Ruthenium-Catalyzed Heck-Type Alkenylation of Alkyl Bromides

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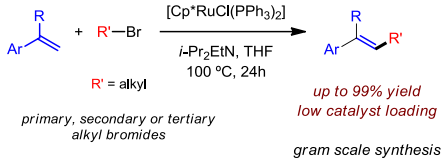
ABSTRACT: The complex [Cp*RuCl(PPh$_3$)$_2$] displays a high catalytic activity for the Heck-type alkenylation of alkyl bromides, in the first example using this metal under thermal conditions. The coupling reaction proceeds efficiently with a variety of functionalized tertiary, secondary, and primary alkyl bromides. The presence of Hünig's base has been revealed crucial for this transformation. Preliminary mechanistic studies support the participation of alkyl radicals in the reaction.

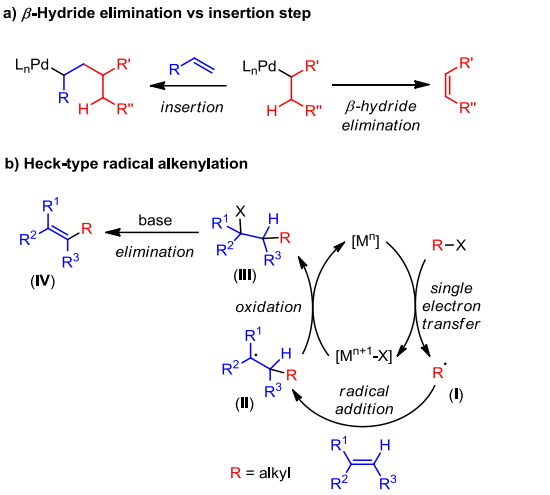


KEYWORDS : *ruthenium catalysis, alkenylation, cross-coupling, single electron transfer, homogeneous catalysis.*

The palladium-catalyzed Heck reaction has become a fundamental tool for carbon–carbon bond formation in organic synthesis.[1] Although a number of examples have been reported for the alkenylation of aryl and vinyl halides and sulfonates, the use of alkyl halides as the electrophile partner still remains an important challenge.[2] This limitation is mainly due to the tendency of alkyl-palladium intermediates to undergo *β*-hydride elimination competing with the olefin insertion step (Scheme 1a). As an alternative strategy, transition metal-catalyzed Heck-type radical reactions have emerged in recent years,[3] where the metal center triggers a single electron transfer (SET) to an alkyl organic halide (RX) to generate a carbon-centered radical **I** (Scheme1b, I). The addition of the latter to an olefin generates a new carbon–carbon bond and another radical **(II)**, that undergoes a deactivation step in which the metal is reduced to the initial oxidation state and the addition product is formed **(III)**. Next, the presence of a base affords the formal Heck coupling product **(IV)**, recovering the alkenyl functionality. This mechanism resembles somehow that of the atom transfer radical addition (ATRA) reactions.[4]

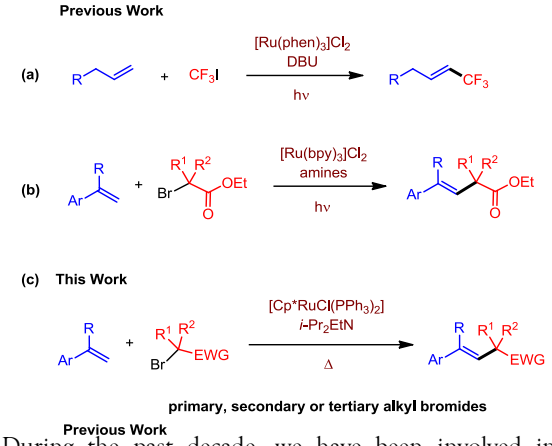
In the past few years, several catalytic systems have been described for radical Heck-type alkenylations.[5] Among them, Pd, Ni, Cu, and Fe have provided the best results,[6] although highly-efficient catalyst systems are yet scarce.[7] In general, large amounts of catalyst are need (10–30 mol%), thus limiting potential practical applications. Surprisingly, in spite of the work from Severin,[8] Demonceau[9] and Stephenson[10] groups

Scheme 1. (a) The Competing *β*-Hydride Elimination in Palladium-Catalyzed Heck Reactions using Alkyl Halides; (b) Mechanistic Proposal for the Transition Metal-Catalyzed Radical Alkenylation of Alkyl Halides.



with ruthenium-based complexes toward ATRA reactions, their use in the radical Heck-type alkenylations is limited to just two examples provided, independently, by Cho and Lei, and operating under photolysis activation (Scheme 2).[11]

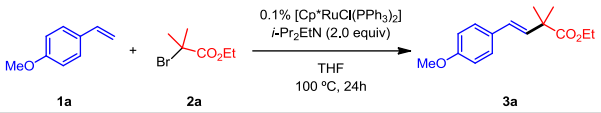
Scheme 2. Ruthenium-catalyzed alkenylation of alkyl halides.



During the past decade, we have been involved in the development of highly efficient and selective catalyst systems for ATRA reactions and related processes.[5] In view of the aforementioned similarities with such transformation and the lack of efficient ruthenium-based catalytic systems for the alkenylation of alkyl halides, we have turned our attention into a well-defined and commercially available ruthenium complex as a potential catalyst. In particular, we have investigated the coupling of styrenes and alkyl bromides in the presence of the complex $[Cp^*RuCl(PPh_3)_2]$, an ATRA catalyst previously reported by Demonceau and co-workers.[7] Herein we report the remarkable catalytic activity displayed by this complex in the alkenylation of alkyl bromides, with broad substrate scope and degrees of conversions much higher than the previously described Ru-based photocatalysts,[11] which are at least comparable to the best catalytic systems known to date.[7]

We initiated our research by exploring the benchmarking reaction of 4-methoxystyrene with ethyl 2-bromo-2-methylpropionate toward the formation of the corresponding styrene derivative **3a** in the presence of $[Cp^*RuCl(PPh_3)_2]$ as the catalyst. Optimization of the reaction conditions provided us with a method that affords **3a** in quantitative yield (Table 1, entry 1). Control reactions established the importance of the Ru complex and *i*-Pr_2EtN (Hünig's base) for efficient coupling under these conditions (entries 2–3): the reaction can be accomplished in high yield with TONs up to 4300 (entry 4), although the use of a very low catalyst loading resulted in considerably less coupling product formation (entry 5, no further reaction after 24 h). Remarkably, other Ru-based complexes, previously described as active ATRA[13] or Heck catalysts[5b] such as first generation Grubbs catalyst or $[RuCl_2(p\text{-cymene})]_2$ were less effective than complex $[Cp^*RuCl(PPh_3)_2]$ for this transformation (entries 6–7). While our standard reaction conditions employ the Hünig's base, the use of other organic or inorganic bases led to substantially less product formation (entries 8–10). Regarding the effect of the solvent, coupling reaction proceeds less efficiently when MeCN, DMF, or toluene were used as the solvent instead of THF (entries 11–13). Experiments carried out at room temperature (entry 14), 50 °C (entry 15), with shorter reaction times (entry 16), or in the presence of a small amount of air (entry 17) reduced the reaction outcome at different extent. On the other hand, the addition of a small amount of water did not alter the final yield (entry 18).

Table 1. Ruthenium-catalyzed alkenylation of an alkyl bromide: effect of reaction parameters.[a]



entry	variation from the standard conditions	yield **3a** [%][b]
1	none	>99
2	no $[Cp^*RuCl(PPh_3)_2]$	<1
3	no base	17
4	0.02% $[Cp^*RuCl(PPh_3)_2]$	86
5	0.01% $[Cp^*RuCl(PPh_3)_2]$	12
6	$[RuCl_2(p\text{-cymene})]_2$, instead of $[Cp^*RuCl(PPh_3)_2]$	6
7	Grubbs 1st catalyst, instead of $[Cp^*RuCl(PPh_3)_2]$	11
8	Cs_2CO_3, instead of *i*-Pr_2EtN	0
9	K_2CO_3, instead of *i*-Pr_2EtN	79
10	2,3,5-collidine, instead of *i*-Pr_2EtN	52
11	CH_3CN instead of THF	95
12	DMF instead of THF	17
13	toluene instead of THF	90
14	room temperature	13
15	50 °C	60
16	14 h	90
17	under air (capped ampoule)	15
18	0.5 equiv H_2O added	98
19	in the dark	>99
20	in the dark, using $[Ru(bpy)_3]Cl_2$ instead of $[Cp^*RuCl(PPh_3)_2]$	0

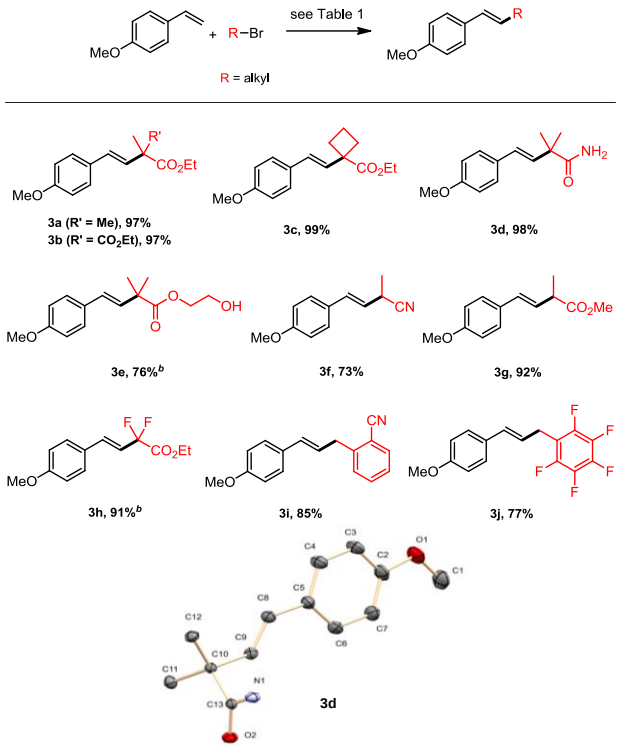
[a]See SI for full details. 0.2 mmol of 4-methoxystyrene and 2 equiv of **2a** were employed. [b]Yields were determined via ^1H NMR analysis versus diphenylmethane as internal standard.

Since previous work by Lei using $Ru(bpy)_2Cl_2$ employed photochemical conditions[11b] for this transformation, control experiments have been carried out to assess the influence of light in our system. When the probe reaction was carried out in the dark, the same quantitative formation of **3a** was observed (Table 1,entry 19). At variance with that, $[Ru(bpy)_3]Cl_2$ did not induce the catalytic reaction in the dark (entry 20). These experiments evidence that $[Cp^*RuCl(PPh_3)_2]$ operates under thermal conditions, with no effect of external light.

Once established reaction conditions, we then examined the scope of this ruthenium-catalyzed method for alkenylation by coupling a variety of tertiary, secondary and even primary alkyl bromides with 4-methoxystyrene (Scheme 3). The reaction proceeds in good to excellent yields and is compatible with a variety of functional groups, including ester, amide, alcohol, and nitrile. Moreover, a difluoroalkyl bromide and a perfluorinated benzyl bromide can be employed as reactants with moderate to high yields. Derivative **3d** has been characterized by X-ray studies (CCDC 1899012) to unambiguously demonstrate the structure of the compounds obtained by this methodology, showing the trans geometry of the substituent of the C=C bond. To test the practical applicability of the protocol, we have run a gram scale coupling reaction of 4-methoxystyrene with ethyl 2-bromo-2-

methylpropionate that proceeds in 97% yield (1.20 g of product **3a**).

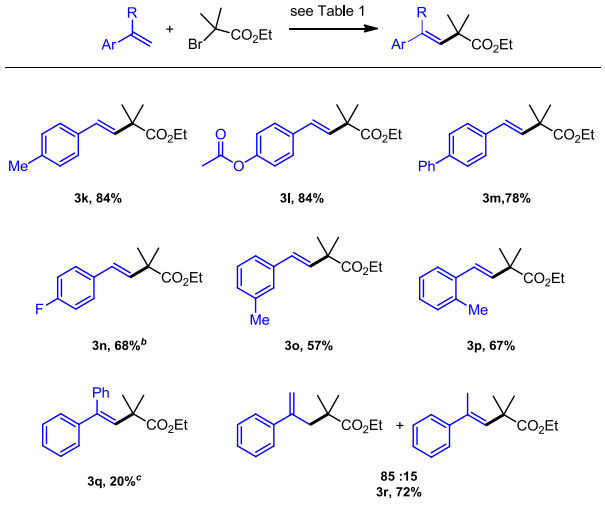
Scheme 3. Scope of ruthenium-catalyzed radical alkenylation with respect to the alkyl halide.[a]



[a]0.5 mmol of alkene employed. Yields as average of two experiments. [b]1 mol % of **1** was used.

With respect to the alkene, the scope of this method for the alkenylation of alkyl halides is also broad (Scheme 4). Thus, styrene derivatives bearing a variety of substitution patterns serve as suitable coupling partners, including electron-rich and

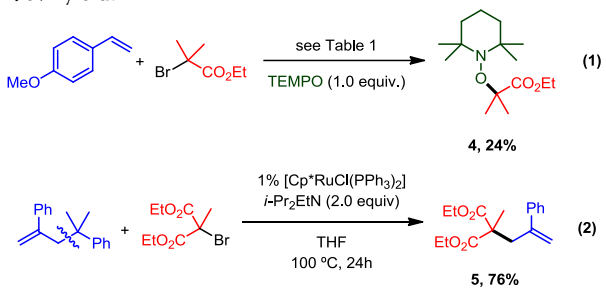
Scheme 4. Scope of ruthenium-catalyzed radical alkenylation with respect to the alkene.[a]



[a]0.5 mmol of alkene employed. Yields as average of two experiments. [b]1 mol % of **1** was used. [c]Yield determined via ^{1}H NMR analysis versus diphenylmethane as internal standard.

electron-poor substrates with yields within the range 57-84%. However, the reaction proceeds less efficiently when using a sterically hindered styrene (Scheme 4, **3q**). The reaction with α–methylstyrene gave the corresponding alkenylation product **3r** as a mixture of *endo*- and *exo*-isomers (85:15) in 72% yield. Aliphatic olefins such as 1-hexene or those bearing electron-withdrawing groups such as *n*-butyl acrylate do not verify this transformation.

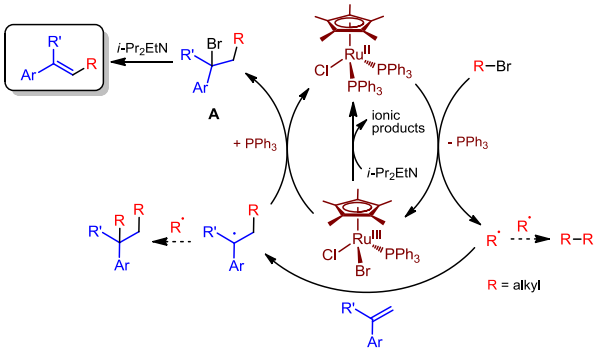
To gain insights on the reaction mechanism, we have used radical scavengers to gather evidence for the presence of radical intermediates. The standard reaction (Table 1, entry 1) in the presence of 1.0 equiv of BHT (2,6-di-*tert*-butyl-4-methylphenol) proceeds with quantitative yield. However, the addition of 1.0 equiv TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) at the beginning of a standard experiment induced the complete inhibition of the catalytic reaction, and the isolation of the alkylated TEMPO product **4** from the reaction mixture in 24% yield (eq 1).[14] This effect of TEMPO was verified in a separate standard experiment that was treated with such radical scavenger after 2 h of reaction, the formation of **3a** being inhibited at that precise moment. This is in agreement with the involvement of C-centred radicals in this transformation. In line with that, when a cumyl-containing α–alkylstyrene (2,4-diphenyl-4-methyl-1-pentene) was employed as reactant (eq 2), we observed a C-C bond-cleavage reaction,[15] in which a stable cumyl radical is the leaving group, leading to the formation of **5** in 76% yield.



Tertiary amines have been proposed as reducing agents in copper-catalyzed ATRP reactions[16] and could be responsible for the in situ constant regeneration of the active Ru(II) catalyst in the event of radical recombination reactions. We have monitored the reaction of the catalyst with the alkyl bromide **2a** at room temperature by ^{31}P{^{1}H} NMR. After 6 h, the spectrum remained unmodified, only a small amount of free PPh_3 being detected along with the catalyst. The sample was then heated at 100 °C for 14 h, leading to the disappearance of the resonance of the catalyst, and the appearance of free PPh_3 and a new species at 24.5 ppm, in the typical range for similar Ru(III) complexes.[17] Volatiles were removed, the residue dissolved in tol-d_8, and amine was added (no alkyl bromide is present in the mixture at this stage). The presence of the catalyst was inferred by NMR studies, where the resonance of the initial Ru(II) complex was observed upon heating a 100 °C for 2 h (see Supporting Information). These results demonstrate that the alkyl bromide induces the Ru(II)- Ru(III) oxidation whereas the amine originates the Ru(III)-Ru(II) reduction. We have also looked after the generation of nanoparticles that might be responsible for the catalytic reaction. Toward that end we have monitored the reaction in an effort to detect induction periods in which the nanoparticles are formed (see Supporting Information). However, no such periods have been observed, discarding the presence of Ru-NPs in the reaction mixture.

With this information, and the related work in the literature,[3,6] a plausible mechanistic explanation is provided in Scheme 5. The half-sandwich ruthenium(II) complex induces the formation of carbon-centered radicals by a SET process. The anti-Markovnikov addition of the radicals across the olefin delivers another radical species capable of reducing the ruthenium(III) center to the initial oxidation state, affording ATRA product **A**. The based-induced elimination reaction from the latter leads to the final, the formal Heck coupling product. In an effort to detect the intermediate ATRA product **A**, we run the reaction leading to product **3j** (where the less reactive primary site is involved) at 50 °C. NMR spectra showed a mixture of both ATRA and Heck products (see Supporting Information). Additionally, in the event of the coupling of

Scheme 5. Mechanistic proposal for the thermal Ru-catalyzed alkenylation of alkyl bromides.



radical species, the amine acts as a reducing agent which ensures the reduction of the Ru(III) species into the Ru(II) catalyst to re-start the catalytic cycle. Thus, amine can operate in two distintc parts of the catalytic cycle.

In conclusion, we have developed a new ruthenium-catalyzed radical alkenylation protocol, in the first example with this metal under thermal conditions. Well-defined and commercially available [Cp*RuCl(PPh$_3$)$_2$] catalyzed the reaction with high efficiency with the aid of Hünig's base. The reaction proceeds under simple reaction conditions, with broad functional-group tolerance, and the substrate scope covers tertiary, secondary, and even primary alkyl bromides. We have found evidences supporting the dual role of the base, promoting not only the elimination reaction of the ATRA product but also avoiding the catalyst deactivation.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, reactions were carried out under nitrogen atmosphere with standard Schlenck techniques or in a glovebox (MBRAUN UNILAB). All solvents and reagents employed were purchased from Aldrich, Acros, TCI, or dried in a solvent purification system (MB SPS-800, MBRAUN). Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck 60 F254) and UV light as visualizing agent or phosphomolybdic acid solution as developing agent. Chromatography purifications were carried out using silica gel (0.035-0.070 mm, 60 Å). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. NMR spectra were recorded at 298 K on an Agilent 400 MR and Agilent 500 DD2 spectrometers. Chemical shift values for ^{1}H and ^{13}C are reported as δ values (ppm) relative to the deuterated solvent and coupling constants (*J*) in Hz. The multiplicities are stated as follows: s = singlet, br = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Crystal structure determinations were carried out using a BRUKER D8 FIXED-CHI diffractometer equipped with an Oxford Cryosystems low-temperature device. Melting points were determined employing a Dynalon-Stuart SMP10 instrument. Mass spectra were obtained on a Orbitrap Elite mass spectrometer. Ionization method: ESI (positive or negative).

General Procedure: Heck-type Alkenylation of Alkyl Bromides by Employing [Cp*RuCl(PPh$_3$)$_2$] Complex. Under an atmosphere of N_2, a glass ampoule equipped with a stir bar was charged in turn with the corresponding amount of [Cp*RuCl(PPh$_3$)$_2$] (0.0005 mmol, 0.1%) from a THF stock solution, the olefin (0.5 mmol), the alkyl bromide (1 mmol), *N*,*N*-diisopropylethylamine (1 mmol), and dry THF to a total volume of 1.5 mL. The ampoule was placed in an oil bath and the mixture was stirred for 24 h at 100 °C. Next, the mixture was passed through a short plug of silica gel and the solvent was removed.

(E)-ethyl4-(4-methoxyphenyl)-2,2-dimethylbut-3-enoate (**3a**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (5% EtOAc/hexanes→10% EtOAc/hexanes). Colorless oil (120.0 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.36 (d, *J* = 16.2 Hz, 1H), 6.24 (d, *J* = 16.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 1.38 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.4 (s), 159.0 (s), 132.4 (s), 129.9 (s), 127.4 (s), 127.3 (s), 113.9 (s), 60.7 (s), 55.3 (s), 44.3 (s), 25.1 (s), 14.2 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{20}O_3Na$ 271.1305; found 271.1308. Data obtained were in accordance with those previously reported.[6b]

(E)-diethyl-2-(4-methoxystyryl)-2-methylmalonate (**3b**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), diethyl 2-bromo-2-methylmalonate (253.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (5% EtOAc/hexanes→20% EtOAc /hexanes). Colorless oil (149.0 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 16.4 Hz, 1H), 6.42 (d, *J* = 16.4 Hz, 1H), 4.25 – 4.11 (m, 4H), 3.77 (s, 3H), 1.63 (s, 3H), 1.24 (t, *J* = 6.9 Hz, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.2 (s), 159.4 (s), 130.1 (s), 129.3 (s), 127.8 (s), 125.4 (s), 113.9 (s), 61.6 (s), 55.6 (s), 55.3 (s), 20.4 (s), 14.0 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{22}O_5Na$ 329.1359; found 329.1360. Data obtained were in accordance with those previously reported.[6a]

(E)-ethyl-1-(4-methoxystyryl)cyclobutanecarboxylate (**3c**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), ethyl 1-bromocyclobutanecarboxylate (207.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (5% EtOAc/hexanes→10% EtOAc /hexanes). Colorless oil (129.0 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 16.1 Hz, 1H), 6.30 (d, *J* = 16.0 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.62 – 2.53 (m, 2H), 2.27 – 2.18 (m, 2H), 1.97 – 1.85 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.7 (s), 159.0 (s), 129.7 (s), 129.2 (s), 128.2 (s), 127.4 (s), 113.9 (s), 60.7 (s), 55.2 (s), 49.9 (s), 30.9 (s), 15.9 (s), 14.2 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1305; found 283.1307. Data obtained were in accordance with those previously reported.[6a]

(E)-4-(4-methoxyphenyl)-2,2-dimethylbut-3-enamide (**3d**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), 2-bromo-2-methylpropionamide (166.0 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (Et_2O→20% EtOAc/Et_2O). White solid (107.6 mg, 98%). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 16.3 Hz, 1H), 6.22 (d, *J* = 16.2 Hz, 1H), 3.80 (s, 3H), 1.39 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 179.0 (s), 159.3 (s), 132.3 (s), 129.3 (s), 128.7 (s), 127.5 (s), 114.1 (s), 55.3 (s), 44.7 (s), 25.3 (s) ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{17}O_2NNa$ 242.1152; found 242.1154. Mp: 151−152 °C.

(E)-2-hydroxyethyl 4-(4-methoxyphenyl)-2,2-dimethylbut-3-enoate (**3e**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (4.0 mg, 0.005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), 2-hydroxyethyl 2-bromoisobutyrate (211.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (10% Et_2O/DCM→50% Et_2O/DCM). Colorless oil (100.3 mg, 76%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.38 (d, *J* = 16.2 Hz, 1H), 6.23 (d, *J* = 16.2 Hz, 1H), 4.25 – 4.17 (m, 2H), 3.81 (br, 2H), 3.78 (s, 3H), 1.87 (br, 1H), 1.40 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 176.9 (s), 159.1 (s), 131.8 (s), 129.7 (s), 127.7 (s), 127.5 (s), 114.0 (s), 66.5 (s), 61.4 (s), 55.3 (s), 44.5 (s), 25.2 (s) ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{20}O_4Na$ 287.1254; found 287.1258.

(E)-4-(4-methoxyphenyl)-2-methylbut-3-enenitrile (**3f**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), 2-bromopropionitrile (134.0 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (hexanes→5% EtOAc /hexanes). Colorless oil (68.0 mg, 73%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.63 (dd, *J* = 15.8, 1.4 Hz, 1H), 5.90 (dd, *J* = 15.8, 6.2 Hz, 1H), 3.79 (s, 3H), 3.49 – 3.43 (m, 1H), 1.47 (d, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.7 (s), 131.9 (s), 128.4 (s), 127.8 (s), 122.1 (s), 121.1 (s), 114.1 (s), 55.3 (s), 28.4 (s), 19.2 (s) ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{13}ONNa$ 210.0889; found 210.0886. Data obtained were in accordance with those previously reported.[18]

(E)-methyl 4-(4-methoxyphenyl)-2-methylbut-3-enoate (**3g**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), methyl 2-bromopropionate (167.0 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (EtOAc) and purified by column chromatography on silica gel (hexanes→5% EtOAc /hexanes). Colorless oil (102.0 mg, 93%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.11 (dd, *J* = 15.9, 8.1 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.32 – 3.23 (m, 1H), 1.34 (d, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 175.0 (s), 159.1 (s), 130.5 (s), 129.5 (s), 127.4 (s), 126.4 (s), 113.8 (s), 55.2 (s), 51.8 (s), 43.0 (s), 17.4 (s) ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{16}O_3Na$ 243.0992; found 243.0993. Data obtained were in accordance with those previously reported.[6c]

(E)-ethyl 2,2-difluoro-4-(4-methoxyphenyl)but-3-enoate (**3h**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (4.0 mg, 0.005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), ethyl bromodifluoroacetate (195.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (dichloromethane). Colorless oil (116.1 mg, 91%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 1H), 7.00 (dt, *J* = 16.2, 2.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.14 (dt, *J* = 16.2, 11.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 1H), 3.81 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 164.1 (t, *J* = 35.2 Hz), 160.7 (s), 136.3 (t, *J* = 9.5 Hz), 128.9 (s), 126.8 (s), 116.3 (t, *J* = 25.0 Hz), 114.2 (s), 112.9 (t, *J* = 248.2 Hz), 63.0 (s), 55.3 (s), 13.9 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]+ calcd for $C_{13}H_{14}O_3F_2Na$ 279.0803; found 279.0805. Data obtained were in accordance with those previously reported.[19]

(E)-2-(3-(4-methoxyphenyl)allyl)benzonitrile (**3i**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), 2-(bromomethyl)benzonitrile (196.0 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (5% EtOAc /hexanes→10% EtOAc /hexanes). Colorless oil (106.0 mg, 85%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.36 – 7.22 (m, 3H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.26 – 6.13 (m, 1H), 3.81 (s, 3H), 3.75 (d, *J* = 7.0 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.1 (s), 144.3 (s), 132.9 (s), 131.9 (s), 129.7 (s), 127.4 (s), 126.7 (s), 124.2 (s), 118.0 (s), 113.9 (s), 112.4 (s), 55.3 (s), 37.7 (s) ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{15}ONNa$ 272.1046; found 272.1049. Data obtained were in accordance with those previously reported.[6m]

(E)-1,2,3,4,5-pentafluoro-6-(3-(4-methoxyphenyl)allyl)benzene (**3j**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (0.4 mg, 0.0005 mmol), 4-methoxystyrene (67.1 mg, 0.5 mmol), 2,3,4,5,6-pentafluorobenzyl bromide (261.0 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (hexanes→10% EtOAc /hexanes). White solid (121.0 mg, 77%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.09 (dt, *J* = 15.7, 6.8 Hz, 1H), 3.81 (s, 3H), 3.58 (dd, *J* = 6.8, 1.5 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.2 (s), 144.9 (dm, *J* = 245.7 Hz), 139.5 (dm, *J* = 250.2 Hz), 137.5 (dm, *J* = 250.2 Hz), 131.8 (s), 129.3 (s), 127.4 (s), 122.0 (s), 113.9 (s), 113.7 (m), 55.3 (s), 25.6 (s) ppm. HRMS (EI-magnetic sector) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}OF_5$ 315.0803; found 315.0802. Mp: 68−69 °C. Data obtained were in accordance with those previously reported.[20]

(E)-ethyl 2,2-dimethyl-4-(p-tolyl)but-3-enoate (**3k**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (0.4 mg, 0.0005 mmol), 4-methylstyrene (59.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (hexanes→10% EtOAc /hexanes). Colorless oil (97.3 mg, 84%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.39 (d, *J* = 16.2 Hz, 1H), 6.33 (d, *J* = 16.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 2.31 (s, 2H), 1.38 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 176.4 (s), 137.1 (s), 134.3 (s), 133.5 (s), 129.2 (s), 127.7 (s), 126.2 (s), 60.7 (s), 44.3 (s), 25.1 (s), 21.1 (s), 14.2 (s) ppm. Elemental analysis calculated for $C_{15}H_{20}O_2$ C, 77.55; H, 8.68; N, 0.00. Found: C, 77.41; H, 9.66; N, <0.1. Data obtained were in accordance with those previously reported.[6b]

(E)-ethyl 4-(4-acetoxyphenyl)-2,2-dimethylbut-3-enoate (**3l**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (0.4 mg, 0.0005 mmol), 4-acetoxystyrene (81.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (10% EtOAc /hexanes →30% EtOAc /hexanes). Colorless oil (138.2 mg, 84%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 16.2 Hz, 1H), 6.33 (d, *J* = 16.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.38 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 176.1 (s), 169.4 (s), 149.8 (s), 135.0 (s), 134.8 (s), 127.2 (s), 126.9 (s), 121.6 (s), 60.8 (s), 44.3 (s), 25.0 (s), 21.1 (s), 14.1 (s) ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{20}O_4Na$ 299.1254; found 299.1255.

(E)-ethyl 4-([1,1'-biphenyl]-4-yl)-2,2-dimethylbut-3-enoate (**3m**). The title compound was synthesized according to the general procedure from $[Cp^*RuCl(PPh_3)_2]$ (0.4 mg, 0.0005 mmol), 4-vinylbiphenyl (90.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N*,*N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (hexanes→10% EtOAc /hexanes). White solid (115.2 mg, 78%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.39 (m, 4H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.55 – 6.28 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.41 (s, 6H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 176.3 (s), 140.7 (s), 140.1 (s), 136.2 (s), 134.6 (s), 128.8 (s), 127.5 (s), 127.3 (s), 127.2 (s), 126.9 (s), 126.8 (s), 60.8 (s), 44.5 (s), 25.1 (s), 14.2 (s) ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for

$C_{20}H_{22}O_2Na$ 317.1512; found 317.1511. Mp: 50−51 °C. Data obtained were in accordance with those previously reported.[6c]

(E)-ethyl-4-(4-fluorophenyl)-2,2-dimethylbut-3-enoate (**3n**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (4.0 mg, 0.005 mmol), 4-fluorostyrene (61.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N,N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (dichloromethane). Colorless oil (80.2 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.00 – 6.95 (m, 2H), 6.37 (d, *J* = 16.2 Hz, 1H), 6.30 (d, *J* = 16.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.38 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) (126 MHz, $CDCl_3$) δ 176.2 (s), 162.2 (d, *J* = 246.5 Hz), 134.2 (d, *J* = 2.2 Hz), 133.3 (d, *J* = 3.3 Hz), 127.8 (d, *J* = 7.9 Hz), 126.7 (s), 115.4 (d, *J* = 21.6 Hz), 60.8 (s), 44.3 (s), 25.1 (s), 14.2 (s) ppm. HRMS (EI-magnetic sector) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}O_2F$ 237.1285; found 237.1288. Data obtained were in accordance with those previously reported.[6b]

(E)-ethyl-2,2-dimethyl-4-(m-tolyl)but-3-enoate (**3o**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), 3-methylstyrene (59.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N,N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (hexanes→10% EtOAc /hexanes). Colorless oil (66.5 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 3H), 7.03 (dtd, *J* = 6.9, 1.7, 0.7 Hz, 1H), 6.42 – 6.34 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.39 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.3 (s), 138.1 (s), 137.1 (s), 134.3 (s), 128.4 (s), 128.2 (s), 128.0 (s), 127.0 (s), 123.5 (s), 60.8 (s), 44.4 (s), 25.1 (s), 21.4 (s), 14.2 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{20}O_2Na$ 255.1356; found 255.1357.

(E)-ethyl-2,2-dimethyl-4-(o-tolyl)but-3-enoate (**3p**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), 2-methylstyrene (59.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N,N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (hexanes →10% EtOAc /hexanes). Colorless oil (77.9 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 1H), 7.18 – 7.09 (m, 3H), 6.62 (d, *J* = 16.1 Hz, 1H), 6.24 (d, *J* = 16.0 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 1.40 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.3 (s), 136.4 (s), 136.1 (s), 135.3 (s), 130.2 (s), 127.3 (s), 126.0 (s), 125.8 (s), 125.7 (s), 60.8 (s), 44.6 (s), 25.2 (s), 19.7 (s), 14.2 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{20}O_2Na$ 255.1356; found 255.1359.

Ethyl-2,2-dimethyl-4-phenylpent-4-enoate (**3r**). The title compound was synthesized according to the general procedure from [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), α-methylstyrene (59.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N,N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The reaction was purified by column chromatography on silica gel (hexanes→10% EtOAc /hexanes). Colorless oil (83.7 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 5H), 5.21 (d, *J* = 1.8 Hz, 1H), 5.03 (s, 1H), 3.71 (q, *J* = 7.1 Hz, 2H), 2.77 (s, 2H), 1.15 – 1.03 (m, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 177.2 (s), 146.1 (s), 142.3 (s), 128.0 (s), 127.2 (s), 126.7 (s), 116.9 (s), 60.1 (s), 45.8 (s), 42.4 (s), 25.5 (s), 13.9 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{20}O_2Na$ 255.1356; found 255.1358. Data obtained were in accordance with those previously reported.[6c]

Ethyl-2-methyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate (**4**). Under an atmosphere of N_2, a glass ampoule equipped with a stir bar was charged in turn with TEMPO (79.7 mg, 0.5 mmol), [Cp*RuCl(PPh$_3$)$_2$] (0.4 mg, 0.0005 mmol), THF (1 mL), 4-methoxystyrene (67.1 mg, 0.5 mmol), ethyl 2-bromo-2-methylpropionate (195.1 mg, 1.0 mmol), *N,N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The ampoule was placed in an oil bath and the mixture was stirred for 24 h at 100 °C. Next, the reaction mixture was filtered through a short plug of silica gel (EtOAc) and purified by column chromatography on silica gel (hexanes→10% EtOAc /hexanes). Colorless oil (32.0 mg, 24%). ^{1}H NMR (500 MHz, $CDCl_3$) 4.15 (q, *J* = 7.1 Hz, 2H), 1.53 – 1.38 (m, 10H), 1.33 – 1.21 (m, 5H), 1.12 (s, 6H), 0.98 (s, 6H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.0 (s), 81.0 (s), 60.5 (s), 59.5 (s), 40.5 (s), 33.4 (s), 24.4 (s), 20.4 (s), 17.0 (s), 14.1 (s) ppm. HRMS (EI-magnetic sector) m/z: [M + H]$^+$ calcd for $C_{15}H_{30}O_3N$ 272.2220; found 272.2221. Data obtained were in accordance with those previously reported.[6c]

Diethyl-2-methyl-2-(2-phenylallyl)malonate (**5**). Under an atmosphere of N_2, a glass ampoule equipped with a stir bar was charged in turn with [Cp*RuCl(PPh$_3$)$_2$] (4.0 mg, 0.005 mmol), 2,4-diphenyl-4-methyl-1-pentene (118.2 mg, 0.5 mmol), THF (1 mL), diethyl 2-bromo-2-methylmalonate (253.1 mg, 1.0 mmol), *N,N*-diisopropylethylamine (129.2 mg, 1.0 mmol). The ampoule was placed in an oil bath and the mixture was stirred for 24 h at 100 °C. Next, the reaction mixture was filtered through a short plug of silica gel (hexanes→10% EtOAc /hexanes). Colorless oil (110.3 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.11 (m, 5H), 5.22 (d, *J* = 1.7 Hz, 1H), 5.07 (s, 1H), 3.98 – 3.87 (m, 2H), 3.82 (ddt, *J* = 12.4, 10.8, 7.1 Hz, 2H), 3.12 (s, 2H), 1.25 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.8 (s), 144.5 (s), 141.7 (s), 128.0 (s), 127.4 (s), 126.8 (s), 118.2 (s), 61.1 (s), 53.4 (s), 40.4 (s), 19.8 (s), 13.9 (s) ppm. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{20}O_2Na$ 313.1410; found 313.1408. Data obtained were in accordance with those previously reported.[21]

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: ~~~~.

Mechanistic study results, X-ray crystallographic data, copies of NMR spectra (PDF).

Crystal structure data for compound **2d** (CIF).

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Notes

The authors declare no competing financial interest.

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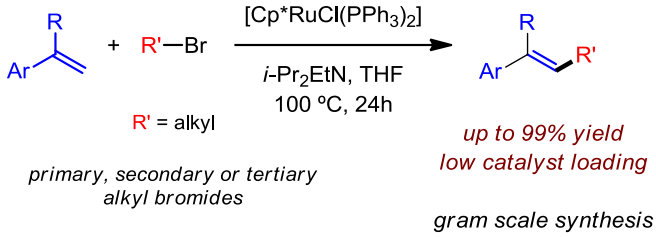
R
Ar
+ R'—Br
[Cp*RuCl(PPh3)2]
i-Pr2EtN, THF
100 ºC, 24h
R
Ar
R'
R' = alkyl
primary, secondary or tertiary
alkyl bromides
up to 99% yield
low catalyst loading
gram scale synthesis