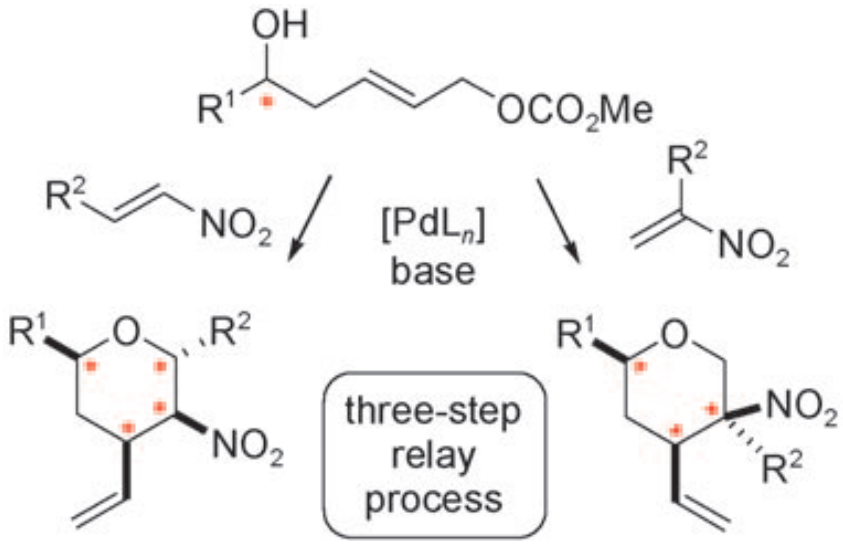
Concise Synthesis of Tetrahydropyrans by a Tandem Oxa-Michael / Tsuji–Trost Reaction

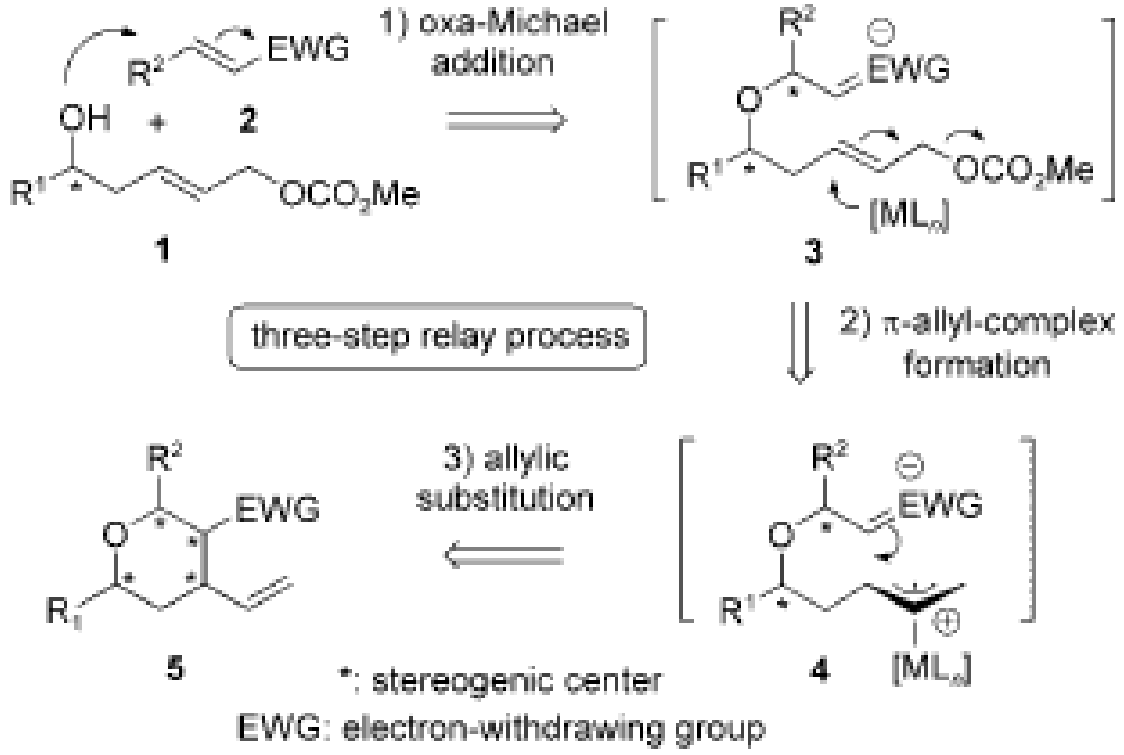


L. Wang, P. Li, and D. Menche, *Angew. Chem. Int. Ed*. 2010, 49, 1–5

❖ **Various strategies for the construction of functionalised tetrahydropyran ring :**

- ✓ Cyclisations onto Oxocarbenium Ions (*Prins*, *Rychnovsky*)
- ✓ Hetero-Diels–Alder Cyclisations
- ✓ Cyclisation of hydroxy groups onto epoxides
- ✓ Michael Reactions
- ✓……

❖ Concept of the novel cascade reaction based on an oxa-Michael addition and an allylic substitution



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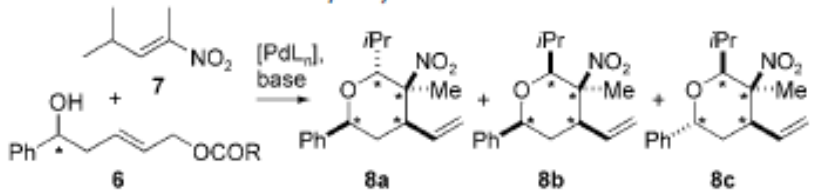
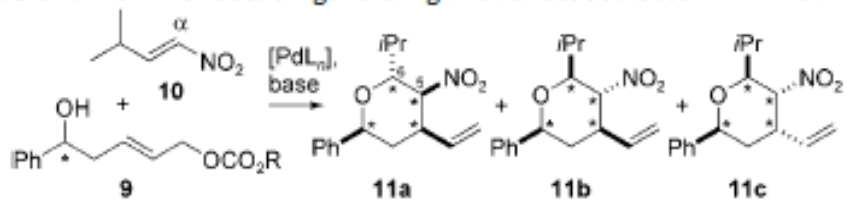
❖ Optimization of the new synthetic approach

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

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

❖ Conclusion

- A one-pot relay process generates up to three new stereogenic centers
- Rapid access of polysubstituted tetrahydropyrans.
- Simple starting materials.