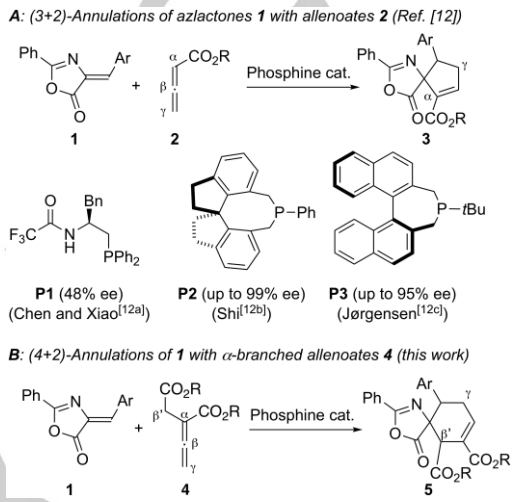
Syntheses of Highly-Functionalized Spirocyclohexenes by Formal (4+2)-Annulation of Arylidene Azlactones with Allenoates

Andreas Eitzinger,[a] Katharina Zielke,[a] Michael Widhalm,[b] Raphaël Robiette,*[c] and Mario Waser*[a]

Abstract: A straightforward phosphine-catalysed formal (4+2)-annulation between α-branched allenoates and arylidene azlactones to access highly functionalized spirocyclohexenes was developed. This cyclization proceeds predominantly through γ-addition of the phosphine-activated allenoates while β'-addition is clearly disfavoured. Detailed computational studies support the proposed mechanism and provide a reasonable explanation for the observed regioselectivity and the noted catalyst effect.

Introduction

Cyclization reactions of allenoates with different acceptor molecules to access (chiral) carbo- or heterocycles have been heavily investigated over the last years.[1] These approaches were found to be highly dependent on the nature of the used reagents and the hereby employed catalysts and different constitutions, regioisomers and/or ring sizes can be accessed by variation of the conditions.[2,3] Classically either *tert.* amines or *tert.* phosphines are used as catalysts for these reactions, which can lead to complementary reaction pathways,[2] thus giving access to a broad variety of different (asymmetric) annulation strategies starting from simple starting materials.[1-9] Azlactones have become a prominent and commonly employed family of easily accessible amino acid precursors,[10] and the corresponding arylidene azlactones **1** turned out to be interesting acceptor molecules for asymmetric (ring-forming) transformations.[11,12] The versatility of these compounds to act as C2 synthons for formal (3+2)-annulations with allenoates **2** under (chiral) phosphine catalysis was recently reported by the groups of Chen and Xiao,[12a] Shi,[12b] and Jørgensen.[12c] It was impressively shown that the phosphine-activated allenoates undergo γ-attack to the acceptor molecule with high preference, yielding the chiral cyclopentene-based masked α-amino acids **3** with high yields and excellent enantioselectivities when using chiral phosphines (Scheme 1A).[12]



Scheme 1. Recent described (3+2)-annulations of azlactones **1** and the herein described novel (4+2)-approach by reacting allenoates **4** with compounds **1**.

We have recently shown that α-branched allenoates **4** can perform in a totally complementary fashion compared to allenoates **2** in the reaction with *ortho*-quinone methides.[13] We therefore got interested in testing whether these allenoates may serve as C4 synthons for formal (4+2)-annulation reactions[6,7] with arylidene azlactones **1** (Scheme 1B). This reaction would give access to highly functionalized cyclohexene-based α-amino acid derivatives in a straight forward manner.

Results and Discussion

Reaction Development.

Our initial screening was carried out by reacting the parent acceptor **1a** with the diethyl allenoate ester **4a**. Table 1 gives an overview of the most interesting results obtained in a detailed screening of different catalysts and conditions. All these reactions were run for 20 h using three equivalents of allenoate **4a** related to **1a** (other ratios were tested as well but turned out to be lower yielding, mainly because of side-reactions of the allenoates[14]).

[a] DI A. Eitzinger, DI[n] K. Zielke, Prof. M. Waser
Johannes Kepler University Linz
Institute of Organic Chemistry
Altenbergerstraße 69, 4040 Linz, Austria
E-mail: mario.waser@jku.at
[b] Prof. M. Widhalm
University of Vienna
Institute of Chemical Catalysis
Währinger Strasse 38, 1090 Vienna, Austria
[c] Prof. R. Robiette
Université catholique de Louvain
Institute of Condensed Matter and Nanosciences
Place Louis Pasteur 1 box L4.01.02, 1348 Louvain-la-Neuve, Belgium
E-mail: raphael.robiette@uclouvain.be

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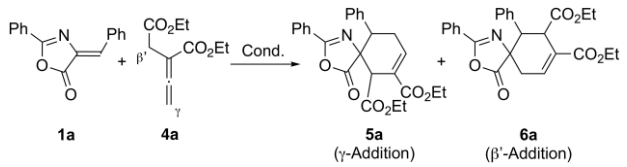
Table 1. Identification of the best-suited conditions for the (4+2)-annulation of arylidene azlactone **1a** with allenoate **4a**.



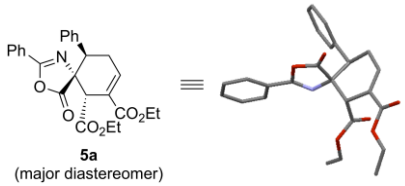
1a **4a** **5a** (γ-Addition) **6a** (β'-Addition)

Entry[a]	Cat.	Solv.	Base	T [°C]	5a : 6a[c]	d.r. (5a)[d]	Yield (5a)[b]
1	PBu_3 (20%)	CH_2Cl_2	Cs_2CO_3 (5 eq.)	25	4.0 : 1	5.2 : 1	29%
2	PPh_3 (20%)	CH_2Cl_2	Cs_2CO_3 (5 eq.)	25	--	--	n.r.
3	DABCO (20%)	CH_2Cl_2	Cs_2CO_3 (5 eq.)	25	--	--	n.r.
4	PBu_3 (20%)	CH_2Cl_2[e]	Cs_2CO_3 (5 eq.)	25	7.0 : 1	8.6 : 1	38%
5	PBu_3 (100%)	CH_2Cl_2[e]	Cs_2CO_3 (5 eq.)	25	5.8 : 1	6.8 : 1	39%
6	PBu_3 (20%)	THF[e]	Cs_2CO_3 (5 eq.)	25	5.0 : 1	5.0 : 1	58%
7	PBu_3 (20%)	toluene[e]	Cs_2CO_3 (5 eq.)	25	5.8 : 1	5.0 : 1	48%
8	PBu_3 (20%)	toluene[e]	--	25	3.8 : 1	5.0 : 1	50%
9	PBu_3 (20%)	toluene[e]	--	60	3.8 : 1	4.2 : 1	65%
10	PBu_3 (20%)	THF[e]	--	60	3.6 : 1	4.0 : 1	71%
11	PEt_3 (20%)	THF[e]	--	60	3.3 : 1	4.1 : 1	73%
12	PEt_3 (20%)	THF[e]	Cs_2CO_3 (5 eq.)	60	3.2 : 1	2.6 : 1	65%
13	PCy_3 (20%)	THF[e]	--	60	2.8 : 1	1.5 : 1	22%
14	$PPhMe_2$ (20%)	THF[e]	--	60	4.5 : 1	6.1 : 1	60%
15	PPh_2Bu (20%)	THF[e]	--	60	4.2 : 1	3.0 : 1	16%
16	**P2** (20%)	THF[e]	--	60	--	--	n.r.
17	**P3** (20%)	THF[e]	--	60	--	--	n.r.

[a] All reactions were run for 20 h with 0.1 mmol **1a** and 0.3 mmol **4a**; [b] Isolated yield of the mixture of diastereomers. [c] Judged by 1H NMR of the crude product. [d] See Fig. 1 for the relative configuration of the major diastereomer. [e] Addition of 4 Å MS.

First experiments using either catalytic amounts of PBu_3, PPh_3, or DABCO in the presence of Cs_2CO_3 in CH_2Cl_2 revealed that only PBu_3 leads to the targeted (4+2)-annulation reaction. It turned out that adduct **5a**, originating from γ-addition of the allenoate to the acceptor, is clearly favoured over the β'-addition product **6a** (entry 1, Table 1).

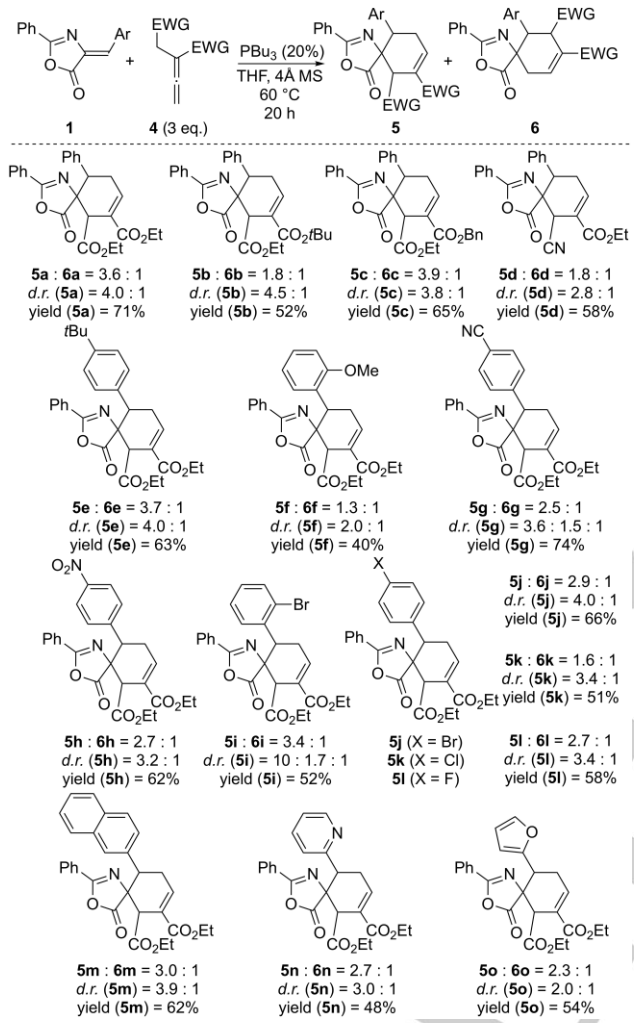
We also soon realized that the use of degassed solvents and the addition of molecular sieves has a beneficial effect on the yield (compare entries 1 and 4). Accordingly, all reactions were carried out in dry and degassed solvents, and in the presence of 4 Å MS. Product **5a** was always obtained as a mixture of two diastereoisomers and the relative configuration of the major diastereomer was unambiguously proven by single crystal X-Ray analysis (Fig. 1).[15] It should be noted that the other 2 possible diastereomers of **5a** were not detected hereby, but we later observed formation of more diastereomers for some of the other derivatives (see Scheme 2). Using a stoichiometric amount of PBu_3 had no positive effect on the yield (entry 5). Among the different solvents that were tested, THF and toluene are better-suited than the initially used DCM (entries 6 and 7), and we also realized that the reaction performs with an even slightly higher yield (but a somewhat lower regioselectivity) in the absence of base (entry 8). The yield could further be increased by carrying out the reaction at elevated temperature with THF giving a slightly better yield than toluene (entries 9 and 10). By testing different achiral *tertiary* phosphines PR_3 next, we realized that short alkyl group containing phosphines (e.g. PEt_3 and PBu_3) perform significantly better than bulkier ones (compare entries 10, 11, 13). It was also shown for PEt_3 that the presence of a base at higher reaction temperature has a detrimental effect on yield and diastereoselectivity (entry 12). Among the aryl-containing phosphines only $PPhMe_2$ allowed us to achieve the (4+2)-annulation with a reasonable yield, whereas diaryl- or triaryl-phosphines performed significantly worse (entries 2, 14, 15). Unfortunately, this observed reactivity trend also lowered the chances to introduce an enantioselective protocol for this reaction, as the majority of chiral phosphines that are useable for such allenoate cyclizations are usually sterically demanding and aryl-group containing ones.[12] Nevertheless we carried out a few reactions with different chiral phosphines such as compounds **P2** and **P3** (which have both been very successfully used for the (3+2)-annulations of azlactones **1** with allenes **2** as shown in Scheme 1[12b,c]), but with absolutely no success (entries 16 and 17; the same lack in reactivity was observed for other known chiral phosphines[16]).



5a
(major diastereomer)

Figure 1. Single crystal X-Ray analysis of the major diastereomer of **5a**.

We next investigated the scope for the racemic protocol of this reaction by using differently substituted acceptors **1** and allenoates **4** in the presence of PBu_3 (reactions with PBu_3 were easier to handle and more robust because PEt_3 was found to be more sensitive towards oxidation than PBu_3) (Scheme 2).



Scheme 2. Application scope of the PBu_3-catalyzed (4+2)-annulation of allenoates **4** with acceptors **1**. Reactions were carried out on 0.1 - 0.25 mmol scale. The ratio of **5**:**6** was determined by 1H NMR of the crude reaction mixture. Compounds **5** were always isolated as diastereomeric mixtures after column chromatography. Analytically clean single diastereomere samples of some derivatives were obtained by preparative HPLC.[16]

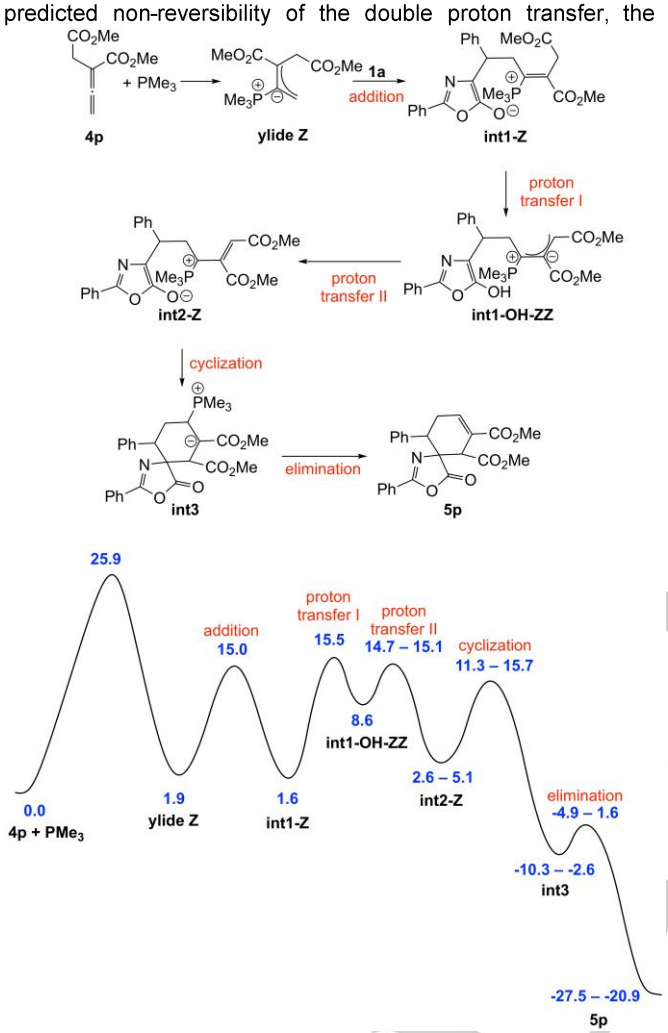
The isolated yields were in most cases in the same range as for the parent system. However, the diastereoselectivities were obviously influenced by the electronic and steric properties of the starting materials and in some cases we also observed formation of a third diastereomer (see compounds **5g** and **5i**). For all substrates, the γ-addition products **5** were favoured over the β'-addition products **6**, although in some cases the selectivity was not that pronounced anymore. This was especially observed when changing the ester groups of the allenoates (towards products **5b**/**6b** and **5d**/**6d**) and when introducing an *ortho*-methoxy group on the acceptor side (products **5f**/**6f**). It has to be admitted that in all cases isolation of the β'-adducts **6** turned out to be very difficult, as these compounds co-eluted with allenoate degradation products which could not be removed by column chromatography and therefore no isolated yields for compounds **6** can be given.

Computational Studies.

To get a fundamental understanding of the mechanism and the origin of regio- and stereoselectiviy in this formal (4+2) annulation reaction, we have investigated the free energy profile of the reaction between acceptor **1a** and allenoate **4p** with trimethylphosphine as a catalyst (Scheme 3). Calculations were carried out at the M06-2X-D3/6-311+G**//B3LYP-D3/6-31G* level of theory including a continuum description of tetrahydrofuran as solvent.[17,18]

All potential mechanisms for the formation of **5p** from **1a** and **4p** were investigated.[18] The mechanistic sequence of the predicted most favoured pathway is depicted in Scheme 3. The first step is formation of **ylide-*Z*** by addition of PMe_3 onto the allenoate. This step is only slightly endergonic (1.9 kcal/mol) but occurs through a significant free energy barrier (25.9 kcal/mol). The so-formed ylide then adds onto **1a** to form the isoenergetic **int1-*Z*** through a low-lying transition state (15.0 kcal/mol). Next, a migration of the double bond occurs to yield **int2** (four diastereomers are possible here and the respective energy values/ranges for the different intermediates and TSs are given in Scheme 3). Many mechanisms can be envisaged for this double bond migration[18] but our calculations indicate that the most favoured pathway consists of two successive intramolecular proton transfer reactions involving the azlactone moiety. Intermediates **int2** can then ring-close to form the zwitterions **int3** which eventually undergo a rapid elimination to yield products **5p** (diastereomers).

The double intramolecular proton transfer process can potentially lead to four diastereomeric **int2**. Our calculations predict the stereoselective formation of **int1-OH-ZZ** and hence of the two **int2** presenting the two methyl ester groups in Z relationship. Each of these two diastereomers can eventually lead to the four possible diastereomers of **5p**. Thus, given the predicted non-reversibility of the double proton transfer, the



overall diastereoselectivity of the formal (4+2) annulation must depend on the interplay between the double proton transfer and the cyclization. The low energetic discrimination of the diastereomeric transition states in these processes (see SI for full data[18]), makes it however very difficult to predict the overall diastereoselectivity in the formal (4+2) annulation reaction. This complexity in the origin of stereoselectivity and the computed low energetic discrimination between the different diastereomeric pathways is in good agreement with the observed variations in diastereomeric ratios according to small structural changes in the structure of substrates (see Scheme 2).

Scheme 3. Computed global mechanistic sequence and free energy profile (free energies in kcal/mol relative to reactants, the values for the four diastereomeric pathways are given as ranges).

Our results indicate that the rate-determining step of the formal (4+2) annulation is the formation of the ylide (see Scheme 3). Experimentally, a drastic influence of the nature of the catalyst on the reactivity was observed: non-hindered trialkylphosphines catalyse the reaction efficiently whereas hindered phosphines such as Ph_2PMe, PPh_3, **P2** or **P3** lead to very low or no conversion (see Table 1). In addition, tertiary amines like DABCO (Table 1 - entry 3) or Et_3N showed also to be inefficient catalysts for this (4+2) annulation reaction. In order to identify the factors responsible for these observations, we explored the two first steps of the process, ylide formation and addition onto azlactone **1a**, with PPh_3 and NMe_3 as a catalyst. Obtained results reveal that the inefficiency of these catalysts to promote the formal (4+2) annulation reaction is mainly due to the increase of the endergonic character of ylide formation in these cases (Figure 2). This trend can be explained by destabilizing steric interactions in the ylide for PPh_3 and the intrinsic lower stabilisation of ammonium ylides as compared to phosphonium ones for NMe_3.[19] In this latter case, another factor plays also a role in determining reactivity, as this ylide is computed to be less nucleophilic than the phosphorous ylides (free energy barrier to addition is 13.1, 13.4 and 17.3 kcal/mol with X = PMe_3, PPh_3 and NMe_3, respectively), thus providing a rational explanation for the observed trend in reactivity when using the different nucleophilic catalysts (compare with the results in Table 1).

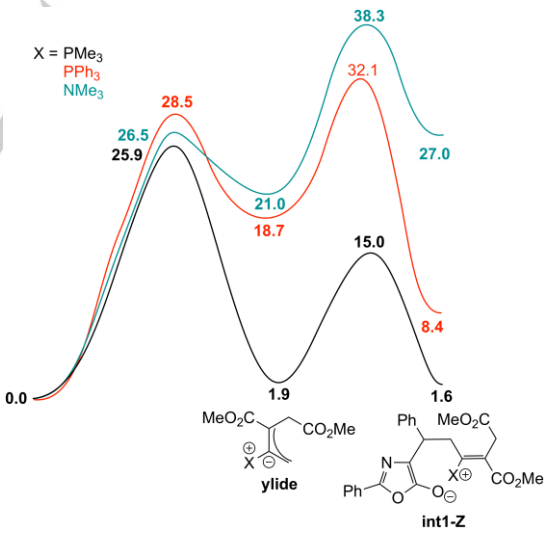
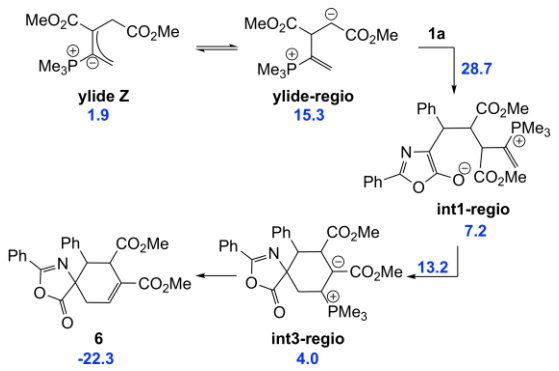


Figure 2. Influence of the nature of the catalyst.

Formation of regioisomers **6** was also computationally investigated. Based on our results, the mechanism depicted in Scheme 4 is the most plausible to account for the formation of **6**.

This mechanism involves formation of **ylide-regio** from **ylide-Z** via a proton transfer. This new ylide can then add onto azlactone **1a** to yield **int1-regio** which can undergo a cyclization to lead to **6** after proton transfer and elimination of the phosphonium group. The rate-determining step of the process is predicted to be addition in this case, with an overall free energy barrier of 28.7 kcal/mol. Our calculations thus indicate that, due to a lower stability of the **ylide-regio** as compared to **ylide Z**, formation of **6** is less favoured than formation of **5** (by 3.4 kcal/mol), which is in good agreement with the experimental outcome.



Scheme 4. Postulated mechanism for the formation of **6.**

Conclusions

It was shown that α-branched allenoates **4** can undergo formal (4+2)-annulations of arylidene azlactones **1** under phosphine catalysis to access highly functionalized spirocyclohexenes **5** in a straightforward manner. This cyclization proceeds predominantly through γ-addition of the phosphine-activated allenoates while β'-addition is clearly disfavoured. The reaction requires the use of small sterically less-hindered tertiary phosphines and does not proceed in the presence of tertiary amines or more hindered phosphines, which unfortunately made an enantioselective protocol not possible. Detailed computational studies support the proposed mechanism and provide a reasonable explanation for the strong influence of the catalyst as well as for the preference of the γ-addition over the β'-addition reaction.

Experimental Section

General details can be found in the online supporting information. This document also contains detailed synthesis procedures for the auxiliaries and the epoxidation reactions and analytical data of novel compounds and reaction products as well as copies of NMR spectra and HPLC traces. The supporting information also includes the details of the computational investigations.

General asymmetric epoxidation procedure: The ammonium salt **1** was dissolved in the given solvent (A: 0.1 M in *i*-PrOH, B: 0.1 M in toluene) and Cs_2CO_3 (20 equiv.) were added followed by the addition of the corresponding carbaldehyde (2 equiv.). The mixture was stirred at room temperature for 24 h (Ar atmosphere). The reaction was quenched by addition of H_2O and extracted with DCM. The combined organic phases were dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (gradient of heptanes and EtOAc) gave the corresponding epoxides in the reported yields and enantiopurities.

Epoxide 3b. Obtained as a white solid on 0.5 mmol scale. Method A: 88% yield and *e.r.* = 93:7 and Method B: 66% yield and e.r. = 95:5. $[\alpha]_D^{20}$ = 106.7 (c = 0.675, DCM, *e.r.* = 95:5); ^{1}H NMR (300 MHz, δ, $CDCl_3$, 298 K): 1.17 (t, *J* = 7.3 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 3.39-3.52 (m, 4H), 3.59 (d, *J* = 1.8 Hz, 1H), 4.10 (d, *J* = 1.8 Hz, 1H), 7.32-7.39 (m, 5H) ppm; ^{13}C NMR (125 MHz, δ, $CDCl_3$, 298 K): 13.1, 15.1, 41.0, 41.6, 57.4, 57.7, 125.8, 128.6, 128.7,135.9, 165.9 ppm. The enantioselectivity was determined by HPLC (Chiralcel OD-H, eluent: hexane:*i*-PrOH = 80:20, 0.5 mL/min, 10 °C, retention times: t_{major} (2S,3R) = 15.1 min, t_{minor} (2R,3S) =17.3 min).

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Keywords: Allenoates • Cyclization Reaction • Diastereoselectivity • Phosphine Catalysis • DFT Calculations

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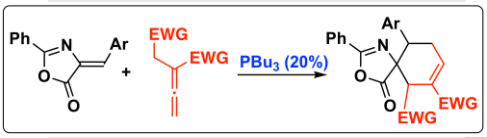

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