Radical carbon–carbon coupling reactions *via* organoboranes

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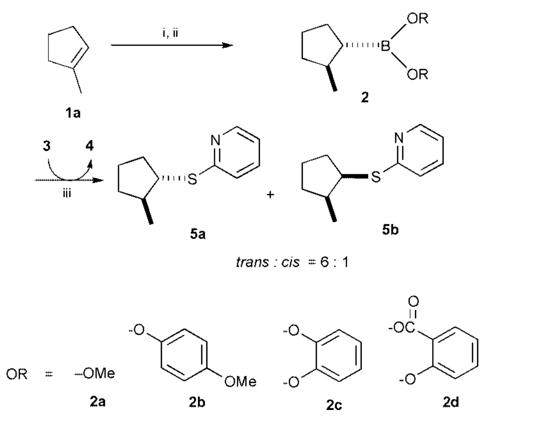
Alkylboronic esters give rise to free-radical alkylation products in the presence of phenylcarbonyloxy(pyridine-2-thione) (Barton's ester) and a variety of Michael acceptors under irradiation.

The use of organoboranes in free-radical reactions[1–5] suffers from a notable limitation. The radicals generated from these compounds using, for example, molecular oxygen fail to add to certain good radical traps such as unsaturated esters, nitriles or sulfones.[1–3] The reason for this lack of reactivity is the unfavourable equilibrium in the postulated enol radical[2] required in the propagation step of the chain process. The design of a simple chain sequence, which eliminates the problem of the propagation step, is therefore of interest.

The boronate intermediates **2a–d** were prepared by hydroboration of olefin **1a** using borane–dimethylsulfide complex, followed by addition of NEt_3 and quenching of the aminoborane intermediate with alcohol or phenol derivatives (Scheme 1). The homolytic fragmentation of the boronates has been studied in the presence of phenylcarbonyloxy(pyridine-2-thione) (PTOC ester) **3**† (2 equiv.),[6] and irradiation at 0–5 °C, using a commercial halogen lamp (300 W).[7]‡ In all experiments, the reaction afforded the desired thiopyridyl derivatives **5a** and **5b** in a 6 : 1 *trans–cis* selectivity, independent of the ligand used. In addition, a variable amount of thiopyridyl dimer, characteristic of the Barton reaction, and benzoic acid arise from the decomposition of the postulated intermediate **4** (*vide infra*, Scheme 4) under the hydrolytic work-up.

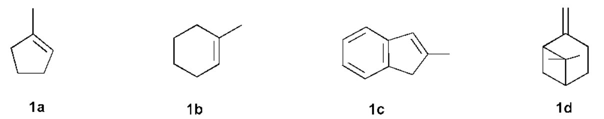


Scheme 1 *Reagents and conditions*: i, $BH_3{\cdot}Me_2S$ (1.25 equiv.), THF, 0–5 °C, 2 h; ii, NEt_3 (1.25 equiv.), 0–5 °C, then alcohol or phenol (1.25 equiv. per OH), room temp.; iii. **3** (2 equiv.), *hν*, CH_2Cl_2/PhH, 0–5 °C, 2 h. Yields (for three steps combined): **a**, 13%; **b**, 43%; **c**, 68%; **d**, 23%.

Among the tested derivatives, dimethyl boronate **2a** afforded poor yield of **5** (13% combined). Better yields were obtained using aryl boronates such as **2b** (43%). Similarly to oxygen initiated reactions, the best results were observed using the catechol derivative **2c** (68%).[5] Ligands substituted by electron withdrawing groups such as the salicylate **2d** afforded lower yields of **5** under the same conditions (23%).

The radical alkylation reaction was examined in the presence of the conventional Michael acceptors, **6a–e**, shown in Scheme 2. The catechol boronates were prepared, as before, by hydroboration of olefins **1a–d** followed by quenching with an equimolar amount of catechol and were not isolated. These intermediates were irradiated, respectively, in the presence of PTOC ester **3** (2 equiv.) and an excess of Michael acceptors **6a–c** (3–5 equiv.) (Scheme 2). The reaction afforded the adducts **7a–h** as inseparable mixtures of the diastereomers.§ In each reaction, a good selectivity, in favour of the *trans* isomer was observed and was determined after the cleavage of the thiopyridyl group (*vide infra*).¶ Likewise, β-pinene **1d** was hydroborated using either borane–dimethyl sulfide complex or thexylborane under standard conditions[10] followed by fragmentation and quenching of the corresponding aminoboranes with equimolar amounts of catechol. As before, the boronate was not isolated. Fragmentation in the presence of an excess (2 equiv.) of PTOC ester **3** and alkylation using methyl acrylate afforded the desired adduct **7i**.‖ The isolated yield of this transformation was considerably lower (30%) than that of the alkylation of secondary radicals. This difficulty in alkylation of primary radicals follows the earlier observed trends.[1–5]

Entry	Olefin	EWG	6	Yield (%)	7	*trans - cis* selectivity§
1	**1a**	CN	**6a**	54	**7a**	88 : 12
2	**1a**	$P(O)(OEt)_2$	**6b**	79	**7b**	99 : 5
3	**1a**	SO_2Ph	**6c**	70	**7c**	92 : 8
4	**1a**	CO_2Me	**6d**	55	**7d**	90 : 10
5	**1b**	CO_2Me	**6d**	82	**7e**	80 : 20
6	**1c**	CN	**6a**	91	**7f**	90 : 10
7	**1c**	COMe	**6e**	70	**7g**	93 : 7
8	**1c**	CO_2Me	**6d**	57	**7h**	95 : 5
9	**1d**	CO_2Me	**6d**	30	**7i**	——



Scheme 2 *Reagents and conditions*: i, $BH_3{\cdot}Me_2S$ (1.25 equiv.), THF, 0–5 °C, 2 h; ii, NEt_3 (1.25 equiv.), 0–5 °C, then catechol (1.25 equiv.), room temp.; iii, **3** (2 equiv.), olefin **6a–e** (3–5 equiv.), CH_2Cl_2/PhH, *hν*, 0–5 °C, 2.5 h.

The relative stereochemistry of the carbon–carbon formation step was established after removing the thiopyridyl group. Although the α-keto thiopyridyl derivative **7g** (Scheme 3, entry 7) was reduced easily using samarium(II) iodide, other derivatives such as nitriles **7a** and **7f**, phosphonate **7b**, esters **7d**,**e** and **7h** and phenyl sulfone **7c** remained inert under these conditions. In these cases, the thiopyridyl esters were converted into the corresponding sulfones and were reduced using samarium iodide[11,12] in the presence or in the absence of HMPA as cosolvent (Scheme 3). Under these conditions the corresponding alkanes **8** were obtained upon quenching the organosamarium intermediates with water. The reaction conditions were not

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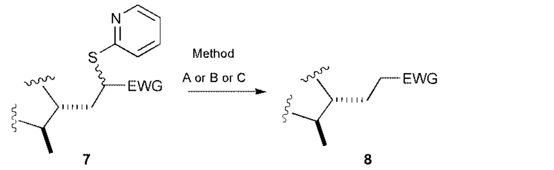
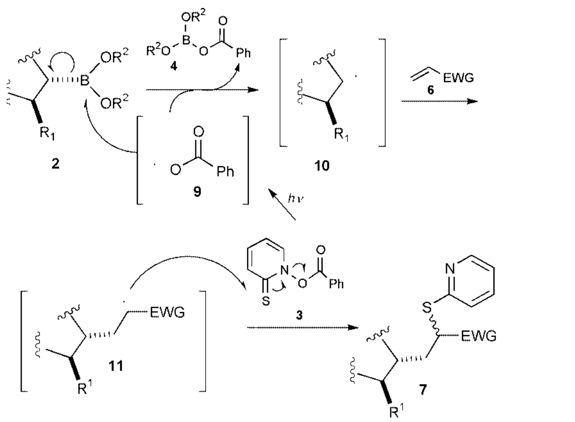
optimised for this reductive step and the low isolated yields observed for **8a**, **8d** and **8e** can be attributed to the volatility of the reduced products. In the examples discussed, this mild cleavage of the thiopyridyl group allowed unambiguous establishment of the stereoselectivity of the crucial carbon–carbon formation step (Scheme 3).



Entry	EWG	7	Method	Yield (%)	8
1	CN	**7a**	C	33	**8a**
2	$P(O)(OEt)_2$	**7b**	B	53	**8b**
3	SO_2Ph	**7c**	B	54	**8c**
4	CO_2Me	**7d**	C	21	**8d**
5	CO_2Me	**7e**	C	14	**8e**
6	CN	**7f**	C	46	**8f**
7	COMe	**7g**	A	51	**8g**
8	CO_2Me	**7h**	C	44	**8h**

Scheme 3 *Reagents and conditions*: method A: SmI_2 (3 equiv.), 0–5 °C, 20 min., then H_2O, room temp.; method B: i, MCPBA (3 equiv.), CH_2Cl_2, 0–5 °C, 3 h; ii, SmI_2 (3 equiv.), THF, 0–5 °C 20 min, then H_2O, room temp.; method C: i, MCPBA (3 equiv.), CH_2Cl_2, 0–5 °C, 3 h; ii, SmI_2 (3 equiv.), HMPA (15 equiv.), THF, 0–5 °C, 10 min, then H_2O, room temp.

In the postulated mechanism of the reaction (Scheme 4) the formed arylcarbonyloxyl radical **9** reacts with the boronic ester **2** resulting in selective fragmentation of the weak B–alkyl bond.** The use of the PTOC esters also offers a logical solution to the chain propagation problem, this being assured by the presence of the thiopyridyl group, and eliminating the necessity of formation of the enol radical form of the addition product.



Scheme 4 Free-radical alkylation of alkylboronates **2** in the presence of phenylcarbonyloxy(pyridine-2-thione) **3** (Barton's ester) and olefin **6**.

In summary, a method, which combines the predictable and high degree of stereoselectivity of boron chemistry with a flexible method for radical carbon–carbon bond formation, is described.[4] In contrast to the previously developed methods,[1–3,5] the alkylation reaction can be extended to a seemingly unrestricted array of Michael acceptors. The reaction proceeds with addition of a thiopyridyl group in the α position of the radical trap. This function eventually can be selectively removed using SmI_2 after converting the thiopyridyl ether to the corresponding sulfone. Whilst organoboronates can be obtained in highly enantioenriched form using asymmetric hydroboration reactions,[13] this free-radical fragmentation/alkylation process may be of interest to develop new arrays of free-radical alkylation reactions in asymmetric synthesis. Beyond this, the synthetic value of the combination of boron and PTOC derivatives should also be contrasted with the generation of radicals by more conventional methods using organotin reagents.[14]

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Notes and references

† The commonly used PTOC esters (Barton esters) are anhydrides of carboxylic acids and the thiohydroxamic acid *N*-hydroxypyridine-2-thione.

‡ The primarily generated acyloxyl radicals may undergo radical decarboxylation reactions.[8] Decarboxylation of such aryl and vinylcarboxyl radicals is generally too slow to be useful for synthetic purposes. Such species may have lifetimes in the microsecond range.[9] This sluggish decarboxylation renders it possible to use them as valuable free-radical chain carriers in the discussed reaction.

§ The diastereoselectivity was measured by GC–MS on the reduced products **8**.

¶ Although NMR analyses showed the formation of the *trans* isomer as the major product, the presence of the two possible thiopyridyl diastereomers rendered it difficult at this stage to establish the precise stereoselectivity.

‖ A roughly 1 : 1 mixture of the two inseparable diastereomers was obtained, according to ^{13}C NMR spectroscopy (162.5 MHz).

** The aryl radical, formed by classical decarboxylation of **9** would lead to a similar chain reaction. No evidence, however, of formation of aryl boronates in the reaction was found.

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