Domino Reactions

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Concise Synthesis of Acetal-Protected *syn* 1,3-Diols by a Tandem Hemiacetal Formation/Tsuji–Trost Reaction**

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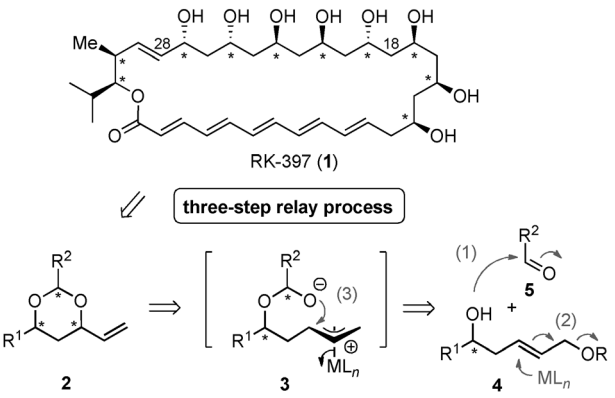
Dedicated to Professor Lutz Tietze on the occasion of his 70th birthday

The palladium-catalyzed allylic substitution reaction is one of the most versatile and efficient methods for C–C and C–X bond formation and consequently a broad range of procedures for the effective coupling of C- and N-nucleophiles with π-allyl metal intermediates have been reported.[1] In contrast, protocols for the corresponding addition of O-nucleophiles are less advanced,[2] despite the paramount importance of oxygen-containing substituents in numerous functional compounds.[3] Furthermore, standard reaction conditions that work well for C- and N-nucleophiles are usually not suitable for O-nucleophiles and reported O-nucleophiles are mainly limited to phenolates, alkoxides, and carboxylates.[2,4,5] From the perspective of synthetic efficiency, novel cascade reactions involving allylic substitution reactions with O-nucleophiles are particularly attractive as these lead to the rapid increase of structural complexity.[6] Herein, we report the design, development, and application of a conceptually novel domino sequence that relies on a combination of hemiacetal formation with a Pd-catalyzed allylic substitution reaction and enables the concise construction of acetal-protected *syn* 1,3-diols. Notably, this sequence presents one of the first examples of the use of hemiacetal alkoxides as nucleophiles in allylic substitution reactions.[7]

As exemplified by the macrolide antibiotic RK-397 (**1**, Scheme 1),[8] proximal 1,3-arrays of hydroxy-bearing stereogenic centers are prevalent structural phenotypes in a wide variety of natural products, pharmaceuticals, and bioactive agents,[3] rendering the development of effective synthetic approaches an important research goal and a large number of methods have been developed for this purpose.[9] Motivated by present targets in our group,[3e,10] in combination with certain limitations of these existing methods, in particular with regard to access to the required starting materials and efficient chirality transfer, we desired a more direct and concise sequence for the stereoselective synthesis of 1,3-diols.



Scheme 1. Three-step tandem concept for the synthesis of 1,3-diol motifs in polyketides. *: stereogenic center.

Inspired by previous cascade concepts developed in our group,[6j,11] our synthetic approach relied on a three-step relay process. As shown in Scheme 1, this involves addition of a homoallylic alcohol (**4**) to a suitable carbonyl compound (**5**) giving the corresponding hemiacetal alkoxide (step 1). Formation of an electrophilic π-allyl complex (step 2) then results in the generation of intermediate **3**, which finally undergoes an intramolecular allylic substitution reaction to give the desired 1,3-allylic diols (**2**) in a suitably protected form (step 3).[12] Notably, the synthetic design of this two-component coupling is highly convergent and results in a considerable increase in structural complexity through the assembly of two new stereogenic centers from simple and readily available starting materials.

After initial exploratory studies with different ketones and aldehydes,[13] the coupling of homoallylic alcohol **6** with acetaldehyde **5** was further evaluated in more detail, giving the 1,3-*syn* and the 1,3-*anti* products **7a** and **7b** as the main products. Importantly, ethylidene acetals are valuable protective groups, which add to the value of this transformation. As shown in Table 1 for representative examples, the stereoselectivity and yield of this process with various bases and solvents (entries 1–12) as well as catalysts and ligands (entries 12–20) was evaluated. KHMDS in toluene proved to be the optimal combination (d.r. 12:1, 83%; entry 12), while alternative bases (DBU, TMG, LDA) led to little or no conversion (entries 5–7). We observed only a minor influence of the counterion (entries 1, 2, 4, 9–12), crown ethers (entry 3), and the solvent on the stereochemical outcome. We evaluated various Pd sources having mono- and bidentate ligands (entries 18–21) as well as ligands with modified

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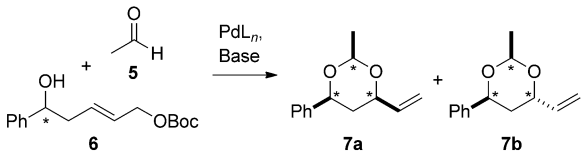
Table 1: Tandem hemiacetal formation/Tsuji–Trost reaction.[a,b]



5 **6** **7a** **7b**

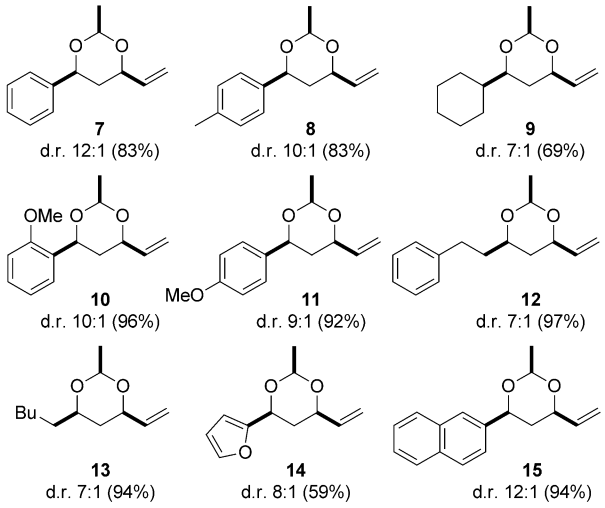
Entry	Pd source	Ligand	Base	Solvent	Yield [%]	d.r. **7a**/**7b**
1	[{Pd(allyl)Cl}$_2$]	PPh_3	KO*t*Bu	THF	83	8:1
2	[{Pd(allyl)Cl}$_2$]	PPh_3	LiHMDS	THF	56	8:1
3	[{Pd(allyl)Cl}$_2$]	PPh_3	LiHMDS/ [12]crown-4	THF	71	7:1
4	[{Pd(allyl)Cl}$_2$]	PPh_3	NaHMDS	THF	86	9:1
5	[{Pd(allyl)Cl}$_2$]	PPh_3	LDA	THF	41	8:1
6	[{Pd(allyl)Cl}$_2$]	PPh_3	DBU	THF	–	–
7	[{Pd(allyl)Cl}$_2$]	PPh_3	TMG	THF	–	–
8	[{Pd(allyl)Cl}$_2$]	PPh_3	LiHMDS	CH_2Cl_2	61	10:1
9	[{Pd(allyl)Cl}$_2$]	PPh_3	KO*t*Bu	Et_2O	83	9:1
10	[{Pd(allyl)Cl}$_2$]	PPh_3	KO*t*Bu	CH_3CN	76	8:1
11	[{Pd(allyl)Cl}$_2$]	PPh_3	KO*t*Bu	DME	93	7:1
12	[{Pd(allyl)Cl}$_2$]	PPh_3	KHMDS	toluene	83	12:1
13	[{Pd(allyl)Cl}$_2$]	dppp	KHMDS	toluene	73	6:1
14	[{Pd(allyl)Cl}$_2$]	dppe	KHMDS	toluene	93	6:1
15	[{Pd(allyl)Cl}$_2$]	dppf	KHMDS	toluene	91	6:1
16	[{Pd(allyl)Cl}$_2$]	$AsPh_3$	KHMDS	toluene	60	8:1
17	[{Pd(allyl)Cl}$_2$]	$P(OiPr)_3$	KHMDS	toluene	69	7:1
18	[{Pd(allyl)Cl}$_2$]	$P(OEt)_3$	KHMDS	toluene	73	7:1
19	[$Pd_2(dba)_3$]	PPh_3	KHMDS	toluene	79	8:1
20	[$Pd(PPh_3)_4$]	–	KHMDS	toluene	78	9:1
21	$Pd(OAc)_2$	PPh_3	KHMDS	toluene	88	9:1

[a] Conditions: **6** (1.0 equiv), **5** (130 equiv), catalyst (0.1 equiv), ligand (0.3 equiv), base (1.5 equiv), room temperature, 2 h. [b] Abbreviations: Boc = *tert*-butoxycarbonyl, HDMS = hexamethyldisilazide, LDA = lithium diisopropylamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine, DME = 1,2-dimethoxyethane, dppp = 1,3-bis(diphenylphosphanyl)propane, dppe = 1,2-bis(diphenylphosphanyl)ethane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, dba = *trans*,*trans*-dibenzylideneacetone.

electronic and/or steric properties (entries 12–18). The optimized conditions for the selective generation of the 1,3-*syn*-dioxane product **7a** involved treatment of homoallylic alcohol **6** in acetaldehyde as cosolvent[14] with a slight excess of KHMDS (1.5 equiv), catalytic amounts of [{Pd(allyl)Cl}$_2$] (10 mol%), and PPh_3 (30 mol%) and conducting the reaction in toluene at room temperature (entry 12).

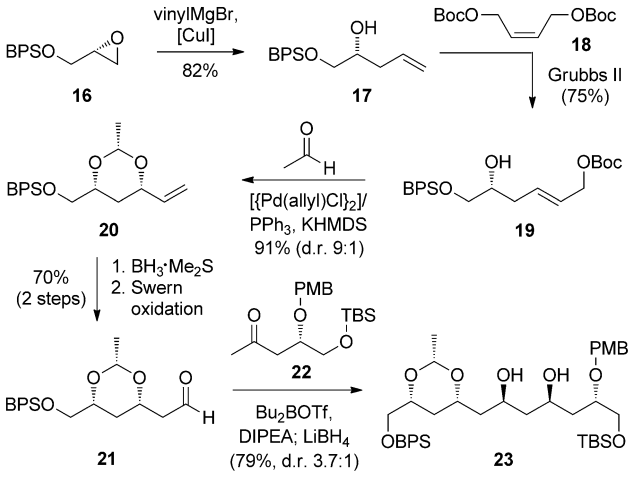
This novel domino process was readily applicable for the stereoselective synthesis of various dioxanes (**7**–**15**). In all cases, the desired trisubstituted products were obtained in good selectivity and yield, and the reaction conditions did not have to be adjusted to suit specific substrates.

Furthermore, this novel concept may be readily applicable to the convergent synthesis of polyketides, as demonstrated in the concise synthesis of the C18–C28 fragment of macrolide RK-397 (Scheme 2). Importantly, the required chiral homoallylic alcohol substrates **19** are readily accessible, for example, by the ring-opening of terminal epoxides (see the transformation of **16** to **18**) or by asymmetric allylation of aldehydes (not shown) and subsequent cross-metathesis of the resulting terminal alkene (see the conversion of **17** to **19** with **18**). The pivotal two-component coupling of **19** with



acetaldehyde proceeded again in high yield and with high selectivity, demonstrating again the general usefulness of this method. Importantly, the terminal alkene of derived *syn* 1,3-diol product **20** may be efficiently used as a functional handle for further elaboration, as shown here for the conversion **19** to the corresponding aldehyde **21**. Further elaboration of **21** with methyl ketone **22** by a 1,5-*anti* aldol coupling[15] and subsequent in situ 1,3-*syn* reduction gives the desired polyol **23** in a concise and effective manner. Notably, this route compares favorably to all previous synthetic approaches to this unit.[16,17]

Stereochemically, this domino process places all three substituents of the six-membered-ring products in equatorial positions, which may be explicable if these reactions proceed via a Zimmerman–Traxler-type transition state. The high degree of selectivity observed in this process can only be rationalized mechanistically if the initial hemiacetal formation is reversible and not stereodiscriminating. Out of this initial equilibrium only one of the two possible hemiacetal diastereomers may be preferentially transformed into the more favorable all-*syn* product, suggesting that a dynamic kinetic resolution process is involved in this cascade sequence.



Scheme 2. Concise synthesis of the C18–C28 fragment **23** of RK-397. BPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, DIPEA = ethyldiisopropylamine, Tf = trifluoromethanesulfonyl.

In conclusion, we have designed, developed, and applied a novel approach to stereoselectively synthesize biologically significant *syn*-1,3-diol motifs. The mechanistically intriguing two-component reaction is based on an innovative domino sequence involving hemiacetal formation and an intramolecular allylic substitution reaction. The starting materials are readily available in enantiomerically pure form and the assembled products bear a terminal allylic alkene, which may be directly used as a functional handle for further elaboration. This process presents one of the first examples of hemiacetal nucleophiles in allylic substitutions.[7] The effectiveness of this method for the convergent synthesis of polyketides has been demonstrated in a concise and stereoselective construction of the C18–C28 fragment of macrolide RK397. This method will be highly useful in the synthesis of functional molecules and may inspire further developments of O-nucleophiles in allylic substitution reactions as well as conceptually related relay sequences.

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