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Regioselective Rhodium-Catalyzed Allylic Alkylation with a *Modified* Wilkinson's Catalyst

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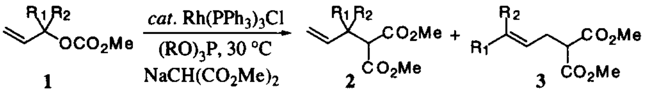
Abstract: *Treatment of the secondary and tertiary allylic carbonates 1 with the sodium salt of dimethyl malonate and a catalytic amount of Wilkinson's catalyst* modified *with a triorganophosphite, furnished the tertiary and quaternary carbon stereogenic centers 2 in high yield with excellent regioselectivity.*

The construction of quaternary carbon stereogenic centers continues to be a challenge for classical synthetic methods. Despite extensive work in this area, a general solution to the problem has not been forthcoming.[1] The allylic alkylation reaction is a powerful synthetic transformation that may be catalyzed using a wide range of transition metal complexes.[2-4] The palladium catalyzed reaction has been extensively investigated, with ever-increasing emphasis on asymmetric catalysis.[5,6] However, one of the major limitations with this process, is the necessity to often utilize symmetrical substrates in order to circumvent problems with regioselectivity. Recent work has demonstrated that the regiochemical outcome is a function of the transition metal complex.[4] In this paper, we describe our results on the rhodium catalyzed allylic alkylation of secondary and tertiary allylic carbonates **1** using a *modified* Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, to furnish the tertiary and quaternary allylic products **2** in high yield with excellent regioselectivity (**Scheme 1**).



Scheme 1

Our initial studies focused on the development of general reaction conditions for this transformation. Treatment of the secondary carbonate **1a** (R_1 = H, R_2 = Me) with the sodium enolate of dimethylmalonate in the presence of a catalytic amount of Wilkinson's catalyst furnished the primary and secondary substituted derivatives **2a/3a** in excellent yield, as a 2.3:1 mixture of regioisomers. In order to improve the regioselectivity the catalyst was modified *in situ* with a series of triorganophosphite additives. Triphenyl- and triisopropylphosphite gave a modest improvement in the selectivity, while trimethylphosphite led to substantial improvement in the formation of **2a** over **3a**

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(40:1). The regioselectivity was further improved (83: 1) by lowering the reaction temperature from 69 °C to 30 °C.

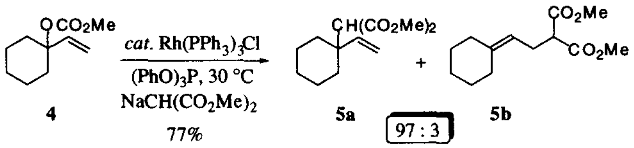
Treatment of the tertiary allylic carbonate **1g** under analogous conditions furnished the allylic alkylation products **2g/3g** in modest yield and with poor regiocontrol. Hence, alternative reaction conditions were explored. Preliminary work demonstrated that 10 mol% of Wilkinson's catalyst modified with less triorganophosphite were necessary for good catalytic turnover and selectivity. Interestingly, triphenylphosphite rather than trimethylphosphite proved optimal for good regioselectivity with the tertiary allylic carbonates. Indeed, this transformation represents the first example of a rhodium catalyzed allylic alkylation with tertiary allylic carbonates for the preparation of quaternary carbon centers, and it is likely to have ***significant*** synthetic utility.

Table 1: Regioselective Rhodium Catalyzed Allylic Alkylation of Secondary and Tertiary Allylic Carbonates **1** with the Sodium Salt of Dimethyl Malonate[7]

entry	allylic carbonate **1**[a]			reaction	ratio **2** : **3**[c,d]	yield (%)[e]
	R_1	R_2		conds.[b]		
1	H	Me	**a**	A	99 : 1	91
2	"	^{n}Pr	**b**	A	98 : 2	89
3	"	Ph	**c**	A	98 : 2	95
4	"	^{c}Hex	**d**	A	93 : 7	84
5	Me	Me	**e**	B	≥99 : 1	89
6	"	Et	**f**	B	96 : 4	78
7	"	^{n}Pr	**g**	B	96 : 4	73
8	"	^{c}Hex	**h**	B	NA	trace
9	"	Ph	**i**	B	≥99 : 1	32[f]

[a] Reactions were all carried out on a 1 mmol reaction scale. [b] Method A: 5 mol% [$Rh(PPh_3)_3Cl$] with $P(OMe)_3$ (20 mol%) then $NaCH(CO_2Me)_2$ (2 eq.) in THF at 30 °C. Method B: 10 mol% [$Rh(PPh_3)_3Cl$] with $P(OPh)_3$ (15 mol%) then $NaCH(CO_2Me)_2$ (3 eq.) in THF at 30 °C. [c] Ratios determined by capillary GC. [d] The primary product was prepared independently in each example *via* Pd(0) catalysis. [e] Isolated yields. [f] 5:3 Mixture of 3°:1° allylic carbonates **1i/1i'** furnished recovered allylic carbonate **1i/1i'** (3°:1° = 1:2.7; 56%; see ref. 8).

Table 1 summarizes the various secondary and tertiary allylic carbonates that were examined. The allylic alkylation of the secondary allylic carbonates **1a-d** proceeded in excellent yield with good to excellent regiocontrol. While the tertiary allylic carbonates **1e-i** proved slightly less reactive, the yields and selectivity's were comparable. The cyclohexyl derivatives **1d** and **1h** were significantly less reactive, in which the latter furnished only a trace of the alkylated products **2h/3h**. Another interesting observation is that the phenyl substituted allylic carbonate **1i** undergoes allylic alkylation along with competitive rearrangement to the primary allylic carbonate **1i'**.[8] The reaction was also applied to cyclic systems, as outlined in **Scheme 2**. Treatment of the tertiary allylic carbonate **4** under the standard conditions, furnished the quaternary substituted cyclohexyl derivatives **5a/5b** in 77% yield as a 97:3 ratio favoring the more substituted product.[9]



Scheme 2

The origin of the increased turnover rate and excellent regioselectivity may be attributed, at least in part, to the increased π-accepting ability of the triorganophosphite additives.[10] The phosphite presumably undergoes ligand exchange with the phosphine ligands on Wilkinson's catalyst to produce a new catalytically active species, the nature of which is currently being elucidated.

In conclusion, we have developed a series of allylic alkylation reactions that utilize a *modified* Wilkinson's catalyst to facilitate the formation of tertiary and quaternary carbon stereogenic centers. The advantage of this method is that it *modifies* a commercially available catalyst *in situ* making the procedure very practical.

Acknowledgments

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References and Footnotes

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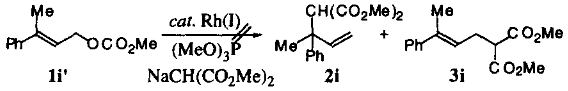
7. All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}C-NMR) and analytical (HRMS) data in accord with the assigned structure.

8. Resubmission of **1i'** to the reaction conditions led to 95% recovery of the carbonate, which presumably rules out a direct-insertion type mechanism.



9. *Representative Experimental Procedure*: Triphenylphosphite (81 μL, 0.3 mmol) was added directly to a red solution of Wilkinson's catalyst (95.3 mg, 0.1 mmol) in anhydrous THF (3.5 mL). The mixture was sonicated for 1-2 minutes, and then stirred at room temperature for 10 minutes resulting in a light orange homogeneous solution. Dimethyl malonate (403 mg, 3.05 mmol) was added dropwise, *via* a tared 500 μL syringe, over *ca.* 5 minutes to a slurry of sodium hydride (60% w/w in mineral oil, 115 mg, 2.9 mmol) in anhydrous THF (4.0 mL), resulting in the evolution of H_2 gas. The tertiary allylic carbonate **6** (185.7 mg, 1.01 mmol) was then added dropwise, *via* a tared 250 μL syringe, to the preformed rhodium catalyst. This solution was then added *via* Teflon® cannula to the malonate solution, rinsing with anhydrous THF (0.5 mL). The mixture was heated at 30 °C for *ca.* 4 hours (t.l.c. control). The reaction mixture was partitioned between diethyl ether and sequentially 1.5N aqueous NaOH and saturated aqueous NaCl. The organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with a 5-20% gradient of diethyl ether/pentane) furnished the allylic alkylation products **5a/5b** (185.5 mg, 77%) as a colorless oil, in a 97:3 ratio favoring **5a**.

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