Tetrahedron 65 (2009) 5024–5029

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Hydroacylation of 2-butyne from the alcohol or aldehyde oxidation level via ruthenium catalyzed C–C bond forming transfer hydrogenation

Vanessa M. Williams, Joyce C. Leung, Ryan L. Patman, Michael J. Krische *

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712, United States

ARTICLE INFO

Article history:
Received 20 February 2009
Received in revised form 21 March 2009
Accepted 23 March 2009
Available online 1 April 2009

ABSTRACT

Under the conditions of ruthenium catalyzed transfer hydrogenation, 2-butyne couples to alcohols **1a**–**1j** to deliver α,β-unsaturated ketones **3a**–**3j** in good to excellent isolated yields with complete *E*-stereoselectivity. Under identical conditions, aldehydes **2a**–**2j** couple to 2-butyne to provide an identical set of α,β-unsaturated ketones **3a**–**3j** in good to excellent isolated yields with complete *E*-stereoselectivity. Nonsymmetric alkyne **4a** couples to alcohol **1d** or aldehyde **2d** in good yield to deliver enone **3k** as a 5:1 mixture of regioisomers. Thus, intermolecular alkyne hydroacylation is achieved from the alcohol or aldehyde oxidation level. In earlier studies employing the same ruthenium catalyst under slightly different conditions, alkynes were coupled to carbonyl partners from the alcohol or aldehyde oxidation level to furnish allylic alcohols. Therefore, under the conditions of C–C bond forming transfer hydrogenation, all oxidation levels of substrate (alcohol or aldehyde) and product (allylic alcohol or α,β-unsaturated ketone) are accessible.

Published by Elsevier Ltd.

1. Introduction

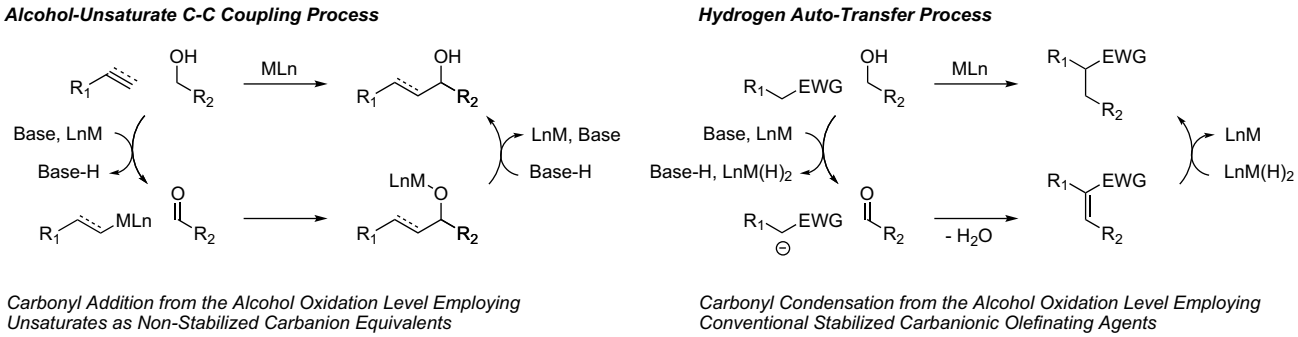
Whereas rhodium catalyzed intramolecular alkene hydroacylation using aldehydes as acyl donors is well developed,[1] intermolecular variants typically suffer from competitive aldehyde decarbonylation.[2–7] Although exceptions exist for certain substrate combinations,[3,4] efficient intermolecular alkene hydroacylation generally requires acyl donors that exploit β-chelation to suppress decarbonylation, such as γ,δ-unsaturated aldehydes,[5a] salicylaldehydes,[5b–e] β-sulfido-aldehydes,[5f,9c–e,g] and (*N*-2-pyridyl)aldimines.[5g] While cobalt[6] and ruthenium[7] catalysts have been explored, rhodium appears unique in its ability to promote intermolecular alkene hydroacylation under mild conditions in a selective fashion, notwithstanding the aforementioned limitations. Alkyne hydroacylation is far less developed. To our knowledge, efficient and stereoselective intermolecular alkyne hydroacylation is restricted to systems that exploit β-chelation to suppress decarbonylation,[9,10] and the first efficient intramolecular alkyne hydroacylations only recently were disclosed by Fu and Tanaka.[8]

In prior work from our laboratory, ruthenium catalyzed diene–alcohol and diene–aldehyde transfer hydrogenative C–C couplings were developed.[11a,b,12] The former process belongs to a broad new subset of alcohol–unsaturate C–C couplings that are related conceptually to hydrogen auto-transfer processes.[12,13] Whereas conventional hydrogen auto-transfer reactions provide products of alcohol substitution by way of oxidation–condensation–reduction mechanisms, alcohol–unsaturate couplings provide products of carbonyl addition by way of hydrogen shuffling to generate nucleophile–electrophile pairs. A unique feature of alcohol–unsaturate C–C coupling resides in the ability to achieve formal C–H functionalization at the carbinol carbon through introduction of a nonstabilized carbanion equivalent (Scheme 1).

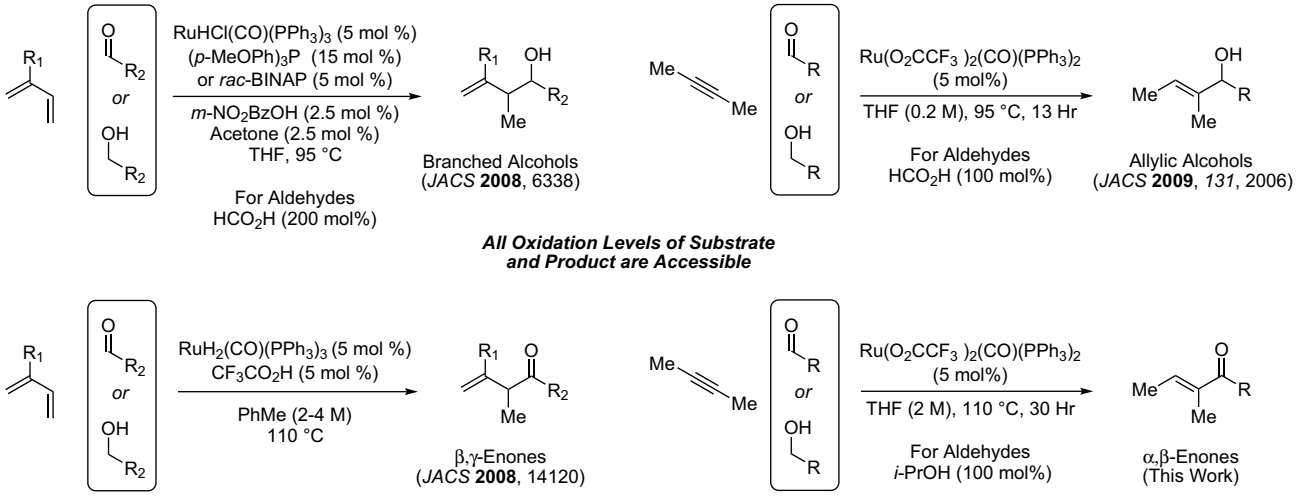
Remarkably, for the ruthenium catalyzed diene–alcohol and diene–aldehyde transfer hydrogenative C–C couplings, conditions were identified such that formation of either the homoallylic alcohol or β,γ-unsaturated ketone is achieved from the alcohol or aldehyde oxidation level, the latter process representing a formal diene hydroacylation.[11b] The step-economy associated with the ability to access alternate oxidation levels of starting material or product compelled us to explore the generality of this concept in the context of alkyne–carbonyl coupling.[11e,14] Here, we report that under the conditions of ruthenium catalyzed C–C bond forming transfer hydrogenation,[11,12] efficient intermolecular alkyne hydroacylation is achieved from either the alcohol or aldehyde oxidation level with complete levels of *E*/*Z*-stereoselectivity, and in the absence of β-chelation assistance. As in earlier studies conditions for ruthenium catalyzed alkyne–carbonyl coupling en route to products of carbonyl vinylation were established,[11e] all oxidation levels of substrate (alcohol or aldehyde) and product (allylic alcohol or α,β-unsaturated ketone) are accessible (Scheme 2).

* Corresponding author. Tel.: +1 512 232 5892; fax: +1 512 471 8696.
E-mail address: mkrische@mail.utexas.edu (M.J. Krische).

0040-4020/$ – see front matter Published by Elsevier Ltd.
doi:10.1016/j.tet.2009.03.068



Scheme 1. Simplified schematic depictions of the catalytic mechanism of an alcohol–unsaturate C–C coupling reaction and a related hydrogen auto-transfer process.

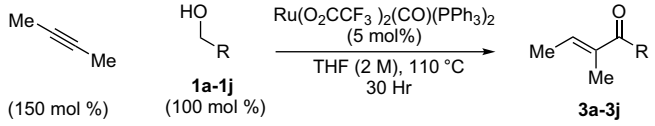


Scheme 2. Transcending the boundaries of oxidation level through C–C bond forming transfer hydrogenation.

2. Results and discussion

In previously disclosed alkyne–carbonyl couplings employing $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ as precatalyst,[11e] small quantities of α,β-unsaturated ketone accompanied formation of the desired allylic alcohols. Hence, it was postulated that efficient formation of conjugated enones could be achieved simply by conducting the reaction at higher temperature and longer reaction times. Higher reaction concentration also should promote oxidation of the initially formed allylic alcohol by facilitating formation of the allylic

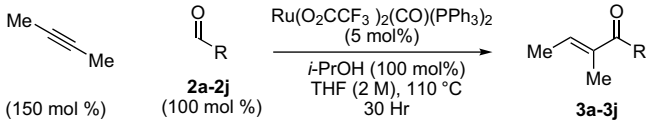
Table 1
Hydroacylation of 2-butyne from the alcohol oxidation level[a]



Entry	Alcohol	Product	R group	Yield
1	**1a**	**3a**	*p*-NO_2Ph	88%
2	**1b**	**3b**	Ph	79%
3	**1c**	**3c**	*m*-MeOPh	71%[b]
4	**1d**	**3d**	*p*-BrPh	90%
5	**1e**	**3e**	*p*-(MeO_2C)Ph	91%
6	**1f**	**3f**	3,5-Me_2Ph	80%
7	**1g**	**3g**	*p*-CF_3Ph	82%
8	**1h**	**3h**	CH_2Ph	81%
9	**1i**	**3i**	*n*-C_6H_{17}	70%
10	**1j**	**3j**	$(CH_2)_2$NPhtl	99%[c]

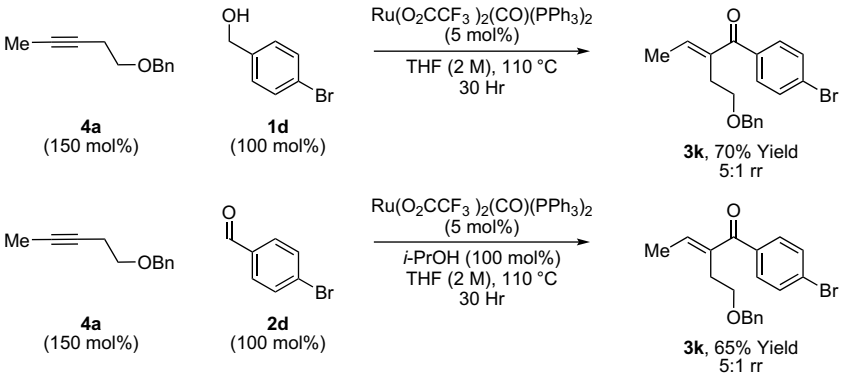
[a] In all cases, cited yields are of isolated material. See Supplementary data for detailed experimental procedures.
[b] The reaction was conducted at 130 °C.
[c] The reaction was conducted for 40 h.

Table 2
Hydroacylation of 2-butyne from the aldehyde oxidation level[a]



Entry	Alcohol	Product	R group	Yield
1	**2a**	**3a**	*p*-NO_2Ph	85%
2	**2b**	**3b**	Ph	85%[d]
3	**2c**	**3c**	*m*-MeOPh	74%[d]
4	**2d**	**3d**	*p*-BrPh	84%
5	**2e**	**3e**	*p*-(MeO_2C)Ph	76%[c]
6	**2f**	**3f**	3,5-Me_2Ph	80%[d]
7	**2g**	**3g**	*p*-CF_3Ph	80%[b]
8	**2h**	**3h**	CH_2Ph	81%[d,e]
9	**2i**	**3i**	*n*-C_6H_{17}	69%
10	**2j**	**3j**	$(CH_2)_2$NPhtl	66%[b]

[a] In all cases, cited yields are of isolated material. See Supplementary data for detailed experimental procedures.
[b] The reaction was conducted at 130 °C.
[c] The reaction was conducted for 40 h.
[d] The reaction was conducted using 2-MeTHF as solvent.
[e] The reaction was conducted using 10 mol % $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$.



Scheme 3. Regioselective hydroacylation of nonsymmetric alkyne **4a** from the alcohol or aldehyde oxidation level.

ruthenium alkoxide, which upon β-hydride elimination generates the enone. This hypothesis was borne out experimentally in the coupling of 2-butyne to *p*-nitrobenzyl alcohol **1a**. By extending reaction time from 13 h to 30 h, modestly raising the temperature from 95 °C to 110 °C and increasing concentration from 0.2 M to 2.0 M, the α,β-unsaturated ketone **3a** was formed in 88% isolated yield to the exclusion of the allylic alcohol (Table 1, entry 1).

To explore the scope of this process, 2-butyne was coupled to benzylic alcohols **1a**–**1g**. In each case, good to excellent isolated yields of enones **3a**–**3g** were obtained. As demonstrated by the formation of **3h**–**3j**, aliphatic alcohols also participate in the coupling. For all coupling products **3a**–**3j**, the enone moiety appears as a single geometrical isomer (>95:5, *E*/*Z* selectivity). For the corresponding aldehyde couplings, isopropanol, a hydride donor, is required to initiate the purported hydrometallative mechanism. Although, in principle, only substoichiometric quantities of isopropanol are required to initiate the catalytic cycle, slightly better isolated yields were obtained using 1 equiv of isopropanol. Notably, an identical set of enone products **3a**–**3j** were formed as single geometrical isomers (>95:5, *E*/*Z* selectivity) from the aldehydes **2a**–**2j** (Table 2). Thus, ruthenium catalyzed hydroacylation of 2-butyne is achieved with equal facility from the alcohol or aldehyde oxidation level.

Preliminary studies on the hydroacylation of nonsymmetric alkynes reveal promising levels of regioselectivity in certain cases. For example, the coupling of nonsymmetric alkyne **4a** to alcohol **1d** occurs in good isolated yield to deliver enone **3k** as a 5:1 mixture of regioisomers and as a single geometrical isomer (>95:5, *E*/*Z* selectivity). Similarly, the coupling of nonsymmetric alkyne **4a** to aldehyde **2d** provides enone **3k** in comparable isolated yield and as a single geometrical isomer (>95:5, *E*/*Z* selectivity) (Scheme 3).

3. Conclusion

In summary, we report a protocol for alkyne hydroacylation under the conditions of ruthenium catalyzed transfer hydrogenation.[11,12] Unlike the prototypical rhodium catalyzed alkyne hydroacylations,[9] efficient intermolecular coupling is observed in the absence chelation assistance. Furthermore, through C–C bond forming transfer hydrogenation, enone formation is achieved from the alcohol or aldehyde oxidation level. In earlier studies employing the same ruthenium catalyst under less forcing conditions, alkynes were coupled to carbonyl partners from the alcohol or aldehyde oxidation level to furnish allylic alcohols. Thus, all oxidation levels of substrate (alcohol or aldehyde) and product (allylic alcohol or α,β-unsaturated ketone) are accessible.

The alcohol–unsaturate C–C couplings developed in our laboratory, as well as related amine–unsaturate C–C couplings (termed hydroaminoalkylation),[15] may be viewed as carbonyl or imine additions from the alcohol or amine oxidation levels, respectively. These transformations, in which a redistribution of hydrogen accompanies covalent bond formation, may be viewed as hydrogen-auto-transfer processes.[13] The ability to circumvent reductive preactivation of nucleophiles (discrete carbanion generation) and oxidative preactivation of electrophiles (discrete alcohol oxidation) is inherently step-economic, redox-economic and defines a departure from the use of preformed organometallic reagents in carbonyl and imine addition chemistry.

4. Experimental section

4.1. General

All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred via oven-dried syringe. Reaction tubes were oven-dried and cooled under a stream of argon. Reaction tubes were purchased from Fisher Scientific (catalog number 14-959-35C). Tetrahydrofuran was purified using the Pure-Solv MD-5 Solvent Purification System (Innovative Technology, inc). 2-Methyl tetrahydrofuran was purified by distillation from calcium hydride and was stored over molecular sieves.

$Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ was prepared in accordance with literature procedure.[16] Anhydrous isopropanol (99.5% over molecular sieves) was purchased from Acros and used as received. Commercially available alcohols and alkynes were used as received. Alkyne **4a** was prepared according to literature procedure.[17] Commercially available aldehydes were purified via distillation or recrystallization prior to use.

Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}) and products were visualized by UV, $KMnO_4$, vanillin and/or anisaldehyde stain. Preparative column chromatography employing silica gel was performed according to the method of Still.[18] Solvents for chromatographic separation are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin–Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as *m*/*z* (relative intensity). Accurate masses are reported for the molecular ion $[M+H]^+$ or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz or 300 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 300 (75 MHz) or 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million

relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

4.1.1. General procedure A for the coupling of 2-butyne to alcohols

To a pressure tube equipped with magnetic stir bar was added $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ (13.2 mg, 0.015 mmol, 5 mol %). At this stage, solid alcohol substrates (0.300 mmol, 100 mol %) were added. The tube was then sealed with a rubber septum, purged with argon and THF (1.5 mL, 0.2 M concentration with respect to the alcohol) was added. At this stage, liquid alcohol coupling partners (0.300 mmol, 100 mol %) were added. The reaction vessel was cooled to −78 °C. 2-Butyne (35 μL, 0.450 mmol, 150 mol %) was added and the rubber septum was quickly replaced with a screw cap. The reaction vessel was allowed to reach room temperature and the reaction mixture was heated to the specified temperature and for the indicated time. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2) under the conditions noted to furnish the α,β-unsaturated ketone.

4.1.2. General procedure B for the coupling of 2-butyne to aldehydes

To a pressure tube equipped with magnetic stir bar was added $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ (13.2 mg, 0.015 mmol, 5 mol %). At this stage, solid aldehyde substrates (0.300 mmol, 100 mol %) were added. The tube was then sealed with a rubber septum, purged with argon and THF (1.5 mL, 0.2 M concentration with respect to the aldehyde) and 2-propanol (36 μL, 0.300, 100 mol %) were added. At this stage, liquid aldehyde coupling partners (0.300 mmol, 100 mol %) were added. The reaction vessel was cooled to −78 °C. 2-Butyne (35 μL, 0.450 mmol, 150 mol %) was added and the rubber septum was quickly replaced with a screw cap. The reaction vessel was allowed to reach room temperature and the reaction mixture was heated to the specified temperature and for the indicated time. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2) under the conditions noted to furnish the α,β-unsaturated ketone.

*4.1.3. Synthesis of (E)-2-methyl-1-(4-nitrophenyl)but-2-en-1-one (**3a**)*

Procedure A was employed using alcohol **1a**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 1:9 ethyl acetate/hexanes) to furnish the title compound (54 mg) as a light brown oil in 88% yield. Procedure B was employed using aldehyde **2a**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 1:9 ethyl acetate/hexanes) to furnish the title compound (52.5 mg) as a light brown oil in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J*=8.7 Hz, 2H), 7.72 (d, *J*=8.7 Hz, 2H), 6.41 (q, *J*=6.8 Hz, 1H), 1.99 (s, 3H), 1.93 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 149.0, 144.6, 144.2, 137.7, 129.7, 123.2, 15.0, 11.7. FTIR (neat): 3022, 1709, 1650, 1524, 1347, 1278, 1104, 748, 715, 667 cm^{-1}. HRMS (CI): calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$: 208.0809, found: 208.0811.

*4.1.4. Synthesis of (E)-2-methyl-1-phenylbut-2-en-1-one (**3b**)*

Procedure A was employed using alcohol **1b**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (39 mg) as a clear oil in 79% yield. Procedure B was employed using aldehyde **2b**. In a modification to procedure B, 2-methyltetrahydrofuran was used as solvent. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (41 mg) as a clear oil in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J*=8.3 Hz, 2H), 7.49 (dt, *J*=8.3, 1.2 Hz, 1H), 7.40 (dt, *J*=8.3, 1.2 Hz, 2H), 6.40 (q, *J*=6.8 Hz, 1H), 1.97 (s, 3H), 1.88 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 141.5, 138.8, 137.6, 131.2, 129.1, 127.9, 14.7, 12.1. FTIR (neat): 3057, 2919, 2847, 1628, 1268, 1023, 970, 698 cm^{-1}. HRMS (CI): calcd for $C_{11}H_{13}O$ $[M+H]^+$: 161.0965, found: 161.0966.

*4.1.5. Synthesis of (E)-2-methyl-1-(3-methoxyphenyl)but-2-en-1-one (**3c**)*

Procedure A was employed using alcohol **1c**. After heating the reaction at 130 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ethyl acetate/hexanes) to furnish the title compound (55 mg) as a clear oil in 71% yield. Procedure B was employed using aldehyde **2c**. In a modification to procedure B, 2-methyltetrahydrofuran was used as solvent. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ethyl acetate/hexanes) to furnish the title compound (55 mg) as a clear oil in 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.27 (m, 1H), 7.18–7.14 (m, 2H), 7.03 (ddd, *J*=8.4, 2.6, 0.8 Hz, 1H), 6.43 (q, *J*=6.8 Hz, 1H), 3.83 (s, 3H), 1.96 (s, 3H), 1.87 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 159.2, 141.5, 140.1, 137.5, 128.9, 121.7, 117.3, 113.9, 55.3, 14.7, 12.1. FTIR (neat): 3003, 2941, 2839, 1642, 1584, 1272, 1241, 1027, 724 cm^{-1}. HRMS (CI): calcd for $C_{12}H_{15}O_2$ $[M+H]^+$: 191.1072, found: 191.1074.

*4.1.6. Synthesis of (E)-2-Methyl-1-(4-bromophenyl)but-2-en-1-one (**3d**)*

Procedure A was employed using alcohol **1d**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ethyl acetate/hexanes) to furnish the title compound (64 mg) as a pale yellow oil in 90% yield. Procedure B was employed using aldehyde **2d**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ethyl acetate/hexanes) to furnish the title compound (60 mg) as a pale yellow oil in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, *J*=8.5, 2.1 Hz, 2H), 7.49 (dd, *J*=8.5, 2.1 Hz, 2H), 6.38 (q, *J*=6.8 Hz, 1H), 1.96 (s, 3H), 1.88 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 141.6, 137.4 (two carbons), 131.2, 130.7, 125.9, 14.7, 12.0. FTIR (neat): 3057, 2919, 2847, 1628, 1575, 1392, 1067, 1005, 1277, 832, 738 cm^{-1}. HRMS (CI): calcd for $C_{11}H_{12}BrO$ $[M+H]^+$: 239.0066, found: 239.0066.

*4.1.7. Synthesis of (E)-methyl 4-(2-methylbut-2-enoyl)-benzoate (**3e**)*

Procedure A was employed using alcohol **1e**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 0:100 to 5:95 ethyl acetate/hexanes) to furnish the title compound (59.4 mg) as a colorless crystalline solid in 91% yield. Procedure B was employed using aldehyde **2e**. After heating the reaction at 110 °C for 40 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 0:100 to 5:95 ethyl acetate/hexanes) to furnish the title compound (49.5 mg) as a colorless crystalline solid in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J*=8.5 Hz, 2H), 7.63 (d, *J*=8.5 Hz, 2H), 6.41 (q, *J*=7.3 Hz, 1H), 3.95 (s, 3H), 1.97 (s, 3H), 1.90 (d, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 166.3, 143.0, 142.8, 137.6, 132.0, 129.2, 128.8, 52.3, 14.9, 11.8. FTIR (neat): 2952, 1722, 1647, 1435, 1404, 1271, 1178, 1106, 720 cm^{-1}. HRMS (CI): calcd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1021, found: 219.1024.

*4.1.8. Synthesis of (E)-2-methyl-1-(3,5-dimethylphenyl)but-2-en-1-one (**3f**)*

Procedure A was employed using alcohol **1f**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo

and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (57 mg) as a pale yellow oil in 80% yield. Procedure B was employed using aldehyde **2f**. In a modification to procedure B, 2-methyltetrahydrofuran was used as solvent. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (57 mg) as a pale yellow oil in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 2H), 7.12 (s, 1H), 6.39 (q, J=6.8 Hz, 1H), 3.41 (s, 6H), 1.95 (s, 3H), 1.87 (d, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 141.1, 138.9, 137.7, 137.5, 132.7, 126.9, 21.2, 14.7, 12.1. FTIR (neat): 3043, 2914, 2856, 1646, 1596, 1303, 1232, 1152, 738 cm^{-1}. HRMS (CI): calcd for $C_{13}H_{17}O$ $[M+H]^+$: 188.1279, found: 188.1281.

4.1.9. Synthesis of (E)-2-methyl-1-(4-trifluoromethyl)phenyl)but-2-en-1-one (**3g**)

Procedure A was employed using alcohol **1g**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ethyl acetate/hexanes) to furnish the title compound (69 mg) as a colorless oil in 82% yield. Procedure B was employed using aldehyde **2g**. After heating the reaction at 130 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ethyl acetate/hexanes) to furnish the title compound (55 mg) as a colorless oil in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 4H), 6.40 (q, J=7.2 Hz, 1H), 1.98 (s, 3H), 1.91 (d, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 143.2, 142.2, 137.7, 132.5, 129.2, 125.0, 122.3, 14.9, 11.8. FTIR (neat): 3057, 2932, 2852, 1646, 1321, 1277, 1140, 1125, 1063, 845, 694 cm^{-1}. HRMS (CI): calcd for $C_{12}H_{11}F_3O$ $[M+H]^+$: 229.0840, found: 229.0838.

4.1.10. Synthesis of (E)-3-methyl-1-phenylpent-3-en-2-one (**3h**)

Procedure A was employed using alcohol **1h**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (39 mg) as a pale yellow oil in 81% yield. Procedure B was employed using aldehyde **2h**. In a modification to procedure B, the reaction was conducted in 2-methyltetrahydrofuran, with 10 mol% catalyst loading. After heating the reaction at 110 °C for 24 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (39 mg) as a pale yellow oil in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.18 (m, 5H), 6.87 (q, J=6.8 Hz, 1H), 3.97 (s, 2H), 1.86 (d, J=6.8 Hz, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 138.7, 137.9, 135.5, 129.2, 128.5, 126.5, 44.1, 14.9, 11.1. FTIR (neat): 3030, 2919, 2852, 1655, 1490, 1277, 1023, 1063, 720, 694 cm^{-1}. HRMS (CI): calcd for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123, found: 175.1124.

4.1.11. Synthesis of (E)-3-methyldodec-2-en-4-one (**3i**)

Procedure A was employed using alcohol **1i**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (44 mg) as a clear oil in 70% yield. Procedure B was employed using aldehyde **2i**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 5:95 ether/pentane) to furnish the title compound (43 mg) as a clear oil in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (q, J=6.8 Hz, 1H), 2.63 (t, J=7.3 Hz, 2H), 1.85 (d, J=6.8 Hz, 3H), 1.77 (s, 3H), 1.62–1.55 (m, 2H), 1.27 (s, 10H), 0.88 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 138.3, 136.8, 37.2, 31.8, 29.4 (two carbons), 29.2, 25.0, 22.6, 14.7, 14.1, 11.0. FTIR (neat): 2924, 2854, 1667, 1644, 1460, 1415, 1075, 983 cm^{-1}. HRMS (CI): calcd for $C_{13}H_{25}O$ $[M+H]^+$: 197.1905, found: 197.1904.

4.1.12. Synthesis of (E)-2-(4-methyl-3-oxohex-4-enyl)-isoindole-1,3-dione (**3j**)

Procedure A was employed using alcohol **1j**. After heating the reaction at 110 °C for 40 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 1:9 ethyl acetate/hexanes) to furnish the title compound (76.8 mg) as a colorless crystalline solid in 99% yield. Procedure B was employed using aldehyde **2j**. After heating the reaction at 130 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 1:9 ethyl acetate/hexanes) to furnish the title compound (51.2 mg) as a colorless crystalline solid in 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, J=5.5, 3.1 Hz, 2H), 7.72 (dd, J=5.5, 3.1 Hz, 2H), 6.74 (q, J=6.8 Hz, 1H), 4.00 (t, J=7.5 Hz, 2H), 3.10 (t, J=7.5 Hz, 2H), 1.84 (d, J=6.8 Hz, 3H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 168.1, 138.1, 133.9, 132.0, 123.2, 35.4, 34.0, 14.8, 10.8 (only 10 signals were observed). FTIR (neat): 2927, 1772, 1709, 1663, 1439, 1392, 1365, 998, 910, 717 cm^{-1}. HRMS (CI): calcd for $C_{15}H_{16}NO_3$ $[M+H]^+$: 258.1130, found: 258.1130.

4.1.13. Synthesis of (E)-2-(2-benzyloxy)ethyl-1-(4-bromophenyl)-but-2-en-1-one (**3k**)

In a modification to procedures A and B, alkyne **4a** was used in place of 2-butyne. Procedure A was employed using alcohol **1d**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 1:9 ethyl acetate/hexanes) to furnish the title compound (76 mg) as a colorless oil in 70% yield as a 5:1 mixture of regioisomers. Procedure B was employed using aldehyde **2d**. After heating the reaction at 110 °C for 30 h the mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 1:9 ethyl acetate/hexanes) to furnish the title compound (70 mg) as a colorless oil in 65% yield as a 5:1 mixture of regioisomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.25 (m, 9H), 6.37 (q, J=6.9 Hz, 1H), 6.48 (s, 2H), 3.60 (t, J=6.5 Hz, 2H), 2.82 (t, J=6.5 Hz, 1H), 1.91 (d, J=6.9 Hz, 3H). *Characteristic signals for regioisomer*: 7.81–7.60 (m, 2H), 5.9 (q, J=6.5 Hz, 2H), 4.37 (s, 2H), 3.5 (t, J=6.5 Hz, 2H), 2.93 (t, J=6.5 Hz, 2H), 1.48 (d, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 138.9, 131.8, 131.2, 130.9, 129.5, 128.2, 127.5, 127.4, 72.8, 68.7, 38.4, 29.5, 27.0, 14.7. *Characteristic signals for regioisomer*: 198.4, 138.3, 137.5, 131.9, 131.5, 130.7, 128.3, 127.6, 126.2, 72.9, 70.1, 36.0, 29.6, 25.7, 15.8. FTIR (neat): 3020, 2857, 1647, 1585, 1482, 1294, 1285, 1098, 1070, 729, 697 cm^{-1}. HRMS (CI): calcd for $C_{19}H_{20}OBr$ $[M+H]^+$: 359.0645, found: 359.0642.

Acknowledgements

Acknowledgement is made to the Robert A. Welch Foundation, the ACS-GCI Pharmaceutical Roundtable, the NIH-NIGMS (RO1-GM069445) for partial support of this research, and the C. M. Share graduate fellows program (R.L.P.).

Supplementary data

Supplementary data in association with this article can be found in the online version at doi:10.1016/j.tet.2009.03.068.

References and notes

1. For selected reviews on metal catalyzed hydroacylation, see: (a) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667; (b) Jun, C.-H.; Hong, J.-B.; Lee, D.-Y. *Synlett* **1999**, 1; (c) Tanaka, M.; Sakai, K.; Suemune, H. *Curr. Org. Chem.* **2003**, *7*, 353; (d) Fu, G. C. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; 2005; Chapter 7, pp 79–91; (e) Jun, C.-H.; Jo, E. A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869.
2. For rhodium-catalyzed aldehyde decarbonylation, see: (a) Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *100*, 7083; (b) O'Conner, J. M.; Ma, J. *J. Org. Chem.* **1992**, *57*, 5075; (c) Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Chen, J.; Crabtree, R. H. *Organometallics* **1999**, *18*, 5311.

3. For certain substrate combinations, efficient intermolecular rhodium catalyzed alkene hydroacylation is observed in the absence of β-chelation: (a) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451; (b) Tanaka, K.; Shibata, Y.; Suda, T.; Hagiwara, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 1215; (c) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082.
4. Efficient intermolecular Rh-catalyzed alkene hydroacylation employing anhydrides as acyl donors and hydrogen as terminal reductant is observed in the absence of β-chelation: Hong, Y.-T.; Barchuk, A.; Krische, M. J. *Angew. Chem., Int. Ed.* **2006**, *128*, 6885.
5. For chelation-assisted intermolecular Rh-catalyzed alkene hydroacylation, see: (a) γ,δ-unsaturated aldehydes: Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257; (b) Salicylaldehydes: Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, *5*, 1365; (c) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144; (d) Tanaka, K.; Tanaka, M.; Suemune, H. *Tetrahedron Lett.* **2005**, *46*, 6053; (e) Imai, M.; Tanaka, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2007**, *72*, 2543; (f) β-sulfido-aldehyde: Willis, M. C.; McNally, S. J.; Beswick, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 340. Also see Refs. 9c–e,g; (g) (*N*-2-pyridyl)aldimines: Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489; (h) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200; (i) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070; (j) Jun, C.-H.; Chung, J.-W.; Lee, D.-Y.; Loupy, A.; Chatti, S. *Tetrahedron Lett.* **2001**, *42*, 4803; (k) Willis, M. C.; Sapmaz, S. *Chem. Commun.* **2001**, 2558; (l) Yañez, X.; Claver, C.; Castillon, S.; Fernandez, E. *Tetrahedron Lett.* **2003**, *44*, 1631.
6. Efficient intermolecular cobalt catalyzed hydroacylation is restricted to the use of vinyl silanes as coupling partners: (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165; (b) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965.
7. Intermolecular Ru-catalyzed hydroacylation generally requires exceptionally high reaction temperatures and provides mixtures of linear and branched coupling products: (a) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1982**, *240*, 285; (b) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1983**, *256*, 135; (c) Kondo, T.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 6229; (d) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286; (e) Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y.; Mitsudo, T.-A. *Organometallics* **1998**, *17*, 2131.
8. For intramolecular rhodium catalyzed alkyne hydroacylation, see: (a) Fu, G. C.; Tanaka, K. *J. Am. Chem. Soc.* **2001**, *123*, 11492; (b) Fu, G. C.; Tanaka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1607; (c) Fu, G. C.; Tanaka, K. *J. Am. Chem. Soc.* **2002**, *124*, 10296; (d) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031; (e) Fu, G. C.; Tanaka, K. *J. Am. Chem. Soc.* **2003**, *125*, 8078; (f) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem.—Eur. J.* **2004**, *10*, 5681; (g) Tanaka, K.; Sasaki, K.; Takeishi, K.; Hirano, M. *Eur. J. Org. Chem.* **2007**, 5675.
9. For chelation-assisted intermolecular alkyne hydroacylation, see: (a) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4564; (b) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. *Angew. Chem., Int. Ed.* **2002**, *41*, 2146; (c) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; Currie, G. S. *Org. Lett.* **2005**, *7*, 2249; (d) Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7618; (e) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; McNally, S.; Currie, G. S. *J. Org. Chem.* **2006**, *71*, 5291; (f) Rueda, X. Y.; Castillon, S. *J. Organomet. Chem.* **2007**, *692*, 1628; (g) Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Weller, A. S.; Willis, M. C. *Chem.—Eur. J.* **2008**, *14*, 8383.
10. There exists an example of Ni-catalyzed intermolecular alkyne hydroacylation that does not require chelation-assistance, however, incomplete regio- and *E*/*Z*-stereoselectivity is observed: Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554.
11. For Ru-catalyzed C–C bond forming transfer hydrogenation, see: (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338; (b) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120; (c) Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705; (d) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220; (e) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066.
12. For reviews encompassing Ru-catalyzed C–C bond forming transfer hydrogenation, see: (a) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102; (b) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34.
13. For recent reviews of conventional hydrogen auto-transfer processes, see: (a) Guillena, G.; Ramòn, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358; (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.
14. For selected examples of nickel catalyzed alkyne–carbonyl reductive coupling, see: (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065; (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098; (c) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950; (d) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221; (e) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442; (f) Takai, K.; Sakamoto, S.; Isshiki, T. *Org. Lett.* **2003**, *5*, 653; (g) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698; (h) Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156.
15. For amine–unsaturated C–C coupling (hydroaminoalkylation), see: (a) Maspero, F.; Clerici, M. G. *Synthesis* **1980**, 305; (b) Nugent, W. A.; Ovenall, D. W.; Homes, S. J. *Organometallics* **1983**, *2*, 161; (c) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690; (d) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940; (e) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1153; (f) Bexrud, J. A.; Eisenberger, P.; Leitch, D. C.; Payne, P. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 2116.
16. Dobson, A.; Robinson, S. D.; Uttley, M. F. *J. Chem. Soc., Dalton Trans.* **1975**, 370.
17. Alonso, F.; Osanto, I.; Yus, M. *Tetrahedron* **2006**, *63*, 93.
18. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.