Intermolecular radical addition reactions of α-iodo cycloalkenones and a synthetic study of the formal synthesis of enantiopure fawcettimine†

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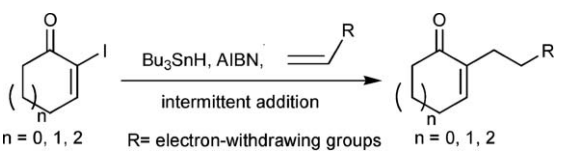
The generation of α-carbonyl vinyl radicals from α-iodo cycloalkenones, the scope of their participation in intermolecular addition reactions with electron-withdrawing olefins are studied and a synthetic study of the formal synthesis of enantiopure fawcettimine using this reaction is described.

Inter- and intramolecular radical reactions have been some of the most important and effective synthetic methods in organic synthesis, and they have frequently been used as key steps in the construction of natural products.[1] Synthetic applications of vinyl radicals are often limited to intramolecular reactions; this may be due to the fact that vinyl radicals are more reactive than alkyl radicals and can easily be trapped by hydrogen, electron-deficient double or triple bonds in the same molecule, or radical mediators, such as Bu_3SnH, in a reaction. In our previous studies, we have demonstrated that the intramolecular cyclization of an α-carbonyl radical could be used as an efficient step in the total synthesis of several natural products, including (±)-modhephene, (−)-dendrobine, (−)-5-oxosilphiperfor-6-exe, (+)-paniculatine and (−)-bakkenolide III, and in the formal synthesis of (−)-pinguisenol and (−)-α-pinguisene.[2]

To the best of our knowledge, no reports so far have described the use of an α-carbonyl vinyl radical for intermolecular carbon–carbon bond formation. Herein, we report the intermolecular addition reactions of α-carbonyl vinyl radicals generated from α-iodo cycloalkenones with electron-withdrawing olefins (schematically shown in Scheme 1). This reaction has important synthetic value in the preparation of chiral α-substituted cyclic enones that are difficult to obtain by other methods. In order to demonstrate the versatility of this reaction, we also report a synthetic study of the formal synthesis of enantiopure fawcettimine by an intramolecular radical cyclization.



Scheme 1 Intermolecular addition reactions of α-carbonyl vinyl radicals with electron-withdrawing olefins.

Our experiment began by treating a refluxing benzene solution of 2-iodocyclohex-2-enone (**2**) and acrylonitrile (1 equiv.) with a benzene solution of Bu_3SnH (1.2 equiv.) and AIBN (0.12 equiv.); however, the expected amount of adduct was not obtained. We believe that one of the reasons leading to the failure of this reaction was the low concentration of acrylonitrile. To solve this problem, we examined the dependence of the amount of acrylonitrile on the yield of the product by increasing its amount from 3 equiv. up to 10 equiv. The desired adduct **2a** was then successfully obtained in yields of 13 and 39%, respectively. The yield of the adduct did not increase any further, even when the amount of acrylonitrile was increased above 10 equiv. In addition to the concentration of acrylonitrile, the concentration of the resulting α-carbonyl vinyl radical may also be an important factor in the success of this intermolecular radical addition reaction. If the concentration of the α-carbonyl vinyl radical is very high, the self-coupling reaction would be significant. Based on this consideration, we attempted to maintain a low concentration of generated radical at any given instant by using the slow addition method. We found that the yield of the product increased slightly; however, the reaction became more complicated, and some of the enone was recovered. Therefore, we used the intermittent addition method, in which the reaction was performed by adding a benzene solution (0.5 M with respect to Bu_3SnH) of AIBN (0.12 equiv.) and Bu_3SnH (1.2 equiv.) to a refluxing benzene solution (0.2 M with respect to α-iodocyclohexenone) of 2-iodocyclohex-2-enone and acrylonitrile (10 equiv.) eight times at 40 min intervals, after which **2a** was obtained in 60% yield. These were the most optimized reaction conditions for the intermolecular α-carbonyl vinyl radical addition reaction with olefins, and were applied in many other cases later. Several other sets of modified conditions were also examined; however, none were better than the present set.

In this study, four α-iodocycloalkenones, including 2-iodocyclopent-2-enone (**1**), 2-iodocyclohex-2-enone (**2**), 2-iodocyclohept-2-enone (**3**) and even (*R*)-2-iodo-5-methylcyclohex-2-enone (**5**) (in the study of the formal synthesis of fawcettimine), were employed as the radical donors and various electron-withdrawing olefins were used as radical acceptors. The final results are summarized in Table 1. In addition, vinyl acetate, which is an electron-rich olefin, was employed in this reaction; however, none of the desired adduct was obtained. Based on these experimental results, we suggest that α-carbonyl vinyl radicals are ideal electron-rich radical donors under radical reaction conditions. To demonstrate the synthetic utility of the intermolecular radical addition reaction, it was treated

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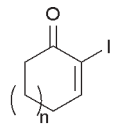
† Electronic supplementary information (ESI) available: Detailed experimental procedures, ^1H and ^{13}C NMR spectroscopic data, and analytical data of all the compounds in Table 1, and Scheme 1, Scheme 2 and Scheme 3. See DOI: 10.1039/b714078a

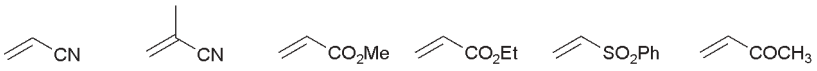
Table 1 Alkylation of α-iodo cycloalkenones with electron-withdrawing acceptors[a]

α-Iodo cycloalkenone



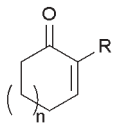
1 (n=0, 2-iodocyclopent-2-enone)
2 (n=1, 2-iodocyclohex-2-enone)
3 (n=2, 2-iodocyclohept-2-enone)

Radical acceptor



a **b** **c** **d** **e** **f**

Product (yield, %)



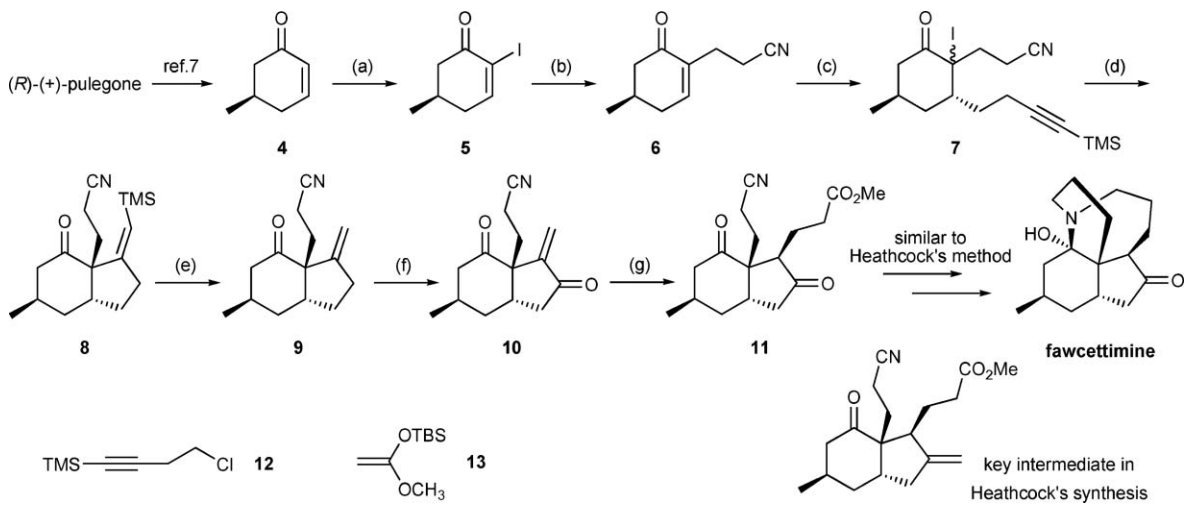
1a n=0, R=CH_2CH_2CN (42)	**2a** n=1, R=CH_2CH_2CN (60)	**3a** n=2, R=CH_2CH_2CN (45)
1b n=0, R=$CH_2CH(CH_3)CN$ (40)	**2b** n=1, R=$CH_2CH(CH_3)CN$ (58)	**3b** n=2, R=$CH_2CH(CH_3)CN$ (42)
1c n=0, R=$CH_2CH_2CO_2Me$ (31)	**2c** n=1, R=$CH_2CH_2CO_2Me$ (48)	**3c** n=2, R=$CH_2CH_2CO_2Me$ (35)
1d n=0, R=$CH_2CH_2CO_2Et$ (38)	**2d** n=1, R=$CH_2CH_2CO_2Et$ (52)	**3d** n=2, R=$CH_2CH_2CO_2Et$ (40)
1e n=0, R=$CH_2CH_2SO_2Ph$ (37)	**2e** n=1, R=$CH_2CH_2SO_2Ph$ (62)	**3e** n=2, R=$CH_2CH_2SO_2Ph$ (48)
	2f n=1, R=$CH_2CH_2COCH_3$ (9)	

[a] Intermittent addition (8 times at 40 min intervals) was performed. The detailed experimental procedure is described in the ESI.

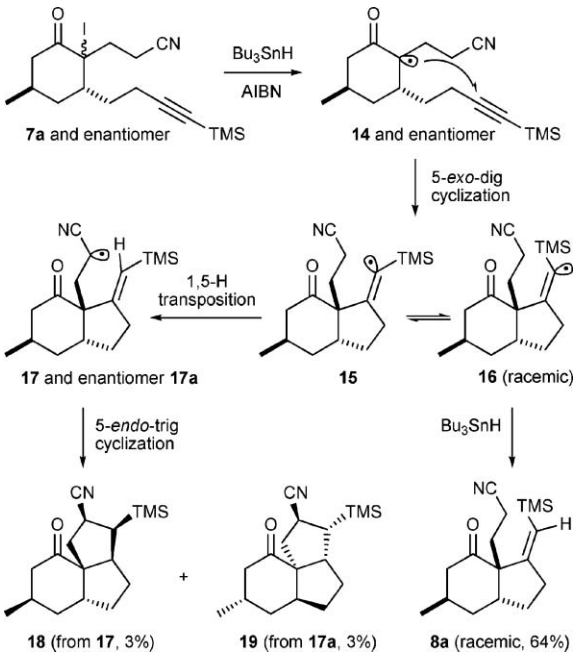
as an important step in the formal synthesis of enantiopure fawcettimine.

Fawcettimine was first isolated from extracts of the alkaloids of *Lycopodium fawcetti* collected in the Blue Mountain range of Jamaica by the Burnell group in 1959. Because of their potent acetylcholine esterase inhibition activity,[3] coupled with an extremely complex structure,[4] various different synthetic methodologies leading to this Lycopodium alkaloid were proposed and studied by many groups.[5] Unfortunately, the total or formal synthesis was a really difficult challenge. Until 1979, the first racemic total synthesis of fawcettimine was accomplished by Inubushi *et al.* using a Diels–Alder reaction as the key step.[5a] To date, there are only three total synthesis reports (Inubushi *et al.* in 1979,[5a] and Heathcock *et al.* in 1986[5c] and 1989[5d]) and one publication of the core skeleton synthesis (Mehta in 1991[5e]) of fawcettimine; however, none of them deals an enantiopure synthesis.

Herein, we propose a unique methodology for the formal synthesis of enantiopure fawcettimine by using chiral enone **4**[6] as the starting material, and inter- and intramolecular radical reaction sequences as the key steps. The synthetic scheme for obtaining compound **11**, whose structure is almost the same as that of the



Scheme 2 Reagents and conditions: (a) I_2, pyridine, CH_2Cl_2, 95%; (b) acrylonitrile, AIBN, Bu_3SnH, PhH, 70%; (c) **12**, Mg, CuI, TMSCl, HMPA, THF; NaI, *m*-CPBA, THF, 78% (2 steps); (d) Bu_3SnH, AIBN, PhH, slow addition, 60 °C, 64%; (e) TFA, CH_2Cl_2, 78%; (f) SeO_2, ^tBuOOH, CH_2Cl_2; Jones' reagent, 52%; (g) **13**, $LiClO_4$, Et_2O; AcOH, THF, H_2O, 40%.



Scheme 3 Proposed formation pathway of desired product **8a**, and by-products **18** and **19**.

key intermediate in Heathcock *et al.*'s synthesis of fawcettimine, is illustrated in Scheme 2. We suggest that compound **11** could be converted into fawcettimine *via* a procedure similar to Heathcock *et al.*'s process developed in 1989.[5d]

Optically pure cyano-enone **6** could be obtained in 70% yield from chiral α-iodoenone **5** *via* a intermolecular radical addition reaction with acrylonitrile. The CuI-mediated conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride was followed by the trapping of the resulting enolate with chlorotrimethylsilane (TMSCl) to obtain the trimethylsilyl enol ether. Without purification, the resulting enol ether was then treated with a mixture of NaI and *m*-CPBA to afford the unstable iodo ketone **7** in 78% yield. The intramolecular radical cyclization of **7** was then carried out by using a benzene solution of AIBN and Bu_3SnH, which was introduced using a syringe pump at reflux, and the desired cyclized product **8** was obtained in 64% yield. It is noteworthy that in the model study of fawcettimine, wherein the racemic 5-methylcyclohex-2-enone was used as the starting material, trace amounts of compounds **18** and **19** were separately isolated during the radical cyclization reaction and their structures ascertained by single crystal X-ray analysis.‡ This result may be rationalized by the 1,5-hydrogen transposition of vinyl radical **15**, formed by the 5-*exo*-dig cyclization of radical **14**, followed by the intramolecular 5-*endo*-trig radical cyclization of the resulting radical **17**. The proposed mechanism is illustrated in Scheme 3. Based on the single crystal X-ray analyses, we suggested that the relative stereochemistry of compounds **18** and **19** could be the indirect evidence that allows the relative stereochemistry of optically pure compound **11** to be assigned.

The exposure of compound **9** to SeO_2, followed by Jones' oxidation, gave the allylic oxidation product, enone **10**. The lithium perchlorate-mediated conjugate addition of freshly prepared ketene silyl acetal, **13**, to enone **10** afforded compound **11**, which was almost identical to the key intermediate in Heathcock's synthesis of fawcettimine, except for the carbonyl functionality on the five-membered ring.

In conclusion, a useful intermolecular radical addition reaction of α-iodo cycloalkenone has been described. The formal synthesis of enantiopure fawcettimine has been accomplished stereoselectively, during which inter- and intramolecular radical reactions were employed as key steps to facilitate the construction of the core skeleton of the product. Further applications using this strategy are currently under development in our laboratory.

Notes and references

‡ *Crystal data*: For **18**: $C_{17}H_{27}NOSi$, M = 289.49, T = 296(2) K, monoclinic, space group $P2_1/c$, a = 7.5791(14), b = 12.075(2), c = 19.243(4) Å, β = 91.904(3)°, V = 1760.1(6) Å^3, Z = 4, F(000) = 632, reflections collected: 10942, independent reflections: 4155 (R_{int} = 0.0240). Final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0499, $wR2$ = 0.1341; R indices (all data): $R1$ = 0.0780, $wR2$ = 0.1503.

For **19**: $C_{17}H_{27}NOSi$, M = 289.49, T= 296(2) K, monoclinic, space group $P2_1/c$, a = 11.6687(8), b = 12.3423(9), c = 12.2850(9) Å, β = 95.921(2)°, V = 1759.8(2) Å^3, Z = 4, F(000) = 632, reflections collected: 10218, independent reflections: 3920 (R_{int} = 0.0201). Final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0463, $wR2$ = 0.1348; R indices (all data): $R1$ = 0.0577, $wR2$ = 0.1435.

CCDC 663530 and 663530. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b714078a

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