EDGE ARTICLE

Check for updates

Cobalt-catalyzed hydroxymethylarylation of terpenes with formaldehyde and arenes†

Jun Yang,[ab] Ding-Wei Ji, [ID][b] Yan-Cheng Hu, [ID][b] Xiang-Ting Min,[b] Xiangge Zhou [ID] *[a] and Qing-An Chen [ID] *[b]

Terpenes, consisting of isoprene monomer units, represent a family of naturally abundant compounds. The difunctionalization of terpenes is highly appealing yet remains challenging, since the multiple unbiased C=C bonds of terpenes lead to difficulty in controlling the regioselectivity. Herein, a cobalt(III)-catalyzed C–H activation strategy has been developed to facilitate hydroxymethylarylation of terpenes with formaldehyde and arenes with high chemo- and regio-selectivities. These (chemo- and regio-) selectivities are governed by the coordination abilities of isoprene, directing groups and the steric effect. This terpene difunctionalization also features high atom and step economy through a C–H addition pathway.

Introduction

Homoallylic alcohols and their derivatives are versatile synthetic intermediates that have been utilized for rapid buildup of molecular complexity.[1] Additionally, the homoallylic alcohol fragment itself is found in a number of biologically active compounds and natural products (Scheme 1). For instance, the cryptophycin family consists of cytotoxins found in blue-green alga and show excellent activity against solid tumors.[2] Pleuromutilins inhibit the growth of predominantly Gram-positive pathogens.[3] Maoecrystal V shows potential selectivity against HeLa cell lines.[4] Bryostatins exhibit remarkable biological activity against a range of cancers and other diseases such as Alzheimer's disease.[5] Therefore, considerable efforts have been devoted to the catalytic synthesis of homoallylic alcohols over the past few decades.[1]

Transition metal-catalyzed reductive allylation of ketones/aldehydes with 1,3-dienes has been shown as an efficient approach for the construction of homoallylic alcohols.[6] Although remarkable progress has been achieved in this field, a three-component cascade reaction of arenes, dienes and carbonyls, which can be used for rapid assembly of more complex molecules, still remains limited. In particular, few reports employed naturally abundant terpenes[7] as allyl precursors. Formaldehyde is an essential C1 bulk chemical that can be employed to introduce the hydroxymethyl group.[8] Owing to this synthons can be produced from both petroleum and biomass, and direct transformation of basic feedstocks into value-added homoallylic alcohols would be highly appealing.

Through a transmetalation pathway, three-component additions of organometallic reagents to isoprene and aldehydes have been developed under Ni or Pt catalysis (Fig. 1a).[9] From the viewpoint of atom and step economy, directed C–H bond addition to terpenes and carbonyls represents a more attractive process.[10] In this regard, Ellman[11] and Zhao[12] recently reported an elegant Co- and Rh-catalyzed C–H bond addition to dienes and aldehydes, respectively. However, these reactions gave modest yields when involving terpenes as substrates and only highly activated aldehyde ethyl glyoxylate was demonstrated (Fig. 1b).[12] Inspired by these studies, we set out to develop a methodology to achieve the hydroxymethylarylation of terpenes with formaldehyde and arenes. To realize this proposal, we had to overcome the following challenges: (1) chemoselectivity control. In terms of electrophilicity, formaldehyde is a better coupling partner than terpenes with initially formed carbon–metal species.[8,13,14] (2) Regioselectivity control.[15]
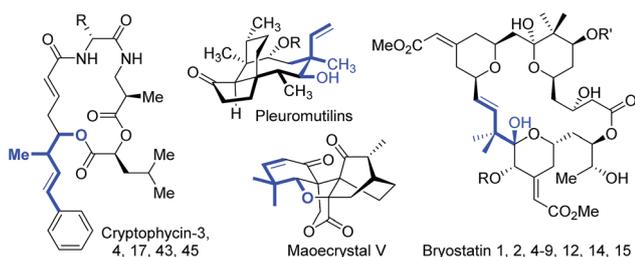
Scheme 1 Representative homoallylic alcohols and their derivatives in nature.

[a]Institute of Homogeneous Catalysis, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China. E-mail: zhouxiangge@scu.edu.cn

[b]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China. E-mail: qachen@dicp.ac.cn; Web: [http://www.lbcs.dicp.ac.cn]

a) Difunctionalization of isoprene with aldehydes through transmetalation

b) Rh-catalyzed difunctionalization of terpenes with aldehydes through C–H activation

c) Co-catalyzed hydroxymethylarylation of terpenes through C–H activation

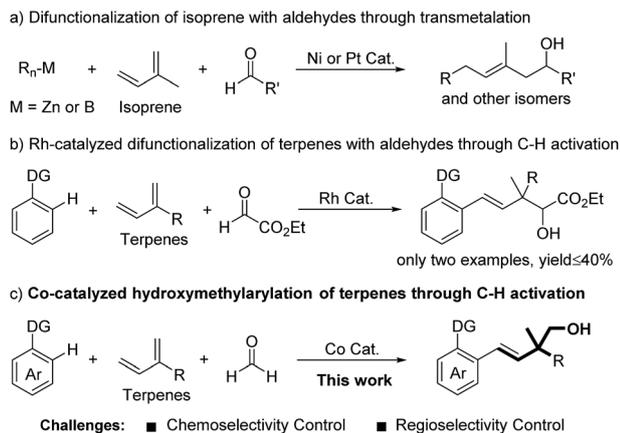Challenges: ■ Chemoselectivity Control ■ Regioselectivity Control

Fig. 1 Catalytic difunctionalization of terpenes with aldehydes.

Terpenes possess at least two unbiased C=C bonds, thus leading to a minimum of four different migratory insertion orientations with carbon–metal species (Fig. 1c). Herein, we demonstrated a Co-catalyzed three-component C–H bond addition to terpenes and formaldehyde.

Results and discussion

We began our investigation by employing 2-phenylpyridine, isoprene, and paraformaldehyde as the model substrates (Table 1). In the presence of Cp*Co(CO)I$_2$ (5 mol%) and AgSbF$_6$, the

Table 1 Optimization for hydroxymethylarylation of isprene[a]

Entry	Additive	x (mol%)	Solvent	Yield[b] (%)
1	—	—	Dioxane	29
2	PivONa	10	Dioxane	39
3	NaOAc	10	Dioxane	48
4	HCO$_2$H	10	Dioxane	41
5	CH$_3$CH$_2$CO$_2$H	10	Dioxane	58
6	PhCO$_2$H	10	Dioxane	32
7	HOAc	10	Dioxane	57
8	HOAc	20	Dioxane	72
9	HOAc	30	Dioxane	86
10	HOAc	40	Dioxane	90(86)[c]
11	HOAc	50	Dioxane	90
12	HOAc	40	MeOH	51
13	HOAc	40	DCM	60
14	HOAc	40	PhCl	56
15	HOAc	40	THF	74
16	HOAc	40	MeCN	14

[a] Conditions: **1a** (0.20 mmol), **2** (0.40 mmol), **3** (0.60 mmol), Cp*Co(CO)I$_2$ (5 mol%), AgSbF$_6$ (10 mol%), additive (10–50 mol%), solvent (0.50 mL), 50 °C, and 16 h. [b] Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield.

desired homoallylic alcohol **4a** can be obtained in 29% yield (entry 1). The evaluation of additives showed that both carboxylate salts and carboxylic acids are able to accelerate the reaction, probably by promoting the C–H activation via a concerted metallation-deprotonation pathway (entries 2–7).[16] Notably, increasing the amount of HOAc to 40 mol% led to a better yield (entries 8–11). A screening of solvents suggests that dioxane is the optimal choice in terms of yield (entries 12–16).

With the optimized conditions in hand, we subsequently explored the substrate scope for this three-component reaction (Table 2). Subjecting benzoquinoline to standard conditions produced homoallylic alcohol **4b** in a nearly quantitative yield. 2-Phenylpyrimidine was a suitable substrate as well (**4c**). Both electron-withdrawing and -donating groups on the pyridine motif were compatible with the process (**4d–f**). The substituents on the phenyl ring were further surveyed. Fluoro-substituted arenes underwent the reaction smoothly, providing the corresponding products in good yields (**4g** and **4h**). Electron-donating MeO (**4i**, **4m**, and **4q**) and Me (**4j** and **4n**), regardless of their positions, were all well tolerated. Notably, the protocol could be successfully extended to hydroxyl-substituted arenes (**4u**). The substrates bearing electron-withdrawing substituents

**Table 2** Substrate scope for hydroxymethylarylation of isoprene

4a: 86% **4b**: >99% **4c**: 40%

4d: 69% **4e**: 66% **4f**: 47%

4g: 86% **4h**: 94% **4i**: 52%

4j: 75% **4k**: 82% **4l**: 62%

4m: 56% **4n**: 35% **4o**: 73%

4p: 51% **4q**: 62% **4r**: 62%

4s: >99% **4t**: 25% **4u**: 64%

such as acetyl (**4k**), chloro (**4l** and **4p**), bromo (**4o**), and trifluoromethyl (**4r**) groups could also participate in the reactions. It is worth mentioning that only a single regioisomer was observed in all cases of *meta*- and *para*-substituted arenes. Remarkably, a 2-naphthyl derived arene could be quantitatively transformed into homoallylic alcohol **4s**.

Next, we explored the scope of terpenes (Table 3). Increasing the isoprene units from 2 to 4 (myrcene **5a**, farnesene **5b**, and geranyl myrcene **5c**) had no significant effect on the reactivity However, attempts to realize the coupling of ocimene, an isomer of myrcene **5a**, with formaldehyde and arenes did not succeed even by varying different directing groups. Solanesene (**5d**) with nine isoprene units, owing to its poor solubility, gave the target product in a lower yield. Phytadiene (**5e**), derived from chlorophyll, was also applicable for the transformation. In the cases of natural terpenoids myrcenol (**5f**) and farnesenol (**5g**), the reactions occurred with high efficiency (79–81%). A bicyclic diterpene sclarene (**5h**) was also suitable for this three-component protocol.

Table 3 Substrate scope of terpenes
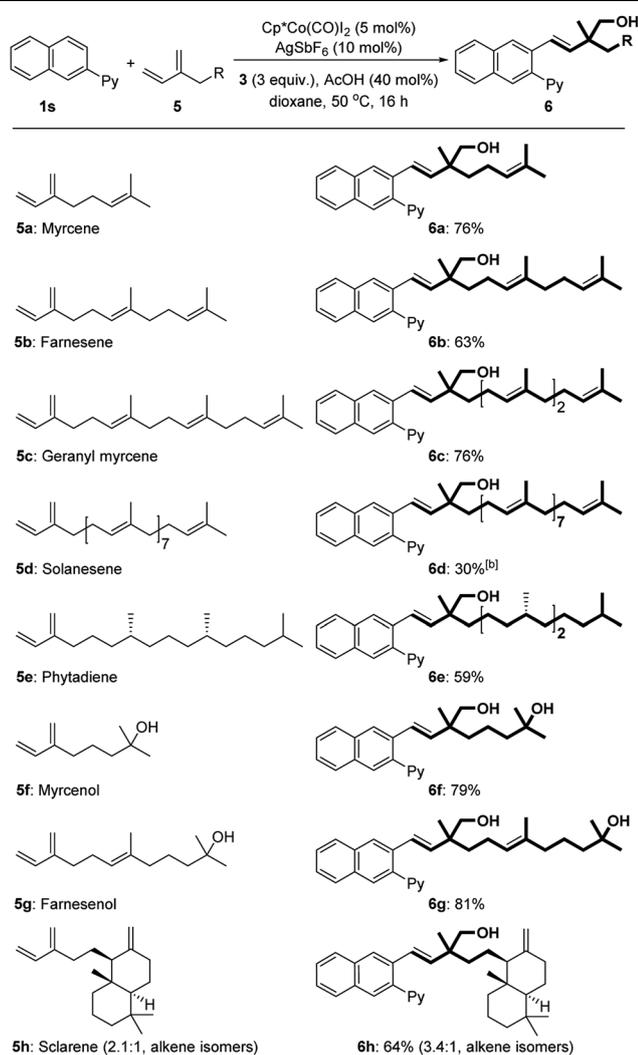
To verify the practical utility of this protocol, a gram scale reaction has been carried out to deliver hydroxymethylarylation product **6a** in 84% yield (1.565 g, Fig. 2). Oxidation of **6a** with *m*CPBA gave epoxide **9** in 54% yield accompanied by a small amount of seven-membered cyclic product **10**. Notably, protic (DCM/H$_2$O 1 : 1) solvent could promote the ring opening of epoxide **9**.[17] This observation inspired us to use HOTf (30 mol%) as an additive, which could facilitate the direct synthesis of **10** (37% yield) from **6a**.

Some control experiments have been performed to explore the mechanism (Fig. 3). Kinetic isotope effect (KIE) experiments were performed with the reactions of **1a** in parallel and in competition with D$_5$-**1a** under standard conditions. The KIE values for the parallel and competitive reactions were determined to be 2.8 and 2.0, respectively (eqn (1)). These results imply that C–H bond cleavage might be involved in the rate-determining step. The incorporation of hydrogen atoms onto the recovered starting material indicates that there is a reversible C–H activation process under this cobalt catalysis (eqn (2)). The employment of AcOD as an additive afforded the target product in 70% yield with deuterium atoms incorporating in the methyl group (D$_1$-**4a**), indicating that relatively few H-D exchange reactions were involved in the process (eqn (3)). When formaldehyde was not involved in the reaction, an oxidative coupling of isoprene with **1a** occurred but gave a low yield of **7**, which presumably was ascribed to the absence of an external oxidant (eqn (4)). A small amount of direct formaldehyde hydroarylation product **8** (ref. 13) could be obtained in the absence of isoprene. However, no hydroarylation product **8** was observed under standard conditions (eqn (5)). Both two-component coupling results (eqn (4) and (5)) suggest the chemoselectivity most likely originates from the difference in coordination ability between terpenes and formaldehyde toward the formed aryl-cobalt intermediate.

To better interpret the origin of regioselectivity, we provided more details about potential pathways for the formation of regiospecific homoallylic alcohol products (Fig. 4). According to different addition orientations, the addition of 5-membered Co-complex **A** (generated from the C–H activation step between the Co precatalyst and **1a**) to isoprene may generate four addition modes (**B1**, **B2**, **B3** and **B4**). However, due to the steric hindrance (**B1** and **B2**) or β-elimination issue (**B3**), 1,2-/2,1- or 3,4-adducts should be disfavored. Instead, 4,3-adduct **B4** can be smoothly
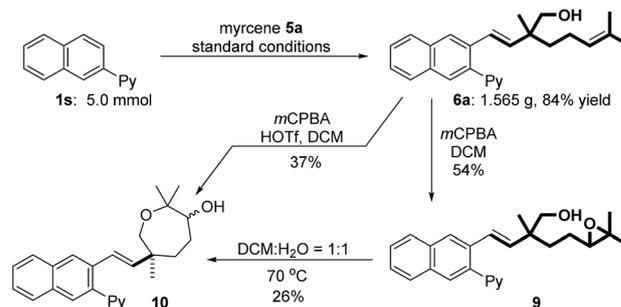

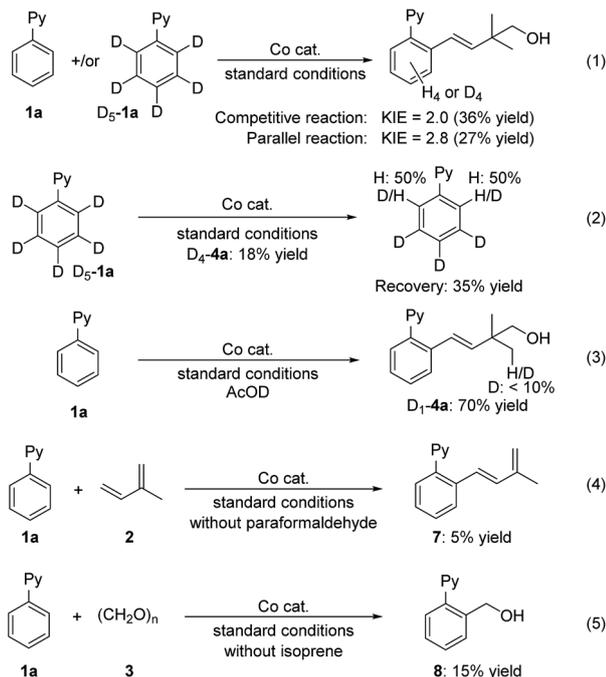**Fig. 2** Scale-up experiment and further derivatization.
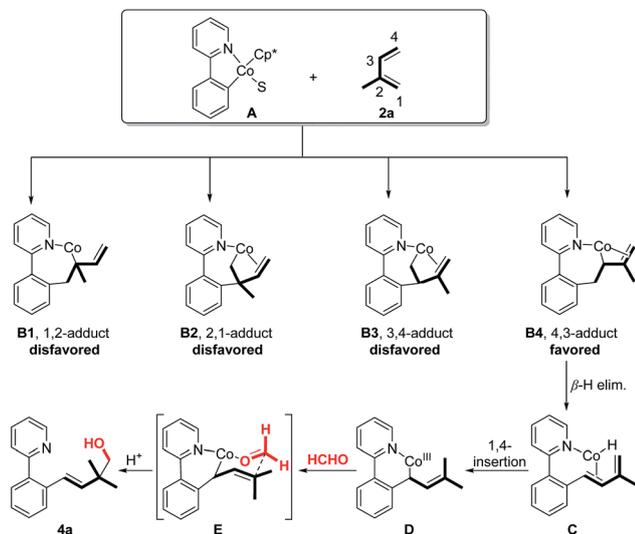
Fig. 3 Mechanistic studies.

Fig. 4 Proposed mechanism for regioselectivity control.

produced through β-elimination to deliver Co-hydride **C**. Then, 1,4-insertion of Co–H into the isoprene unit gives prenyl-Co intermediate **D**. Finally, the directed addition of **D** to formaldehyde through a chair-like transition state **E** yields homoallylic alcohol product **4a** and regenerates the cobalt catalyst.

Conclusions

In conclusion, a three-component protocol for the hydroxymethylarylation of terpenes with paraformaldehyde and arenes has been developed *via* cobalt catalysis.[18] The chemoselectivity

results from the difference in the coordination ability between terpenes and formaldehyde. The steric hindrance and coordination abilities of isoprene and directing groups dominate the regioselectivities. Through a C–H addition pathway, this terpene difunctionalization protocol also features high atom and step economy. Further studies on the enantioselective hydroxymethylarylation of terpenes are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 For representative reviews on the synthesis of homoallylic alcohols see: (*a*) M. Yus, J. C. Gonzalez-Gomez and F. Foubelo, *Chem. Rev.*, 2011, **111**, 7774; (*b*) M. Yus, J. C. Gonzalez-Gomez and F. Foubelo, *Chem. Rev.*, 2013, **113**, 5595; (*c*) H.-X. Huo, J. R. Duvall, M.-Y. Huang and R. Hong, *Org. Chem. Front.*, 2014, **1**, 303; (*d*) J. Feng, M. Holmes and M. J. Krische, *Chem. Rev.*, 2017, **117**, 12564; (*e*) M. Holmes, L. A. Schwartz and M. J. Krische, *Chem. Rev.*, 2018, **118**, 6026; (*f*) Y.-L. Liu and X.-T. Lin, *Adv. Synth. Catal.*, 2019, **361**, 876.

2 (*a*) G. Trimurtulu, I. Ohtani, G. M. L. Patterson, R. E. Moore, T. H. Corbett, F. A. Valeriote and L. Demchik, *J. Am. Chem. Soc.*, 1994, **116**, 4729; (*b*) R. A. Barrow, T. Hemscheidt, J. Liang, S. Paik, R. E. Moore and M. A. Tius, *J. Am. Chem. Soc.*, 1995, **117**, 2479; (*c*) T. Golakoti, J. Ogino, C. E. Heltzel, L. T. Husebo, C. M. Jensen, L. K. Larsen, G. M. L. Patterson, R. E. Moore, S. L. Mooberry, T. H. Corbett and F. A. Valeriote, *J. Am. Chem. Soc.*, 1995, **117**, 12030.

3 (*a*) F. Kavanagh, A. Hervey and W. J. Robbins, *Proc. Natl. Acad. Sci. U. S. A.*, 1951, **37**, 570; (*b*) S. K. Murphy, M. Zeng and S. B. Herzon, *Science*, 2017, **356**, 956; (*c*) M. Zeng, S. K. Murphy and S. B. Herzon, *J. Am. Chem. Soc.*, 2017, **139**, 16377.

4 (*a*) S. H. Li, J. Wang, X. M. Niu, Y. H. Shen, H. J. Zhang, H. D. Sun, M. L. Li, Q. E. Tian, Y. Lu, P. Cao and Q. T. Zheng, *Org. Lett.*, 2004, **6**, 4327; (*b*) P. Lu, A. Mailyan, Z. Gu, D. M. Guptill, H. Wang, H. M. L. Davies and A. Zakarian, *J. Am. Chem. Soc.*, 2014, **136**, 17738; (*c*) A. Cernijenko, R. Risgaard and P. S. Baran, *J. Am. Chem.*

Soc., 2016, **138**, 9425. Maoecrystal V showed little to no activity against cancer cell lines according to Baran's report.

5 (a) G. R. Pettit, J. F. Day, J. L. Hartwell and H. B. Wood, *Nature*, 1970, **227**, 962; (b) G. R. Pettit, C. L. Herald, D. L. Doubek, D. L. Herald, E. Arnold and J. Clardy, *J. Am. Chem. Soc.*, 1982, **104**, 6846; (c) B. M. Trost and G. Dong, *Nature*, 2008, **456**, 485.

6 For selected examples on catalytic reductive coupling of dienes with carbonyl compounds see: (a) M. Kimura, A. Ezoe, M. Mori, K. Iwata and Y. Tamaru, *J. Am. Chem. Soc.*, 2006, **128**, 8559; (b) F. Shibahara, J. F. Bower and M. J. Krische, *J. Am. Chem. Soc.*, 2008, **130**, 6338; (c) H. Y. Cho and J. P. Morken, *J. Am. Chem. Soc.*, 2010, **132**, 7576; (d) M. Fukushima, D. Takushima and M. Kimura, *J. Am. Chem. Soc.*, 2010, **132**, 16346; (e) J. R. Zbieg, E. L. McInturff, J. C. Leung and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 1141; (f) J. R. Zbieg, J. Moran and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 10582; (g) L. T. Kliman, S. N. Mlynarski, G. E. Ferris and J. P. Morken, *Angew. Chem., Int. Ed.*, 2012, **51**, 521; (h) J. R. Zbieg, E. Yamaguchi, E. L. McInturff and M. J. Krische, *Science*, 2012, **336**, 324; (i) B. Y. Park, T. P. Montgomery, V. J. Garza and M. J. Krische, *J. Am. Chem. Soc.*, 2013, **135**, 16320; (j) K. D. Nguyen, D. Herkommer and M. J. Krische, *J. Am. Chem. Soc.*, 2016, **138**, 14210; (k) Y. Y. Gui, N. Hu, X. W. Chen, L. L. Liao, T. Ju, J. H. Ye, Z. Zhang, J. Li and D. G. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 17011; (l) B. Fu, X. Yuan, Y. Li, Y. Wang, Q. Zhang, T. Xiong and Q. Zhang, *Org. Lett.*, 2019, **21**, 3576; (m) C. Li, R. Y. Liu, L. T. Jesikiewicz, Y. Yang, P. Liu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2019, **141**, 5062; (n) R. Y. Liu, Y. Zhou, Y. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2019, **141**, 2251.

7 (a) E. M. Davis and R. Croteau, *Top. Curr. Chem.*, 2000, **209**, 53; (b) K. Chen and P. S. Baran, *Nature*, 2009, **459**, 824; (c) Z. G. Brill, M. L. Condakes, C. P. Ting and T. J. Maimone, *Chem. Rev.*, 2017, **117**, 11753.

8 B. Sam, B. Breit and M. J. Krische, *Angew. Chem., Int. Ed.*, 2015, **54**, 3267.

9 For the catalytic three-component reaction of isoprene and aldehydes through the transmetalation pathway see: (a) M. Kimura, S. Matsuo, K. Shibata and Y. Tamaru, *Angew. Chem., Int. Ed.*, 1999, **38**, 3386; (b) M. Kimura, K. Shibata, Y. Koudahashi and Y. Tamaru, *Tetrahedron Lett.*, 2000, **41**, 6789; (c) J. B. Morgan and J. P. Morken, *Org. Lett.*, 2003, **5**, 2573; (d) M. Kimura, A. Ezoe, M. Mori and Y. Tamaru, *J. Am. Chem. Soc.*, 2005, **127**, 201; (e) H. Y. Cho and J. P. Morken, *J. Am. Chem. Soc.*, 2008, **130**, 16140; (f) Y. Ohira, M. Hayashi, T. Mori, G. Onodera and M. Kimura,

New J. Chem., 2014, **38**, 330; (g) Y. Xiong and G. Zhang, *J. Am. Chem. Soc.*, 2018, **140**, 2735.

10 For representative reviews on C–H functionalization see: (a) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; (b) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (c) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (d) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (e) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (f) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (g) H. M. L. Davies, J. Du Bois and J.-Q. Yu, *Chem. Soc. Rev.*, 2011, **40**, 1855; (h) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (i) J. Wencel-Delord, T. Droege, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (j) J. He, M. Wasa, K. S. L. Chan, O. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754.

11 (a) J. A. Boerth, S. Maity, S. K. Williams, B. Q. Mercado and J. A. Ellman, *Nat. Catal.*, 2018, **1**, 673; (b) J. A. Boerth, J. R. Hummel and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2016, **55**, 12650; (c) J. A. Boerth and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2017, **56**, 9976.

12 R. Li, C.-W. Ju and D. Zhao, *Chem. Commun.*, 2019, **55**, 695.

13 For selective examples on catalytic coupling of formaldehyde with arenes see: (a) Y. Wu and B. Zhou, *ACS Catal.*, 2017, **7**, 2213; (b) G.-F. Zhang, Y. Li, X.-Q. Xie and C.-R. Ding, *Org. Lett.*, 2017, **19**, 1216; (c) C. Zhu, T. Pinkert, S. Gressies and F. Glorius, *ACS Catal.*, 2018, **8**, 10036; (d) S. H. Lee, T. Jeong, K. Kim, N. Y. Kwon, A. K. Pandey, H. S. Kim, J.-M. Ku, N. K. Mishra and I. S. Kim, *J. Org. Chem.*, 2019, **84**, 2307; (e) T. Wan, S. Du, C. Pi, Y. Wang, R. Li, Y. Wu, X. Cui. *ChemCatChem*, 2019, **11**, 3791.

14 For selective examples on catalytic coupling of formaldehyde with isoprene see: (a) T. Smejkal, H. Han, B. Breit and M. J. Krische, *J. Am. Chem. Soc.*, 2009, **131**, 10366; (b) A. Koepfer, B. Sam, B. Breit and M. J. Krische, *Chem. Sci.*, 2013, **4**, 1876.

15 Y.-C. Hu, D.-W. Ji, C.-Y. Zhao, H. Zheng and Q.-A. Chen, *Angew. Chem., Int. Ed.*, 2019, **58**, 5438.

16 (a) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (b) P. Gandeepan, T. Mueller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192.

17 I. Vilotijevic and T. F. Jamison, *Science*, 2007, **317**, 1189.

18 During the preparation of this manuscript, a related study was reported by Ellman's group (Just accepted online, July 16). Our work can serve as a complementary method which focuses on the reactions of terpenes and formaldehyde. D. Sun, Z. Chen and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2019, **58**, 12590.