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Regioselective rhodium-catalyzed allylic alkylation/ring-closing metathesis approach to carbocycles

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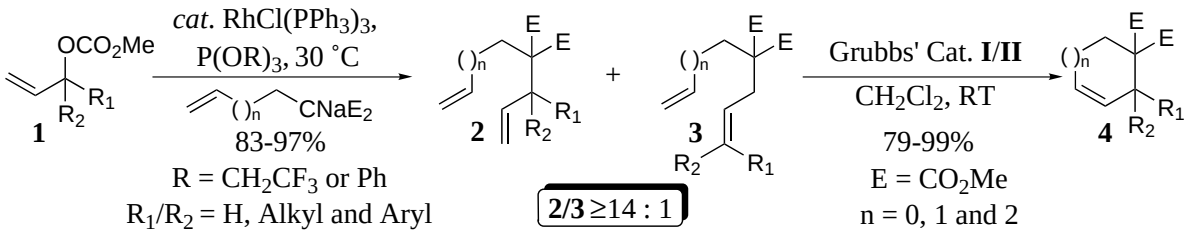
Abstract—Treatment of the allylic carbonates **1a–c** with the sodium anion of the α-substituted malonates ($n=0$–2) and Wilkinson's catalyst *modified* with a triorganophosphite, furnished the allylic alkylation products **2**/**3a–i** in 83–97% yield, favoring **2a–i**. The dienes **2a–i** were then subjected to ring-closing metathesis using either **I** or **II**, to afford the carbocycles **4a–i** in 79–99% yield. © 2001 Elsevier Science Ltd. All rights reserved.

The stereocontrolled construction of carbocyclic systems has stimulated the development of new synthetic methodology for decades. This may be attributed, at least in part, to their ubiquity in pharmacologically relevant molecules. Despite the array of synthetic methods that have been devised to construct these systems, few methods are applicable to the diastereoselective construction of adjacent ternary–quaternary and quaternary–quaternary carbon stereogenic centers.[1]

The metal-catalyzed allylic substitution provides a useful method for the construction of vicinal ternary and quaternary carbon stereogenic centers. However, this approach has been somewhat restricted to symmetrical substrates to circumvent regiochemical problems, particularly with α-branched malonate derivatives.[2,3] We recently demonstrated the rhodium-catalyzed allylic alkylation of *unsymmetrical* chiral non-racemic carbonates with α-branched malonate derivatives, using a trifluoroethyl phosphite *modified* Wilkinson's catalyst, provides a regio- and diastereospecific approach to *anti*-1,3-stereogenic centers.[4–6] Hence, we envisioned the combination of the allylic alkylation with ring closing metathesis would provide a versatile strategy for the construction of various carbocycles, vide infra.[7,8]

Herein, we now describe the regioselective rhodium-catalyzed allylic alkylation, using alkenyl α-branched malonates, followed by ring-closing metathesis (Scheme 1). This study also provided an opportunity to further examine the effect of α-substituted malonates on regioselectivity, and the influence of vicinal substitution on the ring-closing metathesis reaction.

Table 1 summarizes the results for the sequential rhodium-catalyzed allylic alkylation followed by ring-closing metathesis. Treatment of the racemic allylic carbonates **1a–c** with the sodium anion of the α-



Scheme 1.

Keywords: rhodium-catalyzed; allylic alkylation; metathesis; vicinal quaternary and ternary carbon stereogenic carbons.

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Grubbs' Catalyst N-*Heterocyclic Carbene Catalyst*

I **II**

Cy = Cyclohexyl Ar = 2,4,6-Trimethylbenzene

branched malonates and Wilkinson's catalyst *modified* with the requisite triorganophosphite, furnished the allylic alkylation products **2**/**3a**–**i** in 83–97% yield, with excellent regioselectivity (≥14:1) favoring the more substituted products **2a**–**i**.

This study demonstrates that the allylic alkylation of secondary carbonates **1a**/**b** with α-branched malonates using the trifluoroethyl phosphite *modified* Wilkinson's catalyst proceeds with excellent selectivity (entries 1–6).[9] Although the trifluoroethyl phosphite catalyst proved optimum for the secondary carbonates, triphenyl phosphite proved superior for the tertiary carbonates, affording the vicinal quaternary–quaternary alkylation products **2g**–**i** in excellent yield and with good regioselectivity (entries 7–9).[5a]

The dienes **2a**–**i** were then treated with Grubbs' catalyst **I** to facilitate ring-closing metathesis and furnish the monocyclic carbocycles **4a**–**i** in excellent yield, albeit with the exception of **2i** which afforded only a trace amount of **4i**.[7] Subsequent attempts to optimize the cyclization of **2i**, through increased reaction temperature, catalyst loading and dilution (0.001 M), failed to improve the formation of **4i**. However, treatment of the diene **2i** with the more reactive *second-generation* Grubbs' catalyst **II**, furnished the carbocycle **4i** in 87% yield.[7c]

The stereoselective construction of vicinal ternary–quaternary substituted cyclohexene derivatives was also examined, as outlined in Scheme 2. Treatment of the allylic carbonate **1a** under the standard rhodium-catalyzed allylic alkylation conditions, with the sodium salt of methyl homoallylcyanoacetate, furnished the allylic alkylation products **5a**/**b** in 92% yield, with 14:1 regioselectivity favoring the *secondary* adduct **5a** (by GLC analysis).[11] Interestingly, the analogous allylic alkylation with a chiral non-racemic allylic carbonate (***R***)-**1a** (95% ee) furnished the allylic alkylation derivative *ent*-**5a** with modest enantiospecificity (80% cee),[5c,12] in sharp contrast to related stabilized carbon nucleophiles.[5b,f] Although the reason for the diminished selectivity is unclear, it is conceivable that the nitrile coordinates the metal center and disrupts the smooth transfer of chirality.[13]

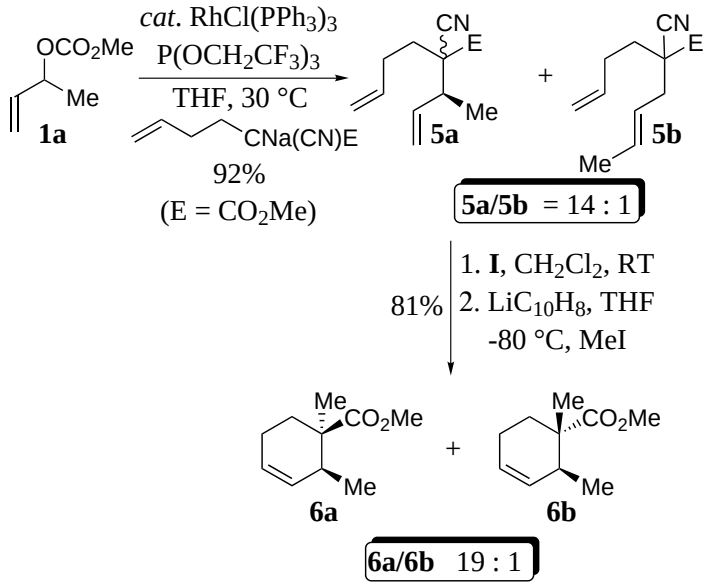
The diene **5a** was then subjected to ring-closing metathesis using the standard Grubbs catalyst **I** to furnish the cyclohexene derivative as a mixture of diastereoisomers. Reductive alkylation of the nitrile, using lithium naphthalenide and methyl iodide at −80°C, furnished the vicinal ternary–quaternary substituted cyclohexene **6a**/**b** in 81% overall yield, as a ≥19:1 mixture of diastereoisomers favoring **6a** (by 400 MHz NMR).[5f,14] The relative configuration of the product **6a** was confirmed by NOE experiments. The obvious advantage of this approach is the ability to utilize a variety of electrophiles in combination with the allylic alkylation to provide a relatively versatile three-step method for the construction of α-quaternary-β-ternary substituted cyclohexene derivatives.

In conclusion, we have developed a convenient synthetic sequence for the construction of vicinal ternary–

Table 1. Scope of the regioselective Rh-catalyzed allylic alkylation/ring-closing metathesis approach to carbocycles[10]

Entry	Allylic carbonate **1**			Nu[a]	Phosphite	M/L ratio	Ratio **2**:**3**[b]	Yield of **2**:**3** (%)[c]	Grubbs' Catalyst[d]	Yield of **4** (%)[c]
	R_1	R_2		$n=$						
1	Me	H	**a**	0	$P(OCH_2CF_3)_3$	1:4	**a** 56:1	87	**I**	93
2	Me	H	**a**	1	$P(OCH_2CF_3)_3$	1:4	**b** 55:1	86	**I**	88
3	Me	H	**a**	2	$(OCH_2CF_3)_3$	1:4	**c** 49:1	90	**I**	89
4	Ph	H	**b**	0	$P(OCH_2CF_3)_3$	1:4	**d** 43:1	95	**I**	87
5	Ph	H	**b**	1	$P(OCH_2CF_3)_3$	1:4	**e** 36:1	83	**I**	84
6	Ph	H	**b**	2	$P(OCH_2CF_3)_3$	1:4	**f** 38:1	84	**I**	94
7	Me	Me	**c**	0	$P(OPh)_3$	1:3	**g** 14:1	85	**I**	79
8	Me	Me	**c**	1	$P(OPh)_3$	1:3	**h** 14:1	91	**I**	99
9	Me	Me	**c**	2	$P(OPh)_3$	1:3	**i** 16:1	97	**II**	87

[a] All alkylation reactions were carried out on a 0.5 mmol reaction scale.
[b] Ratios of regioisomers were determined by GLC analysis of crude reaction mixtures.
[c] Isolated yields.
[d] Reaction carried out on a 0.25 mmol reaction scale, using 5 mol% of **I** or **II** (0.05 M).



Scheme 2.

quaternary and quaternary–quaternary substituted five-, six- and seven-membered monocyclic carbocycles using the regioselective rhodium-catalyzed allylic alkylation in conjunction with ring-closing metathesis. Furthermore, this study demonstrates that α-substituted cyanoacetates may be utilized in the allylic alkylation for the stereoselective construction of α-quaternary-β-ternary cyclohexenes, albeit with diminished enantiospecificity.

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9. The trimethyl phosphite *modified* Wilkinson's catalyst also favors the formation of the *secondary* product **2a** (*2°*:*1°* = 32:1) albeit with slightly reduced selectivity.
10. All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}C NMR) and analytical (HRMS) data in accord with the assigned structure.

11. *Representative experimental procedure*: Wilkinson's catalyst (233 mg, 0.25 mmol) was suspended in anhydrous THF (20 mL) and sonicated for ca. 2 min then warmed to 30°C under an argon atmosphere. Tris(2,2,2-trifluoroethyl) phosphite (221 μL, 1.0 mmol) was added to the deep red solution, resulting in a yellow–orange homogeneous catalyst which was stirred for an additional ca. 30 min. In a separate flask, sodium hydride (289 mg, 7.2 mmol, 60% dispersion in mineral oil) was suspended in anhydrous THF (30 mL), and the homoallylcyanoacetate (1.16 g, 7.5 mmol) added dropwise via tared microsyringe over ca. 10 min at ambient temperature. The resulting anion was then added to the catalyst using a Teflon® cannula, followed by the neat allylic carbonate **1a** (650 mg, 5.0 mmol) via a tared microsyringe. The reaction mixture was then stirred at 30°C for ca. 4 h (tlc control) before being quenched and partitioned between aqueous saturated NH_4Cl solution and diethyl ether. The organic layers were combined, washed with saturated NaCl solution, dried (Na_2SO_4), filtered and concentrated in vacuo to afford a pale-yellow oil. Purification by flash chromatography (SiO_2, gradient elution with 5–10% ethyl acetate/hexane), followed by distillation (Kugelrohr, 125°C, 1 mmHg) afforded the *allylic alkylation product* **5a**/**b** (949 mg, 92%) as a colorless oil; **2**:**1** = 14:1; ds = 1:1 by GLC analysis: IR ($CHCl_3$) 3083 (w), 2982 (w), 2956 (w), 2937 (w), 2850 (w), 2244 (w), 1742 (s), 1449 (m), 1436 (m), 1252 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82–5.68 (m, 2H), 5.24–5.18 (m, 1H), 5.14–4.99 (m, 3H), 3.83 (s, 1.5H), 3.77 (s, 1.5H), 2.69–2.61 (m, 1H), 2.38–2.27 (m, 1H), 2.08–1.85 (m, 3H), 1.23 (d, J = 6.7 Hz, 1.5 H), 1.14 (d, J = 6.7 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.63 (e), 169.07 (e), 137.38 (o), 136.85 (o), 136.15 (o), 136.13 (o), 119.11 (e), 118.18 (e), 118.01 (e), 117.93 (e), 116.47 (e), 116.41 (e), 54.75 (e), 54.23 (e), 53.45 (o), 53.18 (o), 45.48 (o), 45.32 (o), 35.73 (e), 34.53 (e), 30.13 (e), 30.07 (e), 17.48 (o), 15.89 (o); HRMS (ES, M+Na) calcd for $C_{12}H_{17}NO_2Na$ 230.1157, found 230.1158.
12. The analogous allylic alkylation of the enantiomerically enriched carbonate (*R*)-**1a** with the trimethylphosphite *modified* Wilkinson's catalyst, also led to diminished enantiospecificity. Hence, it appears that the nitrile on the nucleophile is responsible for the diminished enantiospecificity rather than the change from the trimethyl to trifluoroethyl phosphite *modified* rhodium-catalyst.
13. For an example of a rhodium complex coordinating a nitrile group of an α-substituted cyanoacetate, see: Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309.
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