Domino Reactions

DOI: 10.1002/anie.201003304

Concise Synthesis of Tetrahydropyrans by a Tandem Oxa-Michael/Tsuji–Trost Reaction**

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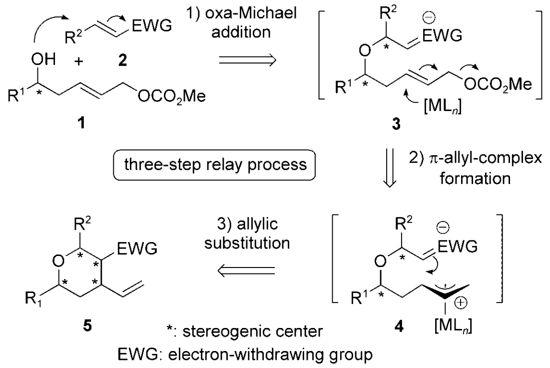
Dedicated to Professor G. Helmchen on the occasion of his 70th birthday

Metal complexes have been successfully applied to a broad range of organic transformations and occupy a central position in preparative organic chemistry. In recent years, the notion of combining several metal-mediated processes in relay-type domino sequences has been attracting attention.[1,2] Through the combination of several synthetic transformations in a one-pot fashion, domino reactions efficiently transform simple starting materials into products of structural complexity. Surprisingly, oxa-Michael reactions have not been developed for such purposes, despite their obvious potential for heterocycle synthesis, presumably because of the inherent instability of the generated enolates towards eliminations or retro processes.[3] Herein, we report the design and development of a conceptually novel cascade reaction based on an oxa-Michael addition and an allylic substitution,[4] and successfully implement this concept for the highly concise synthesis of polysubstituted tetrahydropyrans.

Substituted tetrahydropyrans (THPs) are prevalent constitutional chemotypes and underlying structural motifs in numerous natural products, registered drugs, and bioactive synthons.[5] Various strategies for the construction of such systems have been reported,[6] including cyclizations involving oxocarbenium ions[7] and epoxides,[8] hetero-Diels–Alder reactions,[9,10] Prins cyclizations,[11] intramolecular nucleophilic reactions,[12] Michael reactions,[13] reductions of cyclic hemiacetals,[14] cyclizations involving nonactivated double bonds,[15] and one-pot procedures based on alkene–alkyne couplings followed by ether formation.[16] Inspired by present targets in our group in combination with certain limitations of these existing methods, we desired a more direct and concise sequence for THP synthesis. As shown in Scheme 1, our synthetic concept is based on a three-step sequential process involving an oxa-Michael addition[3,17] and a Tsuji–Trost coupling.[18] Accordingly, the readily available homoallylic alcohol **1** should first add to the suitably acceptor-substituted alkene **2** giving enolate **3** (step 1). A π-allyl complex **4** would then be generated (step 2), which would finally be trapped in an intramolecular fashion through an allylic substitution reaction, generating the desired THP motif in a highly direct fashion (step 3). Notably, three new stereogenic centers are assembled in this process, demonstrating a high increase in structural complexity from very simple starting materials. It should also be noted that the synthetic design is highly convergent and flexible and may be readily adapted to various other substrates enabling direct access to a broad range of heterocycles.



Scheme 1. Three-step tandem concept for the synthesis of tetrahydropyrans.

Based on initial experiments with different Michael acceptors,[19] nitroolefins were selected for further development. The coupling of alcohol **6**[20] and nitroolefin **7**[21] was studied in more detail (Table 1). Gratifyingly, after we had evaluated reagents (bases, catalysts, ligands) and parameters (temperature, solvent) our synthetic strategy could be successfully implemented to generate the desired THP motif **8**. The best conditions included catalytic amounts of [{Pd(allyl)Cl}$_2$] with PPh$_3$ in combination with LiHMDS as th base (Table 1, entry 10).[22] The absence of PPh$_3$ resulted in lower yields (Table 1, entries 8 and 10) and alternative ligands led to lower selectivities [P(*i*OPr)$_3$, P(OEt)$_3$: Table 1, entries 11 and 12] or conversions (dppf, dppp, dppe, dppb: Table 1, entries 13 and 14, footnote [h]). Methyl and *tert*-butyl carbonate proved to be the best leaving groups of those evaluated (Table 1, entries 5–8). While in principle it might be possible to run the reaction with the *tert*-butoxy-substituted substrate using only catalytic amounts of base, only low degrees of conversion were observed in such cases (Table 1, entries 8 and 9). Encouragingly, out of the eight possible products only two major (**8a**, **8b**) and one minor isomer (**8c**) formed, suggesting a high degree of conformational bias in this sequential process (see below). The major products differ

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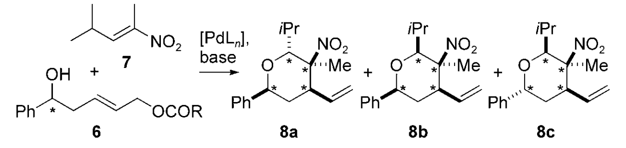
[**] Generous financial support from the Deutsche Forschungsgemeinschaft (SFB 623 “Molekulare Katalysatoren: Struktur und Funktionsdesign”) and the Wild-Stiftung is gratefully acknowledged. We thank Prof. G. Helmchen for helpful discussions and suggestions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201003304.

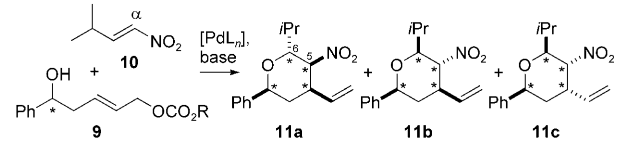
Table 1: Tandem oxa-Michael/Tsuji–Trost reaction.[a],[23]



Entry	R	$[PdL_n]$/base[b]	Yield [%][c]	d.r. **8a/8b/8c**[d]
1	OMe	$[\{Pd(allyl)Cl\}_2]$/LiO*t*Bu	24	6.9:9.1:1
2	OMe	$[Pd_2(dba)_3]$/LiO*t*Bu	14	10.4:12.3:1
3	OMe	$[Pd_2(dba)_3]$/LiHMDS	17	12:11.7:1
4	OMe	$[\{Pd(allyl)Cl\}_2]$/LiHMDS	39	4.8:3.4:1
5	OMe	$[\{Pd(allyl)Cl\}_2]$/LiHMDS	71	10.3:8:1
6	PMB	$[\{Pd(allyl)Cl\}_2]$/LiHMDS	43	14.4:10.2:1
7	*t*Bu	$[\{Pd(allyl)Cl\}_2]$/LiHMDS	44	1.4:1.3:1
8	O*t*Bu	$[\{Pd(allyl)Cl\}_2]$/LiHMDS	47	2.1:1.8:1
9	O*t*Bu	$[\{Pd(allyl)Cl\}_2]$/LiHMDS (10 mol %)[e]	17	n.d.[f]
10	O*t*Bu	$[\{Pd(allyl)Cl\}_2]$/PPh$_3$ (20 mol %)/ LiHMDS	62	1.6:1 : <0.05
11	O*t*Bu	$[\{Pd(allyl)Cl\}_2]$/P(*i*OPr)$_3$ (20 mol %)/ LiHMDS	52	18.4:13.5:1[g]
12	O*t*Bu	$[\{Pd(allyl)Cl\}_2]$/P(OEt)$_3$ (20 mol %)/ LiHMDS	59	9.4:6.9:1[g]
13	O*t*Bu	$[\{Pd(allyl)Cl\}_2]$/dppf (10 mol %)/ LiHMDS	35	13.0:8.8:1.4
14	O*t*Bu	$[\{Pd(allyl)Cl\}_2]$/dppp (10 mol %)/ LiHMDS[h]	25	11.2:6.9:1

[a] The reactions were carried out in 2.5 mL THF with 0.2 mmol homoallylic alcohol **6**, 2 mmol nitroolefin, 0.3 mmol base, and 0.01 mmol (5 mol %) catalyst. [b] Commercially available solutions of the bases in THF were used (Sigma-Aldrich). [c] Yield of isolated product. [d] Ratio was determined by ^{1}H NMR analysis of the crude product. [e] Low degrees of conversion were also observed with other bases (NEt$_3$, DBU, LiO*t*Bu). [f] n.d.: not determined. [g] Formation of two further diastereomers was observed in yields similar to that of **8c**. [h] Similar results were obtained with dppe and dppb. dba = dibenzylideneacetone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, dppb = 1,4-bis(diphenylphosphanyl)butane, dppe = 1,2-bis(diphenylphosphanyl)ethane, dppf = 1,1'-bis(diphenylphosphanyl)ferrocene, dppp = 1,3-bis(diphenylphosphanyl)propane, HMDS = 1,1,1,3,3,3-hexamethyldisilazanide, PMB = *para*-methoxybenzyl.

Table 2: Domino reaction generating the tetrasubstituted THP **11a**.[a,23]



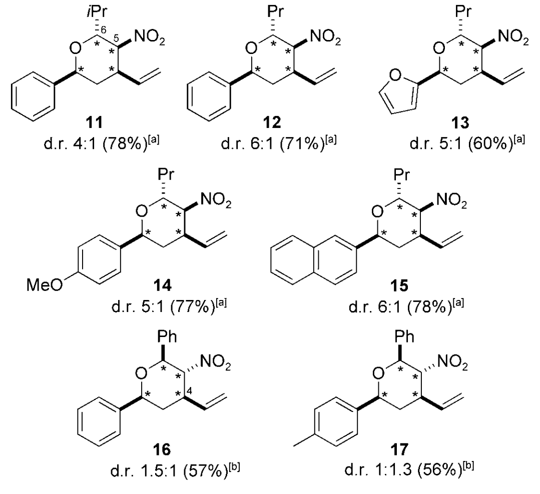
Entry	Substrate; $[PdL_n]$/base[b]	Yield [%][c]	d.r. **11a/11b/11c**[d]
1	R = Me; $[Pd_2(dba)_3]$ (5 mol %)/PPh$_3$ (20 mol %)/LiHMDS (1.5 equiv)	47	5.8:2.5:1
2	R = Me; $[Pd_2(dba)_3]$ (5 mol %)/PPh$_3$ (20 mol %)/KO*t*Bu (1.5 equiv)	63	4.4:1.4:1
3	R = *t*Bu; $[Pd_2(dba)_3]$ (5 mol %)/PPh$_3$ (20 mol %)/LiO*t*Bu (1.5 equiv)	78	5.2:1.4:1

[a] The reactions were carried out on a 0.2 mmol scale with 0.3 to 0.4 mmol of nitroolefin in 3 mL of THF. [b] Commercially available solutions of the bases in THF were used (Sigma-Aldrich). [c] Yield of isolated product. [d] Ratio was determined by ^{1}H NMR analysis of the crude product.

only in the configuration of the isopropyl-bearing center (C-6), while the phenyl and the vinyl substituent are in equatorial positions and the nitro group resides in an axial position.[23]

We then directed our efforts toward increasing the stereoselectivity of this process. In a rational to enhance the influence of the substituents vicinal to the nitro group on the generation of the new stereogenic center in the β position, the α-methyl group of **7** was removed. Accordingly, desmethylnitroolefin **10** was evaluated, and indeed this concept proved successful. The desired THP **11a** was now obtained as the main product with good selectivities (Table 2), considering the stereochemical complexity of this process. In contrast to the previous results, formation of two other side products (**11b** and **11c**) was observed, which underlines the important stereochemical influence of the α substituent. Optimized conditions for the selective generation of tetrasubstituted THP **11a** required a slight excess of nitroolefin **10** (1.5 to 2 equiv), catalytic amounts of $[Pd_2(dba)_3]$ (5 mol %) and PPh$_3$ (20 mol %) and conducting the reaction in THF at room temperature (Table 2, entry 3). Optimum yields for the coupling of nitroolefin **10** were obtained with LiO*t*Bu rather than LiHMDS and KO*t*Bu (Table 2, entries 1–3), while LiHMDS was shown to be optimal for the reaction of nitroolefins lacking a β substituent of (see Table 3).

As shown in Scheme 2, various further THPs (**11**–**15**) were readily obtained by this domino process. In all cases, preparatively useful yields and selectivities resulted, without the need to adjust the reaction conditions to specific substrates. Any minor diastereomer could be readily removed by column chromatography, which underlines the efficiency of the overall process. The selectivities obtained for the generation of THPs bearing a sterically less hindered substituent at C-6 (e.g. **12** and **11**) were slightly better than that of the original system. In contrast, only little selectivity was observed for the corresponding nitrostyrenes: the (5-*epi*,6-*epi*) isomers **16** and **17** were obtained as main products, suggesting that slight structural changes at C-6 have a critical influence on the stereoselectivity at this position.

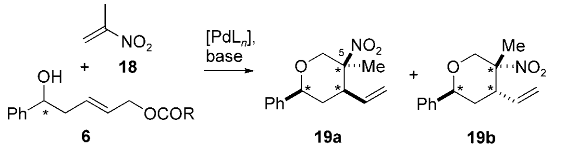


[a] d.r. to (5-*epi*,6-*epi*) isomer [b] d.r. to (4-*epi*) isomer

Scheme 2. Selected tetrasubstituted THPs prepared by our method.[23,24]

The scope of this tandem process was then expanded to the stereoselective generation of THPs in which C-5 is tetrasubstituted. As shown in Table 3, the α-substituted nitroolefin **18** cyclizes with good selectivity to give tetrahydropyran **19a**. As before, the major product bears the nitro group in an axial position. The best results were obtained with 2 equiv nitroolefin, 1.5 equiv LiHMDS and the dimeric catalyst [{Pd(allyl)Cl}$_2$]. Alternative bases (Table 3, entries 1 and 2) and leaving groups (Table 3, entry 3) resulted in lower degrees of synthetic efficiency.

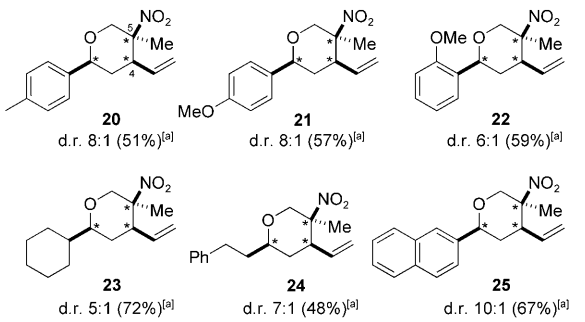
Table 3: Assembly of THPs with a tetrasubstituted carbon center.[a,23]



Entry	R	[PdL$_n$]/base	Yield [%][b]	d.r. **19a**/**19b**[c]
1	OMe	[{Pd(allyl)Cl}$_2$]/KO*t*Bu	16	2.5:1
2	OMe	[{Pd(allyl)Cl}$_2$]/NaHMDS	12	4.4:1
3	OMe	[{Pd(allyl)Cl}$_2$]/LiHMDS	17	8.8:1
4	O*t*Bu	[{Pd(allyl)Cl}$_2$]/LiHMDS	62	8.8:1

[a] The reactions were carried out on a 0.2 mmol scale with 0.4 mmol of nitroolefin in 2.5 mL of THF. [b] Yield of isolated product. [c] Ratio was determined by ^{1}H NMR analysis of the crude product.

As shown in Scheme 3, the method was readily applicable to various trisubstituted THPs, without the need to adjust the reaction conditions to specific substrates. In all cases, the products were obtained with good selectivities, considering the number of possible stereoisomeric products.


20 d.r. 8:1 (51%)[a]

21 d.r. 8:1 (57%)[a]

22 d.r. 6:1 (59%)[a]

23 d.r. 5:1 (72%)[a]

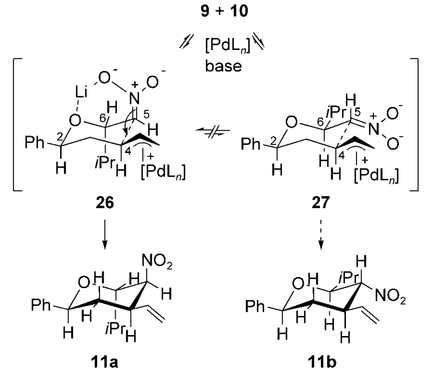
24 d.r. 7:1 (48%)[a]

25 d.r. 10:1 (67%)[a]

[a] d.r. to (4-*epi*,5-*epi*) isomer

Scheme 3. Synthesis of THPs with a tetrasubstituted carbon center.[23,25]

Mechanistically, the observed selectivities and yields of these domino reactions may be explained by a reversible oxa-Michael reaction. As shown in Scheme 4, this first addition may not be stereodiscriminating. However, intermediate **27** may be reversibly transformed into the presumably more favorable diastereomer **26** leading to the major product **11a** together with minor amounts of **11b**. The observed stereoselectivity may arise from a Zimmerman—Traxler-type transition state, in which the substituents at C-2 and C-4 substituents are in equatorial position, in agreement with the observed stereochemical outcome. Generation of the axial configuration at C-5, in turn, may be explained by chelation of the metal counterion to the ether oxygen and the nitro group, which would be more favorable with an axial nitro group, as in **26**. Alternatively, also minimization of dipole–dipole interactions of the nitronate with the π-allyl complex would be more favorable for **26** than for **27**. The intermediate chelate complex **26** may also rationalize the observed selectivity at C-6, as this substituent would reside in a pseudoequatorial position.



Scheme 4. Mechanistic rationale for the stereochemical outcome.

In conclusion, we have designed, developed, and implemented a conceptually novel domino process for the highly concise synthesis of polysubstituted tetrahydropyrans from simple starting materials. Notably, the starting homoallyl alcohols are readily available—also in enantiopure form through asymmetric allylation methodology—adding to the scope and potential of this reaction. Mechanistically, the procedure is based on a sequential oxa-Michael/Tsuji–Trost reaction and generates up to three new stereogenic centers in in a one-pot process. It may also be successfully applied for the stereoselective synthesis of tetrasubstituted carbon centers bearing a nitro group. The heterocyclic products bear two functional handles (NO$_2$, alkene), which may be further elaborated, adding to the synthetic usefulness of the process. It is expected that this novel domino concept will be further explored and applied to the synthesis of functional molecules.

Experimental Section

Representative procedure (THP **11**; Table 2, entry 3): A solution of homoallylic alcohol **9** (R = *t*Bu; 56 mg, 0.2 mmol) and nitroolefin **10** (44 mg, 0.38 mmol) in 1 mL anhydrous THF was treated at −78 °C with a suspension of [Pd$_2$(dba)$_3$]·CHCl$_3$ (10 mg, 0.01 mmol, 5 mol %) and PPh$_3$ (10 mg, 0.04 mmol) in 1.5 mL anhydrous THF and a solution of lithium *tert*-butoxide (1 M in THF, 0.3 mL, 1.5 equiv, as commercially supplied from Sigma-Aldrich). The mixture was then warmed to room temperature and stirred until the alcohol was complete consumed (ca. 2 h). After cooling to −78 °C,[26] the reaction was stopped by addition of sat. aq. NH$_4$Cl solution. After warming to room temperature, the mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried (MgSO$_4$), and filtered. Evaporation of the solvent in vacuo and purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate = 60:1 to 30:1) afforded the diastereomers **11a**, **11b**, and **11c** (d.r. 5.2:1.4:1, 78 %) as viscous oils.

Received: May 31, 2010
Revised: September 9, 2010

Keywords: allylic substitution · domino reactions · heterocycles · homogeneous catalysis · oxa-Michael reactions

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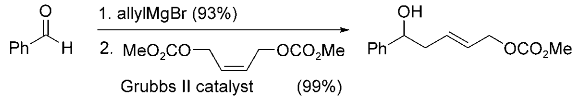
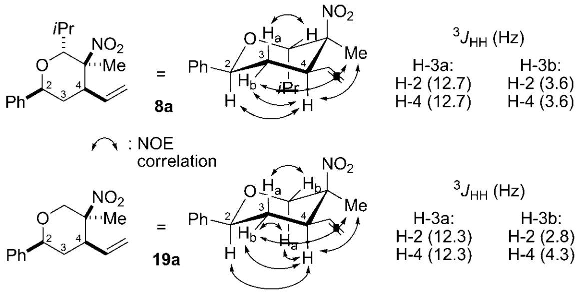


[21] All nitroolefins were readily obtained by base-catalyzed condensation of nitroalkanes with the corresponding aldehydes: A. Duursma, A. J. Minnaard, B. L. Feringa, *Tetrahedron* **2002**, *58*, 5773. For full details see the Supporting Information.

[22] Alternative bases included KHMDS, NaHMDS, and LiO*t*Bu.

[23] In all cases, the stereochemistry was assigned by NMR methods involving the nuclear Overhauser effect (NOE) .



[24] Typical reaction conditions: A solution of the corresponding homoallylic alcohol (1 equiv) and the nitroolefin (1.5 equiv) in THF was treated with $[Pd_2(dba)_3]$ (5 mol%), PPh_3 (20 mol%), and LiO*t*Bu (1.5 equiv) at −78 °C; the reaction mixture was stirred at room temperature until conversion was complete (ca. 2 h). For full details see the Supporting Information.

[25] Typical reaction conditions: A solution of the corresponding homoallylic alcohol (1 equiv) and the nitroolefin (2 equiv) in THF was treated with $[\{Pd(allyl)Cl\}_2]$ (10 mol%), PPh_3 (30 mol%) and LiHMDS (1.5 equiv) at −78 °C; the reaction mixture was stirred at room temperature until conversion was complete (≈2 h). For full details see the Supporting Information.

[26] For convenience, the aqueous workup may also be conducted at 0 °C giving the products with similar yields.