Organic Syntheses

Ruthenium-Catalyzed Direct Oxidative Alkenylation of Arenes through Twofold C–H Bond Functionalization in Water: Synthesis of Ethyl (*E*)-3-(2-Acetamido-4-methylphenyl)acrylate

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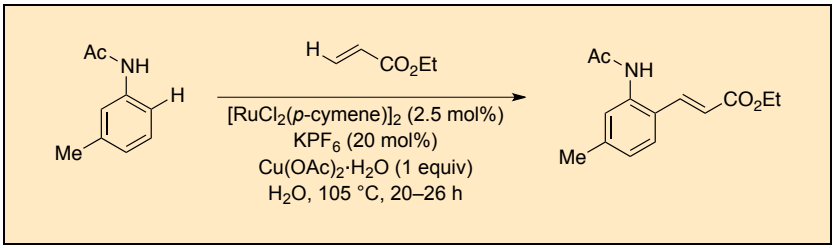
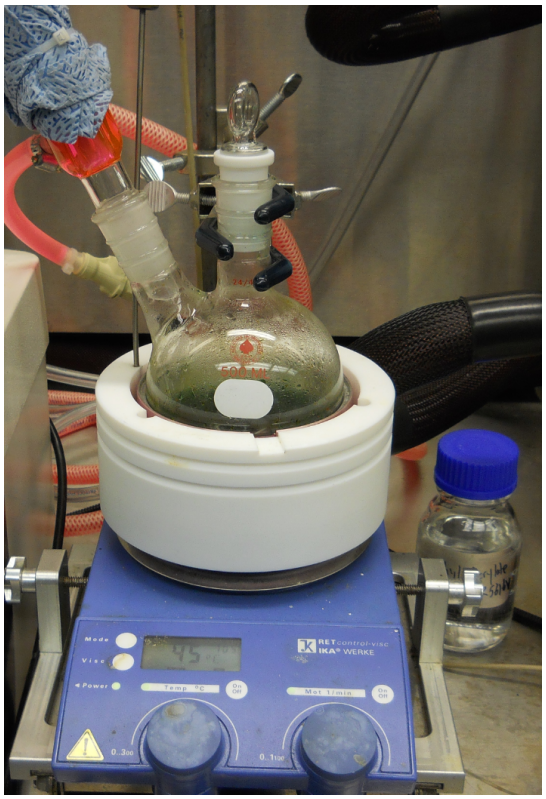
Checked by William Trieu and Margaret Faul



Procedure

A. *Ethyl (E)-3-(2-acetamido-4-methylphenyl)acrylate*. A 500-mL, two-necked, round-bottomed flask is equipped with a 2.5 cm rod-shaped, Teflon-coated magnetic stirring bar, rubber septum, reflux condenser and nitrogen inlet and outlet at the top of the reflux condenser. The flask is flushed with nitrogen (Note 1) and charged with *N*-*m*-tolylacetamide (5.00 g, 33.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (513 mg, 0.84 mmol, 2.5 mol %), KPF_6 (1.233 g, 6.70 mmol, 20.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (6.690 g, 33.5 mmol, 1.0 equiv), (Note 2) and H_2O (100 mL) (Note 3). The reaction mixture is stirred for 10 min at ambient temperature, then ethyl acrylate (3.39 g, 3.6 mL, 33.86 mmol, 1.0 equiv) is added via syringe in one portion, and the rubber septum is changed to a glass stopper. After stirring for additional 15 min at ambient

DOI: 10.15227/orgsyn.092.0131 Published on the Web 5/5/2015



Experimental Set-up

temperature, the reaction mixture is vigorously stirred and heated in an oil bath (105 °C) (Notes 4 and 5). After 16 h of stirring at 105 °C, a second portion of ethyl acrylate (1.70 g, 1.8 mL, 16.95 mmol, 0.5 equiv) is added, and the mixture is stirred at 105 °C for an additional 10 h. After cooling to ambient temperature, the reaction mixture is dissolved in EtOAc (250 mL) and transferred to a 1-L Erlenmeyer flask. Saturated aqueous NH_4Cl and 25% aqueous NH_3 solutions (120 mL each) (Note 6) are added, the resulting mixture is vigorously stirred for 10 min with a 6 cm egg-shaped, Teflon-coated magnetic stirring bar and then transferred to a 1-L separatory funnel. The aqueous phase is extracted with EtOAc (2 × 150 mL). The combined organic phases are washed with brine (100 mL), dried over anhydrous $MgSO_4$ (80 g) for 30 min under stirring, and filtered. The solvent is removed from the filtrate under water-aspirator vacuum at 40 °C (20 mmHg). The residue (8.57 g) is purified by column chromatography on silica gel (Note 7)

to furnish 6.68–6.73 g (81%, potency corrected) of ethyl (*E*)-3-(2-acetamido-4-methylphenyl)acrylate as a colorless solid (Note 8) with a purity ≥98%, as determined by quantitative ^{1}H NMR spectroscopy and GC analysis (Note 9 and 10).

Notes

1. This operation is performed by opening the nitrogen inlet from the condenser and flushing the vessel for 10 minutes.
2. *N*-*m*-Tolylacetamide, $[RuCl_2(p\text{-cymene})]_2$, $Cu(OAc)_2{\cdot}H_2O$, and ethyl acrylate are obtained from Sigma-Aldrich, (97–98% purity). KPF_6 is also obtained from Sigma-Aldrich and used as received. The *N*-*m*-tolyacetamide should be ground with a mortar and pestle if it is supplied as a hardened solid.
3. Water is distilled in a stream of nitrogen prior to its use.
4. The initially deep-green color of the reaction mixture is changed to red-brown after 30 min heating, and subsequently becomes dark after additional 2 h of heating. Heating was performed using an Al block heater in place of an oil bath.
5. The consumption of *N*-*m*-tolylacetamide is monitored by GC-MS. Small aliquots were withdrawn, worked-up by following the extraction procedures to the final EtOAc extraction, and then studied by a coupled gas chromatography/mass spectrometry instrument *7890A GC-System* with mass detector *5975C (Triplex-Axis-Detector)* from Agilent Technologies equipped with *HP-5MS* column (30 m × 0.25 mm, film 0.25 μm). Retention time t_{ret} = 4.65 min with helium flowrate of 3 mL/min, temperature profile T = 70 °C/1 min, then 70–150 °C/2.7 min, then 150 °C/1 min, then 150–250 °C/2.9 min, then 250 °C/3 min. The final conversion of the limiting substrate is 95–100%.
6. Technical grade NH_4Cl and aqueous NH_3 solutions are obtained from Teknova and SAFC respectively.
7. The residue is dissolved in CH_2Cl_2 (60 mL) and then charged onto a column (7 × 20 cm, 300 g of silica gel). The column is eluted with *n*-hexane/EtOAc/CH_2Cl_2 2:2:1 (5 L) collecting the 200-mL fractions that contain material with R_f = 0.22. A total of eighteen 200-mL portions were collected, and the product was identified to be present in fractions 8 through 16.

8. Ethyl (*E*)-3-(2-acetamido-4-methylphenyl)acrylate has the following physicochemical and spectroscopic properties: mp = 155−156 °C; R_f = 0.06 (*n*-hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, *J*=7.1 Hz, 3 H), 2.22 (s, 3 H), 2.34 (s, 3 H), 4.24 (q, *J*=7.0, 2 H), 6.34 (d, *J*=15.9 Hz, 1 H), 7.00 (d, *J*=7.63 Hz, 1 H), 7.44 (d, *J*=7.8 Hz, 2 H), 7.54 (br s, 1 H), 7.77 (d, *J*=15.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 21.3, 21.4, 23.7, 60.5, 118.6, 125.6, 126.5, 126.6, 127.0, 136.1, 139.1, 141.2, 167.1, 169.7; IR (neat): 3225, 1711, 1661, 1635, 1610, 1537, 1492, 1164, 983, 813 cm^{-1}; MS *m*/*z* [M]$^+$: 247, 204, 160, 132, 117. HRMS [M + H$^+$] calcd for $C_{14}H_{18}NO_3$: 248.12812, found: 248.12787; [M + Na$^+$] calcd for $C_{14}H_{17}NNaO_3$: 270.11006, found: 270.10978
9. The analysis is performed applying coupled gas chromatography/mass spectrometry instrument *7890A GC-System* with mass detector *5975C (Triplex-Axis-Detector)* from Agilent Technologies equipped with *HP-5MS* column (30 m × 0.25 mm, film 0.25 μm). Retention time t_{ret} = 7.41 min with 3 mL·min^{-1} of He, temperature profile T = 70 °C/1 min, then 70–150 °C/2.7 min, then 150 °C/1 min, then 150–250 °C/2.9 min, then 250 °C/3 min, then 250–290 °C/1 min.
10. Quantitative ^{1}H NMR was performed on each sample using benzyl benzoate (Sigma-Aldrich, part number 55177) as an internal standard. Analysis of each sample was performed in duplicate. Isolated products from the two replicates analyzed as 99.7 wt% and 98.8 wt%, respectively.

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Discussion

Conventional palladium-catalyzed[2] cross-coupling reactions have matured to being among the most reliable tools for the formation of $C_{sp}2$–$C_{sp}2$ bonds for the preparation of styrene derivatives, which present useful intermediates in synthetic organic chemistry. Based on the pioneering studies by Mizoroki[3a] and by Heck,[3b] regioselective syntheses of styrenes[4] – including naturally occurring products[5] – have predominantly exploited palladium catalysts for reactions between prefunctionalized aryl (pseudo)halides and alkenes (Figure 1a).[6]

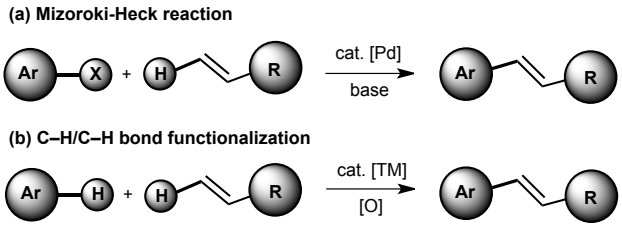
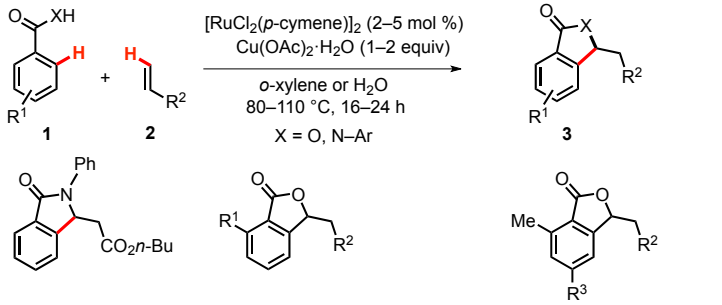


Figure 1. Strategies for transition metal-catalyzed styrene syntheses

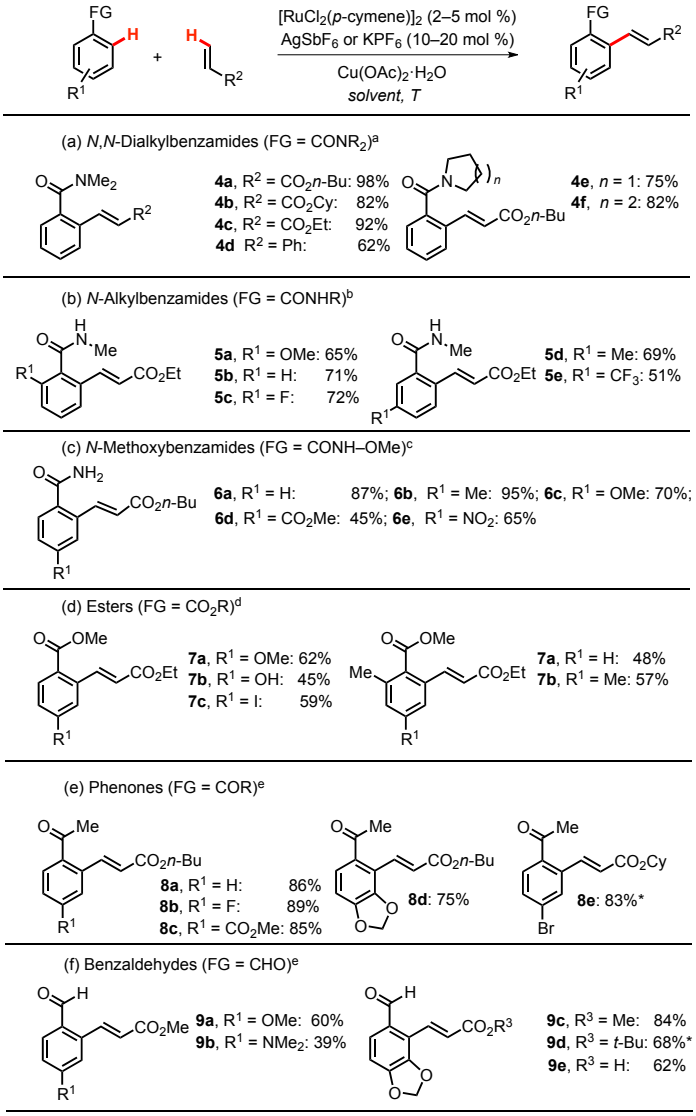
Despite its remarkable importance and the thus achieved considerable advances in organic synthesis, the Mizoroki-Heck reaction is unfortunately accompanied by the formation of stoichiometric amounts of potentially hazardous halide salts which can cause a significant environmental pollution. For this reason, recent research interest has shifted towards the development of more environmentally-friendly halide-free alkenylations. In 1967, Fujiwara and Moritani thus reported the first example of catalyzed direct oxidative coupling of arenes with styrene through a twofold C–H bond activation approach, wherein the C–H bond of the alkene was replaced with the aromatic moiety in the presence of a palladium catalyst.[7] This approach is not only advantageous with respect to the overall minimization of by-product formation (atom-economy),[8a,b] but also enables a streamlining of organic syntheses by significantly reducing the overall number of required reaction steps (step-economy).[8c] As a consequence, a plethora of synthetically useful protocols for palladium-catalyzed direct oxidative couplings between arenes and alkenes (Figure 1b) was elaborated during the last decade.[9] Furthermore, relatively expensive rhodium catalysts were also developed for oxidative alkenylations in recent years.[10,11] Conversely, fourteen times less expensive[12] ruthenium[13] complexes have only recently been exploited as catalysts for direct C–H bond alkenylations on arenes.[14]



Scheme 1. Ruthenium(II)-catalyzed oxidative alkenylation/aza(oxa)-Michael reaction sequence with benzanilides and benzoic acids 1[16]

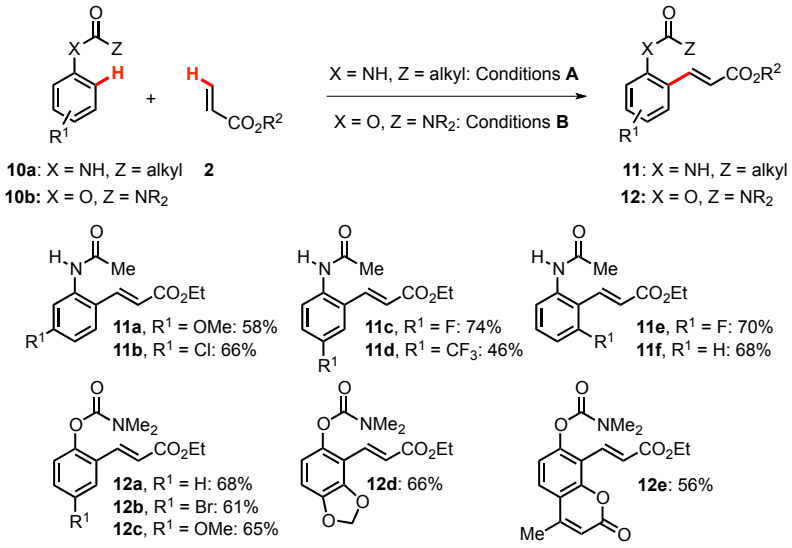
Recent years have witnessed a tremendous development in direct olefinations through twofold C–H bond functionalization of arenes and heteroarenes with readily accessible, selective, and rather inexpensive ruthenium catalysts.[15] Thus, oxidative alkenylations of arenes with electron-withdrawing coordinating substituents proved viable with ruthenium(II) complexes. For instance, ruthenium(II)-catalyzed oxidative alkenylations of benzanilides and benzoic acids **1** with acrylates or acrylonitriles **2** delivered bicycles **3** through intermolecular oxidative alkenylation and subsequent intramolecular aza- or oxa-Michael addition (Scheme 1).[16] Importantly, benzoic acids underwent this transformation with water as an environmentally benign, nontoxic reaction medium.[17]

Two-fold C–H bond functionalizations with *N*,*N*-dialkylbenzamides and their derivatives were, on the contrary, accomplished by Satoh, Miura and co-workers utilizing $[Ru(p\text{-cymene})Cl_2]_2$ as the catalyst, along with $AgSbF_6$ as the additive (Scheme 2a).[18] Notably, the reaction did not proceed in the absence of the silver salt. In independent studies, our research group simultaneously found that the use of less expensive KPF_6 instead of $AgSbF_6$ as the co-catalytic additive enabled the twofold C–H bond functionalizations of *N*-monoalkylated aromatic amides with ample scope and comparable efficacy in water as the reaction media (Scheme 2b).[19] Alternatively, ruthenium-catalyzed C–H bond olefination of benzamides can be realized applying pre-functionalized starting materials bearing an internal oxidizing directing group, such as found in *N*-methoxybenzamides. Their ruthenium-catalyzed C–H bond alkenylations afforded olefinated *N*–H-free benzamides **6** in MeOH as the solvent (Scheme 2c).[20]



Reaction conditions: [a]Alkene (2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.2 mol%), $AgSbF_6$ (20 mol%) $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), *t*-AmOH, 100 °C, 4 h.[18a] [b]Alkene (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (2.5–5.0 mol%), KPF_6 (10–20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv), H_2O, 100 °C, 20 h.[19] [c]Alk (1.8 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol%), NaOAc (30 mol%), MeOH, 60 °C, 4–24 h. [d]$[RuCl_2(p\text{-cymene})]_2$ (3–5 mol%), $AgSbF_6$ (20–40 mol%), $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), DCE, air 100 °C, 12–16 h.[21] [e]$[RuCl_2(p\text{-cymene})]_2$ (2–3 mol %), $AgSbF_6$ (10–20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (25–50 mol%), DCE, air, 100–110 °C, 12–16 h.[22] *Reaction in *tert*-butanol.

Scheme 2. Ruthenium(II)-catalyzed oxidative alkenylations with electron-withdrawing coordinating substituents



Conditions **A**: $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol%), KPF_6 (20 mol%), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), H_2O, 120 °C, 20 h.[19] Conditions **B**: $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2 \cdot H_2O$ (30 mol%), DME, 110 °C, 24 h.[23]

Scheme 3. Ruthenium(II)-catalyzed oxidative alkenylations with electron-donating coordinating substituents

In contrast to these chelation-assisted alkenylations of benzamides, analogous ruthenium-catalyzed oxidative functionalizations of readily available, yet only weakly coordinating esters have until recent proven elusive. Yet, the research groups of Ackermann[21a] and Jeganmohan[21b] independently disclosed reaction conditions for versatile oxidative direct functionalization of diversely decorated esters **7** (Scheme 2d). Notably, the catalytic system consisting of $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$ and $Cu(OAc)_2 \cdot H_2O$ was also found to be effective for alkenylations of phenones (Scheme 2e)[22a] and substituted benzaldehydes (Scheme 2f).[22b] Indeed, a ruthenium-catalyzed C–H bond functionalization of aromatic ketones provided alkenylated products **8** in 75–89% and 55–62% yield, when using substituted acrylates and styrenes, respectively, while alkenylated benzaldehydes **9** were obtained in slightly lower isolated yields.

Until recently, ruthenium-catalyzed oxidative alkenylations through twofold C–H bond functionalizations have proven to be limited to (hetero)arenes bearing electron-withdrawing groups (*vide supra*). Challenging oxidative olefinations with electron-rich arenes **10a**, on the contrary, were elaborated very recently with $[RuCl_2(p\text{-cymene})]_2$, KPF_6 and $Cu(OAc)_2{\cdot}H_2O$ as the catalytic system in water as the reaction medium (Scheme 3).[19] Moreover, a cationic ruthenium (II) catalyst derived from $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$ enabled highly efficient oxidative alkenylations of electron-rich aryl carbamates with weakly coordinating and removable directing groups.[23] These catalytic conditions allowed for highly productive cross-dehydrogenative C–H bond functionalizations of **10b** in a highly chemo-, diastereo- and site-selective fashion, affording diversely decorated phenol derivatives **12** (Scheme 3).[23]

Moreover, ruthenium-catalyzed oxidative alkenylations of arenes *N*-arylpyrazoles **13**, 2-aryl-1*H*-imidazoles, 2-aryl-1*H*-benzo[*d*]imidazoles, 2-arylbenzo[*d*]thiazoles **14** and 2-aryl-4,5-dihydrooxazoles **15** (Figure 2*a*) with heterocyclic directing groups have recently been reported by Dixneuf and coworkers[24] as well as Satoh, Miura and coworkers.[16a,18] Hence, substrates **13** were directly alkenylated with acrylates and acrylamides **2** employing $[RuCl_2(p\text{-cymene})]_2/Cu(OAc)_2{\cdot}H_2O$ or $[Ru(OAc)_2(p\text{-cymene})]/Cu(OAc)_2{\cdot}H_2O$ as the catalysts.[15]

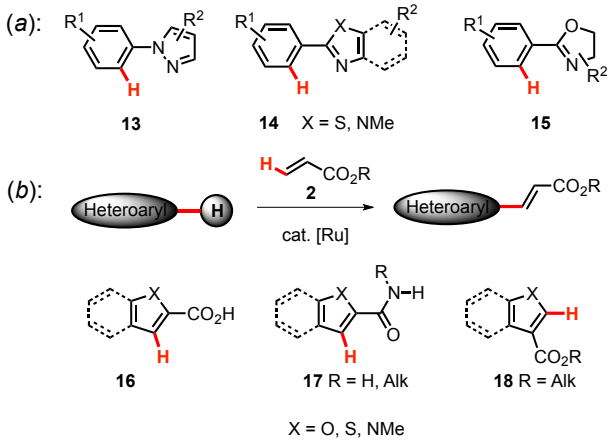


Figure 2. Ruthenium(II)-catalyzed oxidative alkenylations of (*a*) substrates bearing heterocyclic directing groups and (*b*) heteroarenes.

Ruthenium catalysts for oxidative C–H/C–H alkenylation reactions of heteroarenes have hitherto been less explored as compared to palladium- or rhodium-catalyzed analogous transformations. Yet, ruthenium-catalyzed alkenylations of furan-, thiophene-, 1-methyl-1*H*-pyrrole-, benzo[*b*]-thiophene-, benzofuran- or 1-methyl-1*H*-indole-2-carboxylic acids **16**, 2-carboxamides **17** and 3-alkoxycarbonyls **18** (Figure 2*b*) were achieved recently.[19,20,21,22b,25]

In summary, ruthenium(II) complexes allowed for challenging direct double C–H/C–H bond alkenylations of arenes with ample scope. Considering the practical importance of atom- and step-economical C–H bond alkenylations for natural product synthesis, drug discovery and crop protection, along with the unique features of the robust and selective ruthenium catalysts, significant further progress is expected in this rapidly evolving research area.

References

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2. (a) Handbook of Organopalladium Chemistry for Organic Synthesis (Ed.: Negishi, E.), Wiley-Interscience, New York, **2002**; (b) Metal-Catalyzed Cross-Coupling Reactions (Eds.: de Meijere, A.; Diederich, F.), Wiley-VCH, Weinheim, 2nd edn, **2004**; (c) Transition Metals for Organic Synthesis (Eds.: Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, 2nd edn, **2004**.
3. (a) Mizoroki, T.; Mori, K.; A. Ozaki A. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 581; (b) Heck, R. F. Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.
4. Selected reviews: (a). Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614–626; (b) Mc Cartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122–5150; (c) Bellina, F.; Chiappe, C. *Molecules* **2010**, *15*, 2211–2245; (d) Heravi, M. M.; Fazeli, A. *Heterocycles* **2010**, *81*, 1079–2026; (e) The Mizoroki–Heck Reaction (Ed.: Oestreich, M.), Wiley, Chichester, **2009**; (f) Polshettiwar,

V.; Molnar, A. *Tetrahedron* **2007**, *63*, 6949–6976; (g) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710; (h) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321; (i) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

5. An illustrative review: Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964.
6. The use of copper, nickel, platinum, cobalt, rhodium or iridium complexes in the Mizoroki-Heck reactions is significantly less developed; see: Ackermann, L.; Born, R. Mizoroki-Heck Reactions with Metals Other than Palladium. In: The Mizoroki–Heck Reaction (Ed.: Oestreich, M.), Wiley, Chichester, **2009**, pp. 383–403.
7. (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122; (b) Fujiwara, Y.; Moritani, I.; Matsuda, M. *Tetrahedron* **1968**, *24*, 4819–4824.
8. (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477; (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.
9. Reviews: (a) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214; (b) Yeung, C. S. Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292; (c) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K. *Synthesis* **2010**, 1399–1427; (d) Ferreira, E. M.; Zhang, H.; Stolz, B. M. Oxidative Heck-Type Reactions (Fujiwara-Moritani Reactions). In: The Mizoroki–Heck Reaction (Ed.: Oestreich, M.), Wiley, Chichester, **2009**, pp. 345–382. For selected recent communications, see: (e) Min, M.; Kim, Y.; Hong, S. *Chem. Commun.* **2013**, *49*, 196–198; (f) Cong, X.; You, J.; Gao, G.; Lan, J. *Chem. Commun.* **2013**, *49*, 662–664; (g) Harada, S.; Yano, H.; Obora, Y. *ChemCatChem* **2013**, *5*, 121–125; (h) Vasseur, A.; Harakat, D.; Muzart, J.; Le Bras, J. *Adv. Synth. Catal.* **2013**, *355*, 59–67; (i) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2013**, *52*, 1245–1247.
10. Pioneering reports: (a) Hong P.; Yamazaki, H. *Chem. Lett.* **1979**, *8*, 1335–1336; (b) Matsumoto, T.; Yoshida, H. *Chem. Lett.* **2000**, *29*, 1064–1065; (c) Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Catal.* **2002**, *206*, 272–280, and references cited therein.
11. For selected recent examples, see: (a) Yang, X.-F.; Hu, X.-H.; Feng, C.; Loh, T.-P. *Chem. Commun.* **2015**, *51*, 2532–2535; (b) Algarra, A. G.; Davies, D. L.; Khamker, Q.; Macgregor, S. A.; McMullin, C. L.; Singh, K.; Villa-Marcos, B. *Chem. Eur. J.* **2015**, *21*, 3087–3096; (c) Unoh, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* 2014, *17*, 704–707; (d) Becker, P.; Priebbenow, D. L.; Pirwerdjan, R.; Bolm, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 269–271; (e) Parthasarathy, K.; Bolm, C. *Chem. Eur. J.* **2014**, *20*, 4896–4900; (f) Vora, H. U.; Silvestri, A. P.; Engelin, C. J.; Yu, J.-Q. *Angew.*

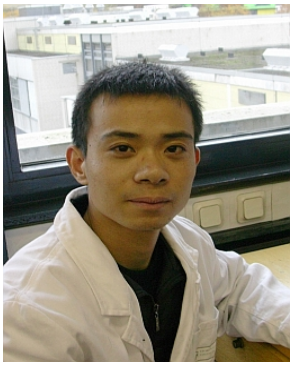
Chem. Int. Ed. **2014**, *53*, 2683–2686; (g) Nobushige, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*. **2014**, *16*, 1188–1191; (h) Suzuki, C.; Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Cat*. **2014**, *356*, 1521–1526; (i) Ye, B.; Cramer, N. *J. Am. Chem. Soc*. **2013**, *135*, 636–639; (j) Patureau, F. W.; Besset, T.; Glorius, F. *Org. Synth*. **2013**, *90*, 41–51, and references cited therein; (k) Zheng, L.; Wang, J. *Chem. Eur. J*. **2012**, *18*, 9699–9704; (l) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem. Int Ed*. **2012**, *51*, 2247–2251; (m) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett*. **2011**, *13*, 540–542; (n) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett*. **2011**, *13*, 2372–2375; (o) Li, X.; Gong, X.; Zhao, M.; Song, G.; Deng, J.; X. Li, X. *Org. Lett*. **2011**, *13*, 5808–5811; (p) Wang, F.; Song, G.; Du, Z.; Li, X. *J. Org. Chem*. **2011**, *76*, 2926 –2932; (q) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2011**, *76*, 3024–3033; (r) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2007**, *72*, 5362–5367; (s) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett*. **2007**, *9*, 1407–1409.

12. Thus, in April 2015, the prices of gold, platinum, rhodium, iridium, palladium and ruthenium were 1210, 1161, 1165, 580, 779 and 50 US$ per troy oz, respectively. See: http://www.platinumgroupmetals.org/
13. For recent reviews on ruthenium-catalyzed C–H bond functionalization, see: (a) Ackermann, L. *Org. Process Res. Dev*. **2015**, *18*, 260–269; (b) Bruneau, C. *Top. Organomet. Chem*. **2014**, *48*, 195–236; (c) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Cat*. **2014**, *356*, 1461–1479; (d) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun*. **2014**, *50*, 29–39; (e) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev*. **2013**, **42**, 5744–5767; (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev*. **2012**, *112*, 5879–5918; (g) Ackermann, L. *Pure Appl. Chem*. **2010**, *82*, 1403–1413; (h) Ackermann, L.; Vicente, R. *Top. Curr. Chem*. **2010**, *292*, 211–229.
14. For a review on related ruthenium-catalyzed oxidative annulations of alkynes through initial C–H bond functionalizations, see: L. Ackermann, L. *Acc. Chem. Res*. **2014**, *47*, 281–295;
15. A review: Kozhushkov, S. I.; Ackermann, L. *Chem. Sci*. **2013**, *4*, 886–896.
16. (a) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett*. **2011**, *40*, 1165–1166; (b) Ackermann, L.; Pospech, J. *Org. Lett*. **2011**, *13*, 4153–4155. Recently reported results: (c) Manoharan, R.; M. Jeganmohan, M. *Chem. Commun*. **2015**, *51*, 2929–2932; (d) Li, J.; John, M.; Ackermann, L. *Chem. Eur. J*. **2014**, *20*, 5403–5408. For the related ruthenium(II)-catalyzed oxidative C–H akenylations of sulfonic

acids, sulfonamides and phenols, see: (e) Fabry, D. C.; Ronge, M. A.; Zoller, J.; Rueping, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 2801–2805. (f) Ma, W.; Mei, R.; Tenti, G.; Ackermann, L. *Chem. Eur. J.* **2014**, *20*, 15248–15251; (g) Ma, W.; Ackermann, L. *Chem. Eur. J.* **2013**, *19*, 13925–13928.
17. Reviews: (a) Simon, M.-O.; Li, C.-J. *Chem. Soc. Rev.* **2012**, *41*, 1415–1427; (b) Organic Reactions in Water (Ed.: Lindstorm, U. M.) Wiley-Blackwell, New York, **2007**.
18. (a) Hashimoto, Y.; Ortloff, T.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *Chem. Lett.* **2012**, *41*, 151–153; (b) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166–4169.
19. Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728–731.
20. (a) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736–739. See also: (b) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551.
21. (a) Graczyk, K.; Ma, W.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4110–4113. See also: (b) Padala, K.; Pimparkar, S.; Madasamy, P.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 7140–7142.
22. (a) Padala, K.; Jeganmohan, M. *Org. Lett.* **2011**, *13*, 6144–6147; (b) Padala, K.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 1134–1137.
23. Li, J.; Kornhaaß, C.; Ackermann, L. *Chem. Commun.* **2012**, *48*, 11343–11345.
24. (a) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, ***13***, 3075–3078; (b) Li, B.; Devaraj, K.; Darcel, C.; Dixneuf, P. H. *Green Chem.* **2012**, *14*, 2706–2709.
25. Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706–708.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Ethyl (*E*)-3-(2-Acetamido-4-methylphenyl)acrylate: 2-Propenoic acid, 3-[2-(acetylamino)-4-methylphenyl]-, ethyl ester, (2*E*); (1355020-48-2)
N-*m*-Tolylacetamide: m-Methyl-acetanilide (537-92-8)
$[RuCl_2(p\text{-cymene})]_2$ (52462-29-0)
KPF_6: Potassium hexafluorophosphate; (17084-13-8)
$Cu(OAc)_2{\cdot}H_2O$: Copper(II) acetate monohydrate; (6046-93-1)
Ethyl acrylate: Ethyl propenoate; (140-88-5)



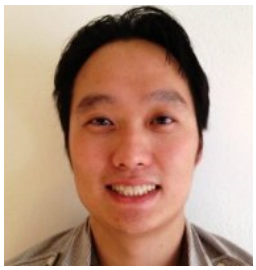
Lianhui Wang was born in Henan, People's Republic of China, in 1983. He received his B. S. in chemistry in 2007 and completed his M. Sc. in chemistry on palladium-catalyzed cross-coupling reactions in 2010 under the supervision of Prof. Dr. Xiuling Cui and Prof. Dr. Zhiwu Zhu from Zhengzhou University (P. R. China). In 2010 he was awarded with the China Scholarship Council doctoral fellowship and started his PhD studies on ruthenium-catalyzed oxidative C–H activation reactions in the group of Prof. Dr. Lutz Ackermann (University of Göttingen, Germany). Upon completion of his Ph.D. in 2014, he initiated his academic career at the Institute of Molecular Medicine and School of Biomedical Sciences at Huaqiao University, Xiamen, P. R. of China.

Karsten Rauch was born in 1963 in Göttingen, Germany. In 1982, he completed his training as a technician in chemistry (University of Göttingen). From 1983 to 1984, he worked in the group of Prof. Dr. Hans Kuhn (MPI for Biophysical Chemistry, Göttingen) on monolayers and amino acid chemistry. Since 1985, he worked in the Department for Organic Chemistry (University of Göttingen) in the group of Prof. Dr. Lüttke on synthetic chemistry, since 1989, in the group of Prof. Dr. Armin de Meijere on synthesis and catalysis. Since 2007, he is working in the group of Prof. Dr. Lutz Ackermann on catalysis.

Alexander V. Lygin was born in 1984 in Krasnokamensk, Russia. He studied chemistry at the M.V. Lomonosov Moscow State University (Moscow, Russia) in 2001–2006 and completed his diploma on metallocene chemistry in 2006 under the supervision of Dr. Alexander Z. Voskoboynikov. He completed his PhD studies on the synthesis of heterocycles from isocyanides in the group of Prof. Dr. Armin de Meijere (University of Göttingen, Germany) and obtained his doctoral degree in 2009. He was a postdoctoral coworker in the laboratory of Prof. Dr. Lutz Ackermann at the University of Göttingen in 2011–2012. Since 2012 he is employed at EVONIC Industries, Darmstadt, Germany. His research interests include organometallic chemistry, chemistry of heterocycles and catalysis.

Sergei I. Kozhushkov was born in 1956 in Kharkov, USSR. He studied chemistry at Lomonosov Moscow State University, where he obtained his doctoral degree in 1983 under the supervision of Professor N. S. Zefirov and performed his "Habilitation" in 1998. From 1983 to 1991, he worked at Moscow State University and then at Zelinsky Institute of Organic Chemistry. In 1991, he joined the research group of Professor A. de Meijere (Georg-August-Universität Göttingen, Germany) as an Alexander von Humboldt Research Fellow. Since 2001 he has a permanent position as a Senior Scientist at the Georg-August-University of Göttingen. Since 2007, he is working in the research group of Professor L. Ackermann (Georg-August-Universität Göttingen, Germany). His current research interests focus on the chemistry of highly strained small ring compounds under transition metals catalysis.

Lutz Ackermann (1972) studied Chemistry at the Christian-Albrechts-University Kiel, Germany, and received his Ph.D. from the University of Dortmund in 2001 for research under the supervision of Alois Fürstner at the Max-Plank-Institut für Kohlenforschung in Mülheim /Ruhr. He was a postdoctoral coworker in the laboratory of Robert G. Bergman at the UC Berkeley before initiating his independent career in 2003 at the Ludwig-Maximilians-University München. In 2007, he became Full Professor at Georg-August-University Göttingen, and serves as the Dean at the Georg-August-University Göttingen since 04.2011. His recent awards and distinctions include a JSPS visiting professor fellowship (2009), an AstraZeneca Excellence in Chemistry Award (2011) and an ERC Consolidates Grant (2012). The development of novel concepts for sustainable catalysis and their application to organic synthesis constitute his major current research interests.



William Trieu received his B.S in chemical engineering in 2007 at the University of California, Berkeley where he worked for Prof. Jay Keasling on the production of an antimalarial drug precursor. He worked at Merck supporting Gardasil fermentation operations prior to joining Amgen in 2008. At Amgen he has worked on a number of projects in which he has optimized chemical processes by utilizing chemical engineering principles. He received his M.S in chemical engineering in 2012 at the University of Southern California.

Multiplets Integrals Sum 16.52	***Number of Nuclei***	17 H's	

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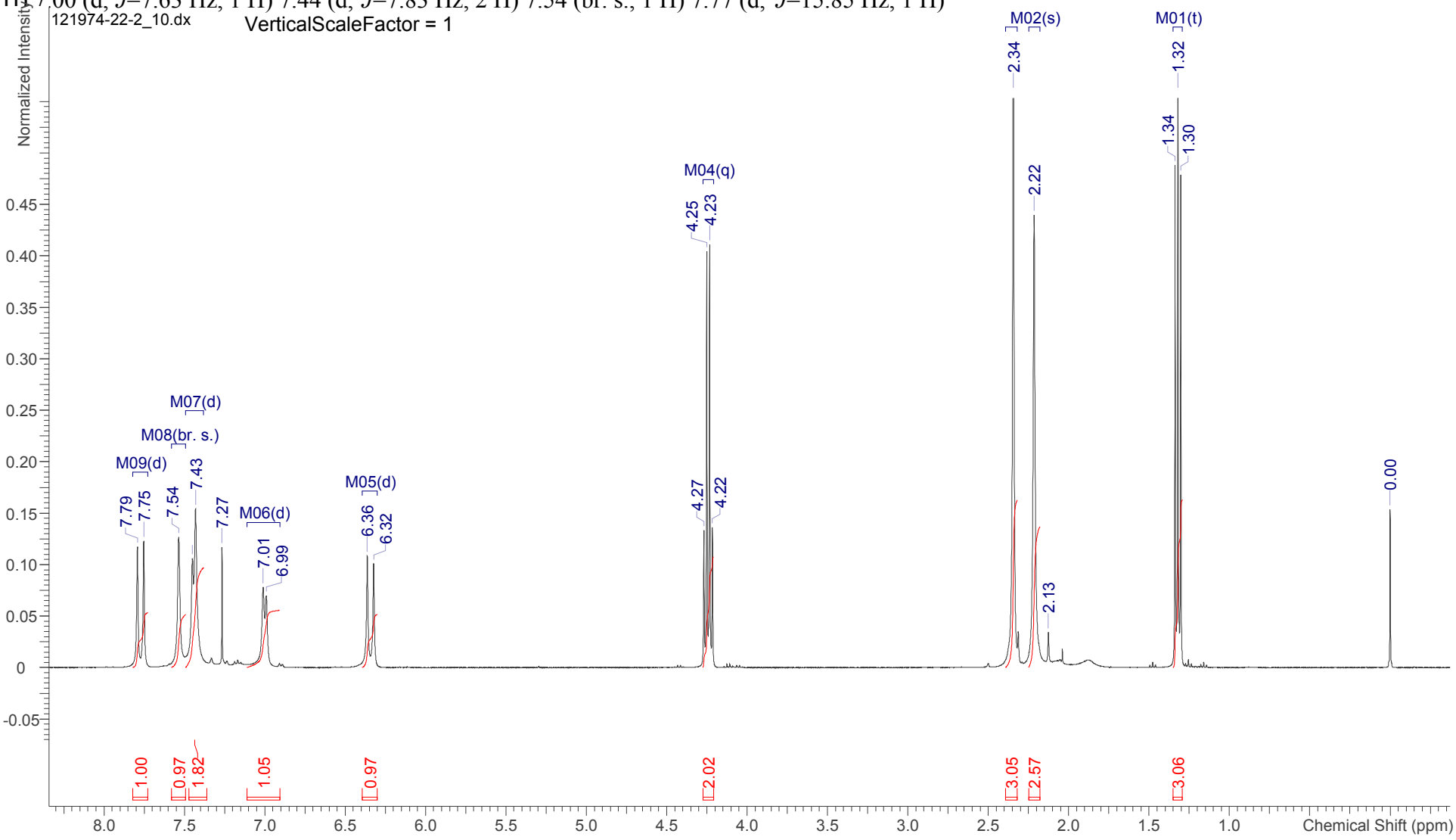
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2393.8423	***Sweep Width (Hz)***	6409.86
Temperature (degree C)	27.000						

^{1}H NMR (400 MHz, CHLOROFORM-*d*) ä ppm 1.32 (t, *J*=7.14 Hz, 3 H) 2.22 (s, 3 H) 2.34 (s, 3 H) 4.24 (q, *J*=7.04 Hz, 2 H) 6.34 (d, *J*=15.85 Hz, 1 H) 7.00 (d, *J*=7.63 Hz, 1 H) 7.44 (d, *J*=7.83 Hz, 2 H) 7.54 (br. s., 1 H) 7.77 (d, *J*=15.85 Hz, 1 H)



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Temperature (degree C) 27.000							

^{13}C NMR (101 MHz, CHLOROFORM-*d*) ä ppm 14.28 (s, 1 C) 21.34 (s, 1 C) 21.42 (s, 1 C) 23.69 (s, 1 C) 60.50 (s, 1 C) 76.88 (s, 1 C) 77.20 (s, 1 C) 77.52 (s, 1 C) 118.56 (s, 1 C) 125.58 (s, 1 C) 126.47 (s, 1 C) 126.62 (s, 1 C) 126.96 (s, 1 C) 136.05 (s, 1 C) 139.72 (s, 1 C) 141.17 (s, 1 C) 167.05 (s, 1 C) 169.66 (s, 1 C)