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# Facile Preparation of Functionalized 1-Substituted Cycloalkenes via an Iodine Atom Transfer Radical Addition–Elimination Process

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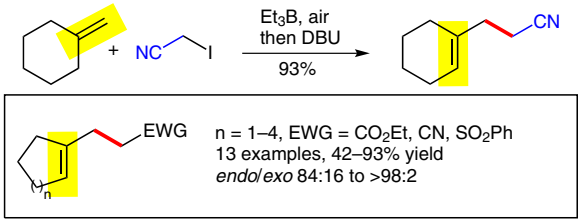


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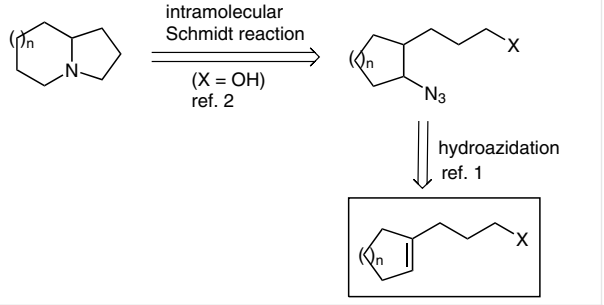
**Abstract** An efficient and scalable two-step one-pot procedure for the preparation of cycloalkenes substituted with a functionalized alkyl side chain is reported. This method is based on a triethylborane-mediated iodine atom transfer radical addition (ATRA) of 1-iodoesters and related compounds to methylenecycloalkanes followed by treatment of the intermediate tertiary iodide with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to promote a selective *endo* elimination.

**Key words** radical reaction, cycloalkenes, *endo* elimination, triethylborane, methylenecycloalkene

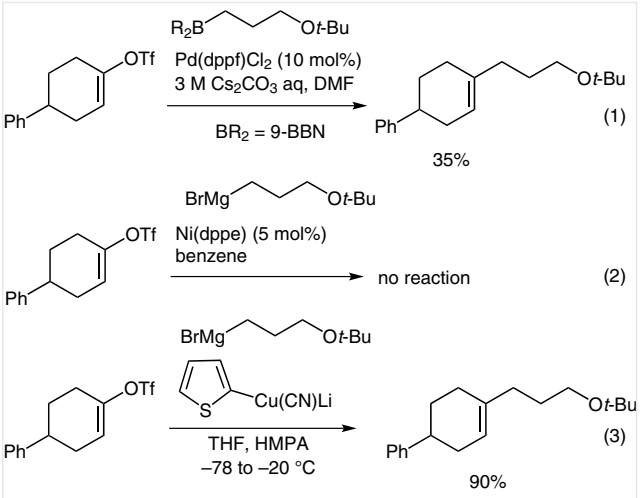
Recently, our group has developed the *anti*-Markovnikov hydroazidation of alkenes.[1] The azides resulting from the hydroazidation of 1-(3-hydroxyprop-1yl)cycloalkenes are potential precursors of indolizidine and related alkaloids via an intramolecular Schmidt reaction (Scheme 1).[2]




**Scheme 1** Retrosynthetic approach for the preparation of indolizidines and related alkaloid skeletons from 1-alkylcycloalkenes

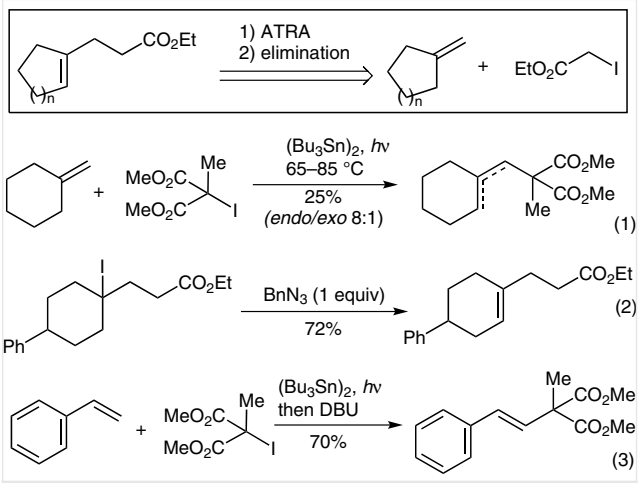
In order to study this chemistry, an efficient access to 1-(3-hydroxyprop-1yl)cycloalkenes was needed. Initially, we focused our attention on transition-metal-catalyzed cross-coupling reactions. Indeed, palladium- or nickel-catalyzed Suzuki–Miyaura or Kumada cross-coupling reactions as well as reactions involving higher order cuprates are powerful methods for the construction of C–C bonds starting from vinyl triflates.[3,4] This approach was tested with the cyclohexenyl triflate derived from cyclohexanone and a *tert*-butyl-protected 3-hydroxypropyl organometallic species (Scheme 2). Suzuki and Kumada cross-couplings gave either low yield or no product (Scheme 2, eq. 1 and 2). Better results were obtained with a higher-order cuprate (Scheme 2, eq. 3). However, scaling up this reaction and removal of the *tert*-butyl protecting group (the only protecting group that gave good results) proved to be difficult. Finally, the high price of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (Comins reagent) used for the formation of the alkenyl triflate led us to abandon this route and to find a more convenient and scalable method.

As an alternative approach, a radical addition of 1-iodoester to methylenecycloalkenes (easily available through methylenation of the corresponding ketones) under iodine atom transfer radical addition (ATRA) conditions followed by a base-induced *endo*-selective elimination could solve the problem (Scheme 3). Interestingly, Curran and coworkers reported a spontaneous HI elimination during the reaction between dimethyl methyliodomalonate and methylenecyclohexane.[5] A mixture of alkenes was obtained in low yields (25%) but encouraging *endo* selectivity (Scheme 3, eq. 1). More recently, we described that the product resulting from iodine ATRA to 4-phenylmethylenecyclohexane affords selectively the *endo*-alkene upon treatment with benzyl azide (Scheme 3, eq. 2).[6] Curran and coworkers reported



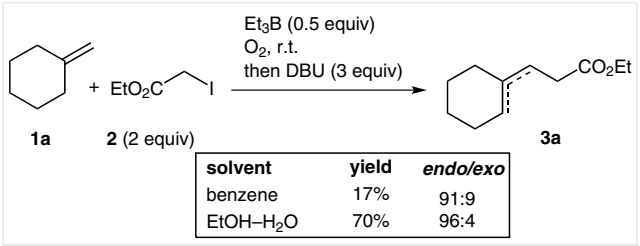

**Scheme 2** Initial attempts to prepare 1-alkylcyclohexane from cyclohexanone via cross-coupling reaction

during their pioneering work with dimethyl iodomethylmalonate[5] that a β-substituted styrene could be prepared by iodine ATRA onto styrene followed by treatment with 1,8-diazabicycloundec-7-ene (DBU) as a base to promote the elimination of HI (Scheme 3, eq. 3).




**Scheme 3** Atom transfer addition followed by DBU-promoted elimination by Curran et al.

Our initial investigation started with the triethylborane-induced reaction of methylenecyclohexane (**1a**) and ethyl 2-iodoacetate (**2**) followed by elimination with DBU in benzene as solvent (Scheme 4). We obtained the corresponding ester **3a** in 17% yield with an *endo*/*exo* selectivity of 91:9. Oshima and coworkers reported excellent results by running iodine ATRA reactions in aqueous media.[7,8] By using EtOH–$H_2O$ as solvent system we were able to increase the yield of **3a** to 70% with an increased regioselectivity for the elimination reaction (*endo*/*exo* = 96:4).



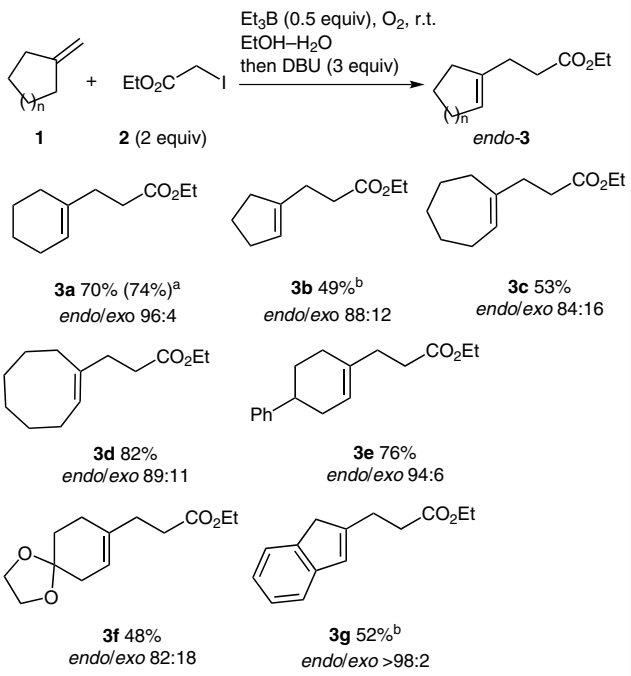

| solvent | yield | *endo*/*exo* |
|---|---|---|
| benzene | 17% | 91:9 |
| EtOH–$H_2O$ | 70% | 96:4 |

**Scheme 4** Iodine ATRA reaction of ethyl 2-iodoacetate (**2**) to methylenecyclohexane (**1a**) followed by DBU-promoted elimination

These optimized reaction conditions were then tested for an iodine ATRA–elimination sequence using iodoester **2** and several methylenecycloalkenes[9,10] **1a**–**g** (Scheme 5).[11] First, the influence of the ring size was examined. The five-, seven-, and eight-membered rings (**1b**–**d**) afforded the desired product in 49–82% yield. The *endo*/*exo* selectivities ranging from 84:16 (seven-membered ring) to 89:11 (eight-membered ring) were obtained. The higher *endo* selectivity obtained for the six-membered ring is ascribed to the perfect antiperiplanar diaxial arrangement of the iodine/hydrogen atoms in the chair conformation that favor the E2 elimination leading to the *endo* product **3a**. Next, we investigated the reaction of substituted methylenecyclohexanes **1e** and **1f**. The 4-phenylmethylenecyclohexane (**1e**) gave the alkene **3e** in good yield (76%) and excellent regioselectivity (*endo*/*exo* = 94:6). The dioxolanyl acetal **1f** gave the product in moderate yield (48%) and regioselectivity (*endo*/*exo* = 82:18). Finally, the reaction with 2-methyleneindane (**1g**) afforded the desired product **3g** in 52% yield as a single *endo* isomer.

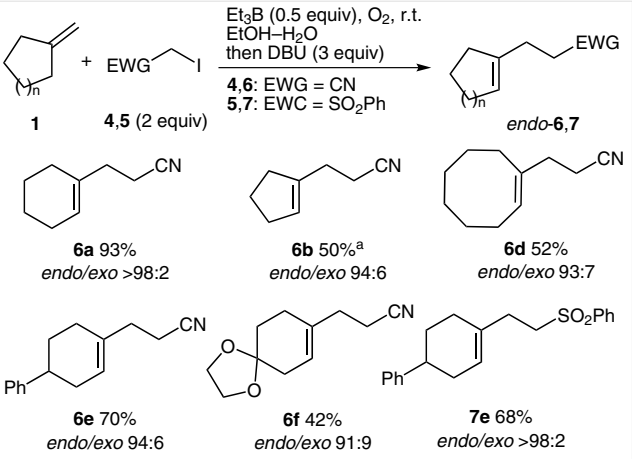
In order to demonstrate the scalability of the reaction, we prepared **3a** on multigram scale starting from 60 mmol of olefin **1a**. The alkene **3a** was obtained in 74% yield as a *endo*/*exo* mixture with a ratio of 96:4.[12] For the scale-up, a 3:1 EtOH–$H_2O$ mixture was used as a solvent in order to form a homogenous solution.

Finally, we turned our attention to the use of other iodides as precursors for the iodine ATRA–elimination sequence. Under the same reaction conditions, 2-iodoacetonitrile (**4**) and the iodomethyl phenyl sulfone (**5**)[13] were tested (Scheme 6). Reactions with nitrile **4** gave yields and regioselectivities similar or higher than the corresponding esters **3**. The reaction of the iodomethyl phenyl sulfone (**5**) with olefin **1e** showed the highest *endo*/*exo* selectivity (>98:2) of all iodides investigated with this substrate.




**Scheme 5** Atom transfer reactions with ethyl 2-iodoacetate **2**. Elimination selectivity was determined by $^1$H NMR spectroscopy [*endo*: (C=C*H*CH$_2$) δ = ca. 5.5 ppm; *exo* (C=CHC*H*$_2$) δ = ca. 3 ppm]. [a] 60 mmol scale reaction. [b] EtOH–H$_2$O (3:1) as solvent.

In conclusion, we have developed an iodine ATRA–elimination process that converts readily available methylenecycloalkenes into functionalized 1-substituted cycloalkenes. This method does not require the use of any transition metal and afforded the desired product in 48–93% yield and *endo*/*exo* selectivities ranging from 82:18 to >98:2. The applicability of the method to multigram synthesis has been demonstrated.




**Scheme 6** Atom transfer reactions with α-iodoacetonitrile (**4**) and iodomethyl phenyl sulfone (**5**). The *endo*/*exo* regioselectivity was determined by $^1$H NMR spectroscopy. [a] EtOH–H$_2$O (3:1) as solvent.

## Acknowledgment

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560555.

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(11) **General Procedure for Iodine ATRA–Elimination Reaction**
A solution of Et$_3$B (0.5 mL, 1.0 M in EtOH, 0.5 mmol) was added over 2 h by syringe pump to a stirred mixture of the iodide **2**, **4**, or **5** (2.0 mmol) and olefin **1** (1 mmol) in EtOH–H$_2$O (1:1, 10 mL) in the dark and open to air. After complete addition, the brown mixture was allowed to stir for 1 h at r.t. DBU (457 mg, 3 mmol) was added at 0 °C, and the mixture was stirred at r.t. overnight. After addition of a sat. aq solution of NH$_4$Cl (50 mL), the mixture was extracted with Et$_2$O (20 and 10 mL), and the organic phases were washed with brine (10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography.
**Ethyl 3-{1,2,3,6-Tetrahydro-[1,1′-biphenyl]-4-yl}propanoate (3e)**
Colorless and clear oil; 76% yield; *endo*/*exo* = 94:6. $^1$H NMR (300 MHz, CDCl$_3$): δ = 7.34–7.15 (m, 5 H), 5.54–5.48 (m, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 2.80–2.67 (m, 1 H), 2.47–2.40 (m, 2 H), 2.35–2.21 (m, 3 H), 2.20–1.91 (m, 4 H), 1.82–1.68 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 173.5, 147.1, 136.1, 128.3 (2 C), 126.9, 126.8, 126.0, 121.2, 60.3, 40.1, 33.4, 32.9, 32.6, 30.0, 28.9, 14.3. IR (neat): 3043, 2915, 2087, 1731, 1602, 1493, 1160, 916. HRMS (ESI-TOF): *m*/*z* calcd for C$_{17}$H$_{23}$O$_2$ [M + H]$^+$: 259.1693; found: 259.1691.
**3-{1,2,3,6-Tetrahydro-[1,1′-biphenyl]-4-yl}propanenitrile (6e)**
Colorless and clear oil; 70% yield; *endo*/*exo* = 94:6. $^1$H NMR (300 MHz, CDCl$_3$): δ = 7.32–7.26 (m, 2 H), 7.25–7.16 (m, 3 H), 5.67–5.61 (m, 1 H), 2.83–2.70 (m, 1 H), 2.51–2.47 (m, 2 H), 2.40–2.27 (m, 3 H), 2.26–2.10 (m, 2 H), 2.08–1.93 (m, 2 H), 1.85–1.71 (m, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 146.6, 133.9, 128.4 (2 C), 126.9 (2 C), 126.1, 123.6, 119.6, 39.8, 33.3, 33.0, 29.8, 28.5, 16.1. IR (neat): 3025, 2919, 2836, 2248, 1602, 1494, 1436, 908, 729,

699. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{18}N$ $[M + H]^+$: 212.1434; found: 212.1427.

**4-[2-(Phenylsulfonyl)ethyl]-1,2,3,6-tetrahydro-1,1′-biphenyl (7e)**

Amorphous white solid; 68% yield; *endo*/*exo* >98:2; mp 80–82 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.88 (m, 2 H), 7.72–7.52 (m, 3 H), 7.32–7.26 (m, 2 H), 7.32–7.25 (m, 3 H), 5.53–5.46 (m, 1 H), 3.28–3.18 (m, 2 H), 2.72–2.58 (m, 1 H), 2.46–2.37 (m, 2 H), 2.28–2.16 (m, 1 H), 2.15–2.00 (m, 2 H), 1.99–1.85 (m, 2 H), 1.75–1.57 (m, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 146.6, 139.3, 133.7, 133.4, 129.3, 128.4, 128.1, 126.8, 126.1, 123.2, 54.8, 39.7, 33.3, 30.3, 29.7, 28.8. IR (neat): 2939, 2892, 2831, 1495, 1446, 1305, 1283, 1147, 1139, 1121, 1088, 887. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{23}O_2S$ $[M + H]^+$: 327.1413; found: 327.1404.

(12) **Scale-up Experiment for Ethyl 3-(Cyclohex-1-en-1-yl)propanoate (3a)**

A solution of $Et_3B$ (30 mL, 1.0 M in EtOH, 30 mmol) was added over 2 h by syringe pump to a stirred solution of ethyl 2-iodoacetate (**2**, 25.68 g, 120 mmol) and methylenecyclohexane (**1a**, 5.77 g, 60 mmol) in EtOH–$H_2O$ (3:1, 60 mL) in the dark and open to air. After complete addition, the brown mixture was allowed to stir for 2 h at r.t. DBU (27.40 g, 180 mmol) was added at <10 °C, and the mixture was stirred at r.t. overnight. After addition of a sat. aq solution of $NH_4Cl$ (150 mL), the mixture was extracted with pentane (150 and 75 mL), and the organic phases were washed with $H_2O$ (75 mL), dried over $Na_2SO_4$, and concentrated. The crude product was purified by column chromatography ($Et_2O$–pentane, 5:95) to provide **3a** (8.06 g, 74%) as a colorless and clear oil. $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.45–5.37 (m, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 2.45–2.33 (m, 2 H), 2.25 (t, *J* = 7.7 Hz, 2 H), 2.02–1.87 (m, 4 H), 1.67–1.47 (m, 4 H), 1.25 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 173.6, 136.1, 121.6, 60.2, 33.1, 33.0, 28.3, 25.2, 22.9, 22.4, 14.3. IR (neat): 2925, 1733, 1445, 1368, 1340, 1288, 1248, 1157, 1081, 1038, 919, 856, 838 $cm^{-1}$. HRMS (ESI-TOF): *m/z* calcd for $C_{11}H_{18}O_2Na$ $[M + Na]^+$: 205.1199; found: 205.1193.

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