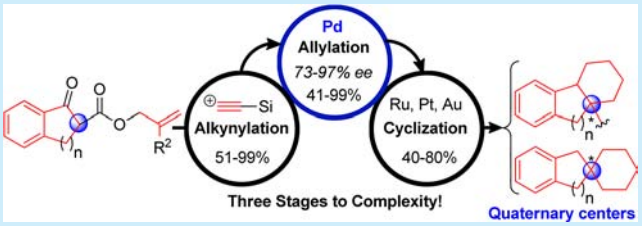
Maria Victoria Vita,[†] Pascal Mieville,[‡] and Jerome Waser*[,†]

[†]Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland

[‡]Institute of Chemical Sciences and Engineering (ISIC), Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland

Supporting Information

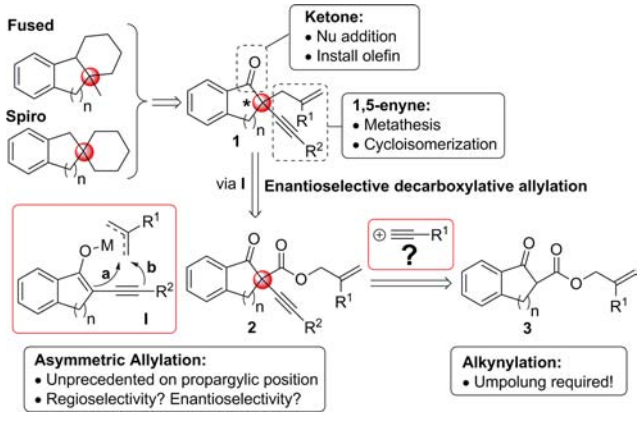
ABSTRACT: A new general three-stage strategy to access polycyclic ring systems bearing all-carbon quaternary centers with high enantioselectivity is reported. The required starting materials were readily accessed in racemic form through the α-alkynylation of ketoesters with EBX (EthynylBenziodoXolone) hypervalent iodine reagents. A Pd-catalyzed asymmetric decarboxylation allylation was then achieved in high yields and enantioselectivities with Trost's biphosphine ligands. Finally, transition-metal catalyzed cyclization of the obtained chiral enynes gave access to fused and spiro polycyclic ring systems constituting the core of many bioactive natural products.



The fascinating structure of natural products is the result of millions of years of evolution in interaction with biological targets. Particularly striking is the high occurrence of complex polycyclic ring systems with numerous stereocenters. An interesting substructure present in natural products is constituted by a benzene ring fused to at least two further saturated carbocycles. Both fused and spiro ring systems can be found in important bioactive compounds including steroids such as estradiol or alkaloids such as buprenorphine.[1] The presence of all-carbon quaternary centers embedded in the polycyclic core of many of these molecules represents a formidable challenge for synthetic chemistry.[2] In this context, we envisioned that ketone **1** bearing a 1,5-enyne substructure around an all-carbon quaternary center would be an ideal precursor for both fused and spiro ring systems (Scheme 1). Addition of an allyl Grignard reagent, followed by olefin ring-closing metathesis (RCM), would give an easy access to fused ring systems. The 1,5-enyne itself can be used to access spiro or rearranged ring systems based on transition-metal catalysis.[3] Whereas RCM is now a mature method, cycloisomerization reactions to access spiro ring systems have been much less investigated. Indeed, there are only two examples of such transformations so far, both occurring on unsubstituted alkane rings.[3h,k]

Nevertheless, the main challenge with the proposed strategy resided in the enantioselective synthesis of enyne **1**. Most synthetic methods known to access 1,5-enynes take advantage of the reactivity of a propargylic cation generated through either catalytic or stoichiometric Lewis acid activation, allowing access only to racemic material.[4] Morken et al. showed recently that a Pd-catalyzed enantiospecific cross-coupling reaction gave 1,5-enynes with high enantiomeric excess starting from enantioenriched activated propargylic alcohols and allyl boronic esters.[5a] In this report only one example leading to all-carbon quaternary centers in a noncyclic product was presented. In 2013, the same group reported a kinetic resolution of racemic propargylic esters using chiral ligands.[5b]

Scheme 1. Our Synthetic Strategy To Access Polycyclic Ring Systems



Clearly, none of the reported methods to access 1,5-enynes appeared promising in the context of our synthetic goal, and we decided to develop a new strategy based on the enantioselective decarboxylative allylation of ketoesters (Tsuji–Trost reaction).[6] This very successful approach to access all-carbon quaternary centers on carbocycles was first introduced by Segusa[7] and Tsuji[8] and then further developed into enantioselective methods by

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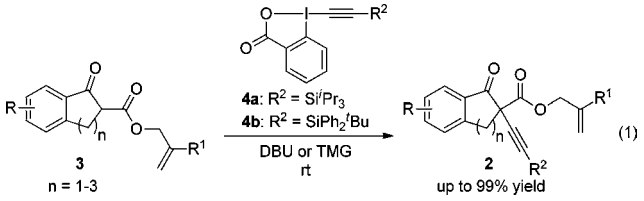
Stoltz[9] and Trost.[10,11] Nevertheless, alkynyl substituents in the α-position of the ketoesters have never been reported. In this class of substrates, the α-alkynyl group would be in conjugation with the formed enolate **I** and will change its electronic properties. It also leads to a major challenge in regioselectivity, as attack at both the α- (pathway a) or γ-position (pathway b) would be possible.[12] Moreover, α-alkynyl ketoesters are difficult to access because both enolates and acetylides are nucleophiles, and connecting them requires therefore an Umpolung of the reactivity. To solve the latter synthetic hurdle, our group has used hypervalent iodine reagents for the α-functionalization of carbonyl compounds.[13] We have in particular developed an efficient α-ethynylation of ketoesters under mild conditions using EBX (EthynylBenziodoXolone) reagents.[13a,b]

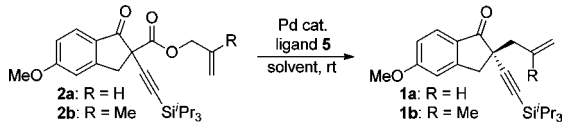
Herein, we would like to present the successful implementation of the outlined three-stage strategy, including: (1) an improved method for the alkynylation of ketoesters at room temperature in up to quantitative yield, (2) the first example of enantioselective decarboxylative allylation at the propargylic position proceeding in up to quantitative yield and with an enantiomeric excess higher than 90% on 5-, 6-, and 7-membered rings, and (3) the use of the obtained enynes to access fused and spiro tricyclic ring systems via an RCM or cycloisomerization strategy, as well as the unanticipated formation of a rearranged [6,6,5,3] ring system.

Preliminary studies showed that the decarboxylation−allylation sequence proceeded only in very low yield with ketoesters bearing a free acetylene obtained using our previously published alkynylation method.[13a] We consequently first investigated the possibility to access protected acetylenes in the α-alkynylation of β-keto esters with hypervalent iodine reagents. Using diazabicycloundecene (DBU) or tetramethylguanidine (TMG) as a base, the desired alkynes **2** could be obtained in up to quantitative yield at rt using TIPS-EBX (**4a**) and TPDPS-EBX (**4b**) starting from the corresponding ketoesters **3** (eq 1).[14]



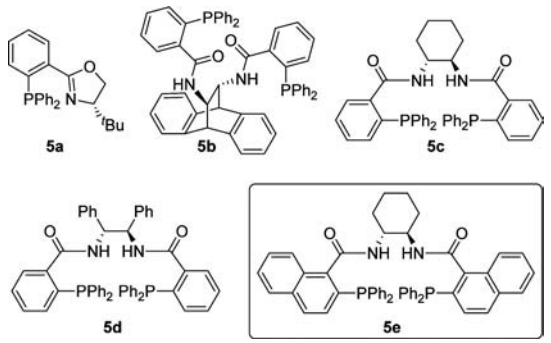
Preliminary studies on the decarboxylative allylation were then conducted using substrate **2a** under the reaction conditions previously reported by Stoltz.[9d] The substrate was converted fully to the desired allylation product **1a**, but no enantiomeric excess was obtained using the PHOX ligand **5a** (Table 1, entry 1). A switch in the Pd source to Pd(cinnamyl)Cp (**6**), an established clean precursor of Pd(0) phosphine complexes,[15] did not improve the result (entry 2). Keeping Pd(cinnamyl)Cp (**6**) as the Pd source, we then turned our attention to Trost ligand **5b** which had been applied previously in the decarboxylation of allyl ketoesters.[10b] Also in this case full conversion to **1a** was observed, but with no enantioselectivity (entry 3). However, changing the solvent to Et_2O gave for the first time a measurable enantioselectivity of 12% (entry 4). A screening of other Trost ligands in Et_2O led to better results with an encouraging 59% *ee* for **5c**, 76% *ee* for **5d**, and 74% *ee* for **5e** (entries 5−7). Changing the solvent to MTBE gave the desired product in 70% *ee* with **5d** and 79% *ee* with **5e** (entries 8 and 9). Final optimization of the

Table 1. Optimization of the Pd-Catalyzed Decarboxylative Allylation



entry	reaction conditions[a]	L	*ee*[b]
1	$[Pd_2(dba)_3]$, THF	**5a**	0
2	Pd(cinnamyl)Cp (**6**), THF	**5a**	0
3	**6**, THF	**5b**	0
4	**6**, Et_2O	**5b**	12
5	**6**, Et_2O	**5c**	59
6	**6**, Et_2O	**5d**	76
7	**6**, Et_2O	**5e**	74
8	**6**, MTBE	**5d**	70
9	**6**, MTBE	**5e**	79
10	5 mol % **6**/5 mol % L, MTBE, 0.1 M	**5e**	86
11	2 mol % **6**/2.5 mol % L, MTBE, 0.1 M[c]	**5e**	93

[a]All the reaction mixtures were degassed three times and stirred at rt for 8−12 h using substrate **2a** (0.01 mmol), the indicated solvent (0.033 M), Pd source (20 mol %), and ligand (44 mol %) unless stated otherwise. All the reactions gave full conversion to the desired product **1a** exclusively (yield >90% by ^{1}H NMR). [b]The ee was determined by HPLC using Chiralcel columns. [c]Substrate **2b** was used.



reaction conditions led to the best results at rt with a 5 mol % palladium loading and a concentration of 0.1 M in MTBE (entry 10).[16] In the case of ketoester **2b** bearing a sterically more hindered methallyl substituent the enantioselectivity reached a remarkably high 93% *ee* even with only 2 mol % palladium (entry 11).[17] This result is impressive, as only moderate enantioselectivity has been reported in the past when using indanone substrates and acyclic allyl groups: 76−84% *ee* with Trost ligands[10] and 71−80% *ee* with phenyloxazoline (PHOX) ligands.[9d]

Several indanone derivatives were then subjected to the optimized reaction conditions on a 0.12 mmol scale. 1,5-Enyne **1a** was obtained in 89% *ee* using indanone **2a** (Scheme 2). Compound **2b** yielded product **1b** in 93% *ee* and quantitative yield. A different silyl group (TBDPS) on the acetylene could also be used to give enyne **1c**. Without a silyl protecting group, the desired product **1d** was obtained in 41% yield and 87% *ee*.[18] A high tolerance toward the electronic properties and the position of the substituents on the aromatic ring was observed. Neutral indanone **1e** was obtained in quantitative yield and 94% *ee*. Bromo and chloro substituents were also well tolerated (products **1f** and **1g**), but a lower enantiomeric excess was observed in the case of trifluoromethylated product **1h**.

Modification of the substituent on the allyl group was also possible: both chloroallyl enyne **1i** and enyne **1j** bearing a

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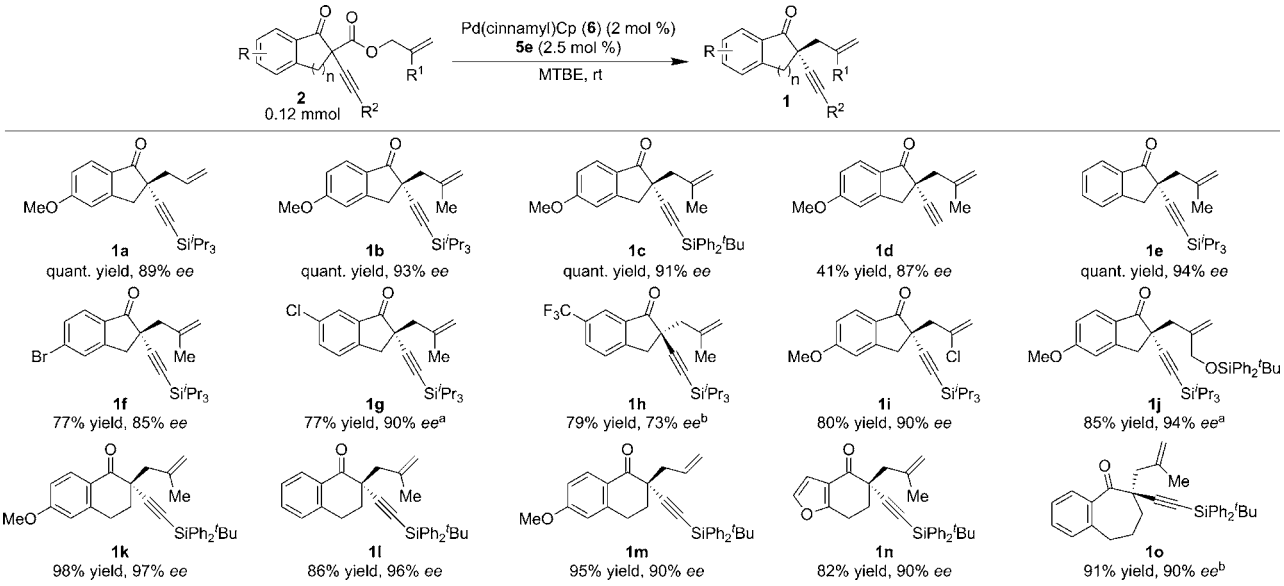
Scheme 2. Scope of the Pd-Catalyzed Decarboxylative Allylation[a]

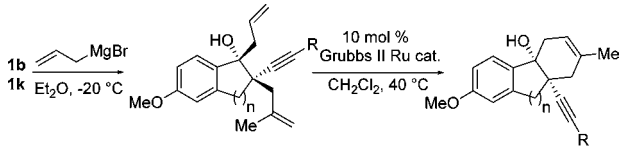


[a]Isolated yields after column chromatography using the conditions of entry 11 in Table 1 on 0.12 mmol scale are reported. [b] Using Pd(cinnamyl)Cp (**6**) (5 mol %) and ligand **5e** (6.5 mol %). [c] The (*S*,*S*)-enantiomer of ligand **5e** was used.

protected alcohol were obtained in high enantiomeric excess and yield. When changing to tetralones, *ee*'s higher than 96% were observed (products **1k–l**). A lower enantioselectivity was obtained for enyne **1m** with a simple allyl substituent. Fused heterocycle **1n** and cycloheptanone **1o** could also be accessed in good yields and 90% *ee*.

In order to access fused ring systems, an allyl Grignard was then added to ketone **1b** and the corresponding alcohol **7b** was obtained in quantitative yield and with 4.5:1 diastereoselectivity (Scheme 3). Fused [6,5,6] tricyclic compound **8b** was then

Scheme 3. Synthesis of Fused Ring Systems



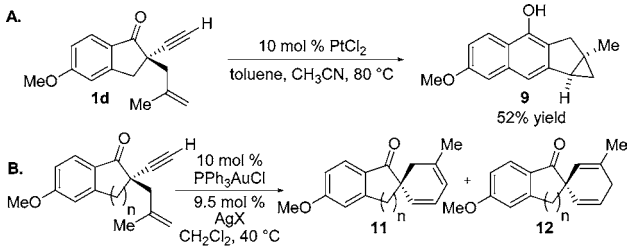
7b, n = 1, R = Si^iPr_3, quant. yield, 4.5:1 dr
7k, n = 2, R = $SiPh_2{}^tBu$, 98% yield, 4.4:1 dr
8b, n = 1, R = Si^iPr_3, 83% yield
8k, n = 2, R = $SiPh_2{}^tBu$, 81% yield

synthesized in 83% yield from the *syn* isomer of **7b** via RCM using a Grubbs II ruthenium catalyst. Using the same synthetic sequence, [6,6,6] tricyclic compound **8k** was obtained in 65% overall yield.[19]

To study new cycloisomerization reactions, free acetylene **1d** and **10** were synthesized in gram scale (9.9 and 3.4 mmol) in a one-pot asymmetric allylation–silyl deprotection sequence from ketoester **2b** and **2k** in 83% yield/95% *ee* and 64% yield/97% *ee* respectively (Scheme 4). When the synthesis of spiro compound **11a** was attempted using $PtCl_2$ as the catalyst with enyne **1d** as reported by Kozmin et al.,[3i] cyclopropane product **9** was obtained instead in 52% yield (Scheme 4A).[20] The formation of **9** can be explained by the intermediacy of a platinum-carbenoid, followed by a 1,2-shift and rearomatization. The first two steps of this sequence have been reported by Toste et al., but using a gold catalyst.[3h]

Fortunately and somewhat surprisingly, we found that gold catalysis, which usually favors formation of the cyclopropane

Scheme 4. Au- and Pt-Catalyzed Cycloisomerizations



1d, n = 1, 9.9 mmol scale
83% yield, 95% ee from **2b**
10, n = 2, 3.4 mmol scale
64% yield, 97% ee from **2k**

With X = ClO_4^-: 88% yield, **11a**:**12a** = 1:1.9
With X = PF_6^-: 64% yield, **11b**:**12b** = 1.7:1

products, could be used in this case to access the spiro carbocyclic compounds. Diene **11a** and its nonconjugated isomer **12a** were obtained in 88% yield using PPh_3AuClO_4 as the catalyst (Scheme 4B). In the case of tetralone **10**, cyclization was much slower and could not be achieved using PPh_3AuClO_4 as the catalyst. Higher activity was displayed by PPh_3AuPF_6, which gave the desired spiro tricyclic ring system in 64% yield.

In conclusion, we have reported a new three-stage strategy to access polycyclic ring systems efficiently and in high enantiopurity. The first step of our approach was the synthesis of α-alkynylated β-ketoesters in high yields using EBX hypervalent iodine reagents to achieve the Umpolung of acetylide. The cornerstone of the strategy was the second step: the first efficient enantioselective synthesis of 1,5-enynes bearing an all-carbon propargylic quaternary center achieved through a Pd-catalyzed decarboxylative allylation starting from racemic ketoesters. The Pd-catalyzed decarboxylation allylation gave high enantioselectivity by using the DACH-naphthyl Trost ligand, which had never been used for the allylation of propargylic positions before. In the third stage, the chiral 1,5-enynes obtained were finally converted into the desired tricyclic [6,5,6] and [6,6,6] fused and spiro ring systems using ring-closing metathesis and cycloisomerization reactions, respectively. Furthermore, the unanticipated synthesis of a new [6,6,5,3] ring system could also

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be achieved with a platinum catalyst. The stage is now ready for using the strategy in the synthesis of natural and synthetic bioactive compounds and for extending it to other types of carbocyclic or heterocyclic scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jerome.waser@epfl.ch.

Notes

The authors declare no competing financial interest.

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(12) To the best of our knowledge, this challenging regioselectivity question has never been addressed in the case of α-alkynyl ketoesters. For a related study on the racemic allylation of α-vinyl ketoesters, see: Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977.

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(14) For some substrates, the use of the more stable TPDPS protecting group was needed to prevent desilylation. Currently, desilylation cannot be prevented in the absence of the benzene ring. See Supporting Information (SI) for further details.

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(16) See SI for a full list of tested conditions.

(17) The absolute stereochemistry was determined using Trost's mandelate ester method: (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. (b) Trost, B. M.; Schroeder, G. M. *Chem.—Eur. J.* **2005**, *11*, 174. The obtained configuration is in accordance with the prediction model developed by Trost et al. for this type of ligands (ref 10; see Figure S1 in SI).

(18) We speculate that interactions between the free alkyne and the Pd catalyst slow down the reaction in this case. Lower *ee*'s were observed with aryl-substituted alkynes. Alkyl-substituted alkynes cannot be synthesized using EBX reagents.

(19) Overall yield of **8k** from ketone **1k** based on 81% isolated yield of the *cis* isomer of **7k**. In the case of the [6.6.6] ring system, ring closing metathesis of the minor *trans* diastereomer of **7k** was also successful. See SI.

(20) Interestingly, **9** was optically active. Further studies will be required to determine the enantiomeric excess and absolute configuration of this compound.