Heterocycles

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Catalytic Methylation of C–H Bonds Using CO_2 and H_2**

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Abstract: *Formation of C–C bonds from CO_2 is a much sought after reaction in organic synthesis. To date, other than C–H carboxylations using stoichiometric amounts of metals, base, or organometallic reagents, little is known about C–C bond formation. In fact, to the best of our knowledge no catalytic methylation of C–H bonds using CO_2 and H_2 has been reported. Described herein is the combination of CO_2 and H_2 for efficient methylation of carbon nucleophiles such as indoles, pyrroles, and electron-rich arenes. Comparison experiments which employ paraformaldehyde show similar reactivity for the CO_2/H_2 system.*

CO_2 is the most abundant carbon source on earth and provides the basis for all organic matter. With the increased availability of renewable energy for the future it also might become a more important feedstock for the chemical industry. Hence, new valorizations of CO_2 are of general interest for chemistry and are highly desired for the production of bulk and fine chemicals.[1,2] Clearly, today most of the catalytic reactions using CO_2 in industry involve C–N or C–O bond formation to give urea, carbonates, etc. Regarding C–C bond-forming reactions, the functionalization of alkenes, alkynes, allenes, organohalides, organometallic reagents, or carbon nucleophiles to generate carboxylic acids (and their derivatives) is important in basic science.[3] In this respect, the groups of Nolan, Hou, and Zhang recently reported M(NHC)-catalyzed carboxylations (M = Au or Cu, NHC = N-heterocyclic carbene) of (hetero)arenes or terminal alkynes.[4] Despite these interesting developments, use of benign CO_2 still constitutes a major challenge because of the thermodynamic stability of the parent molecule.[5] So far, a major drawback of most of the known C–C bond-forming reactions using CO_2 is the requirement of stoichiometric amounts of expensive (organo)metallic reagents or bases to activate the respective carbon nucleophiles. Therefore, the discovery of new transformations of C–H bonds using CO_2 and cheap reductants, such as H_2, is highly desired.[6]

Herein we disclose the first direct catalytic methylations of (hetero)arenes using CO_2 and hydrogen. Based on our recent efforts on N-methylation of amines using CO_2, we became interested in exploring related C–C bond formations.[7] As shown in Scheme 1 known functionalizations of

reaction of CO_2 with C–H bonds:

a) (C)Nu–H $\xrightarrow[\text{base or organo-metallic reagents}]{CO_2}$ (C)Nu–COOH

b) (C)Nu–H $\xrightarrow[\text{catalyst}]{H_2/CO_2}$ (C)Nu–$\mathbf{CH_3}$ (this work)

Nu(C): aryl or heteroaryl groups

Scheme 1. a) Known C–H carboxylation from CO_2. b) This work on C–H methylation from CO_2 and H_2.

(weakly) activated C–H bonds with CO_2 lead to carboxylic acid derivatives. In contrast to these reactions, our concept involves reactions of CO_2 with C–H bonds under reductive conditions (hydrogen). To the best of our knowledge such reactions have not been described yet and are complementary to known reactions in which the corresponding methylated products are generated.

For our initial investigations, the carboxylation of indole (**1a**) under reduction conditions (reductive methylation) was chosen as a benchmark system because of the importance of $C(sp^2)$–H bond methylation for the synthesis of bioactive compounds.[8] As an example, nosiheptide (multhiomycin), a protein medicine, contains the 3-methyl indole moiety.[9] Notably, current methods for the introduction of a methyl group to indoles generally proceeds through several steps, for example, formylation/reduction with formyl chloride or use of toxic methylation reagents (e.g., methyl iodide and dimethyl sulfate).[10]

Based on previous literature on catalytic reduction of CO_2 and carboxylic acid derivatives,[11,18] ruthenium triphos based catalysts were screened. During this work (see Schemes S1 and S2 in the Supporting Information), indoline and 2-methyl indoline (**2a**) were obtained as major products, and no 3-methyl indole was observed. This outcome is in agreement with a recent report by Klankermayer, Leitner, and co-workers, who describe the formation of **2a**.[12] However, we observed the formation of the bis(indole) **4a** in up to 10% yield under specific reaction conditions.[13] It seems probable that the carbon atom of -CH_2- in **4a** should come from CO_2. In general, **4a** is produced by nucleophilic addition of indole to formaldehyde.[14] This result implies that CO_2 and hydrogen can be used as a formaldehyde surrogate, further indicating the possibility of utilizing CO_2, by way of formaldehyde, for the methylation of C–H bonds.[15,16]

Along with this discovery, we studied the methylation of 2-methyl indole (**1b**) to suppress unwanted side-reactions (Table 1; see Table S1 in the Supporting Information).[14] Indeed, the desired methylated product **3b** was obtained as

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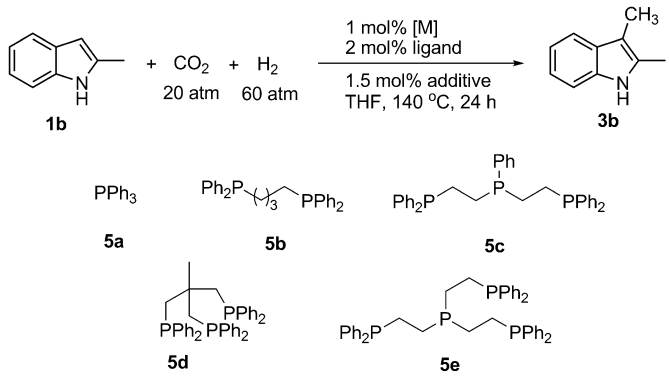
Table 1: Ruthenium-catalyzed methylation of **1b** with CO_2 and H_2.[a]



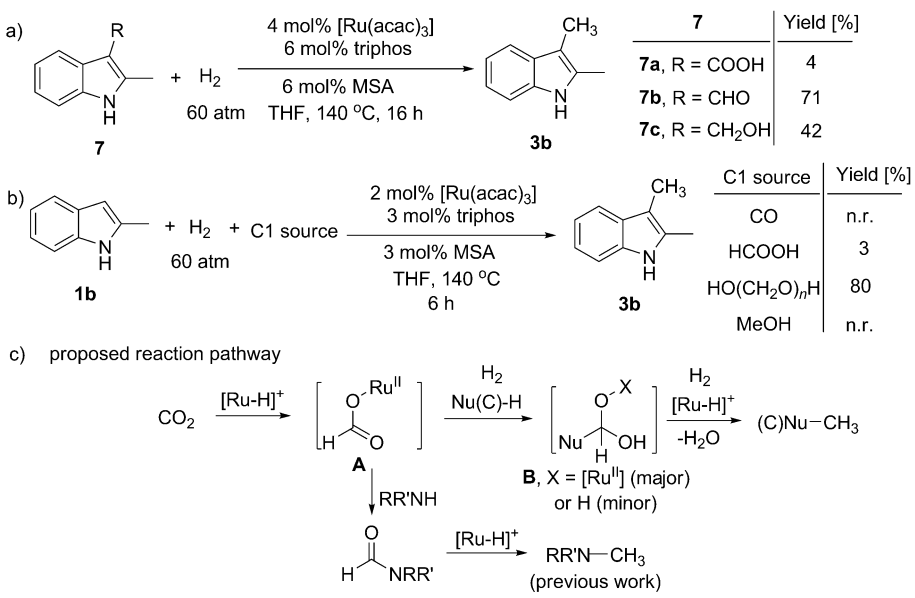
Entry	[M]	Ligand	Additive	Conv. [%][b]	Yield [%][b]
1	$[Ru(acac)_3]$	**5a**	MSA	<1	0
2	$[Ru(acac)_3]$	**5b**	MSA	3	2
3	$[Ru(acac)_3]$	**5c**	MSA	4	<1
4	$[Ru(acac)_3]$	**5d**	MSA	95	73
5	$[Ru(acac)_3]$	**5e**	MSA	<1	<1
6	Ru-Macho-BH	–	MSA	<1	0
7	$[Ru(acac)_3]$	**5d**	–	<1	0
8	$[Ru(acac)_3]$	**5d**	$(PhO)_2(OH)P{=}O$	41	26
9	$[Ru(acac)_3]$	**5d**	$Al(OTf)_3$	73	20
10	$[Ru(acac)_3]$	**5d**	$HNTf_2$	99	1
11	$[Ru(acac)_3]$	**5d**	toluene	57	44
12	$[Ru(acac)_3]$	**5d**	*i*PrOH	99	10

[a] Reaction conditions: 0.5 mmol **1a**, catalyst (1 mol%), ligand (2 mol%), 2 mL solvent, 140°C. [b] Reaction conversion and yield of **3b** were determined by GC using *n*-hexadecane as an internal standard. Ru-Macho-BH = $[RuH(BH_4)(CO)(HN(CH_2CH_2PPh_2)_2)]$, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

a major product with the reduction/N-methylation product 1,2-dimethyl indoline (**2b**) as a minor one.[7b] The most active catalyst system was formed from ruthenium acetylacetonate $[Ru(acac)_3]$, 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos; **5d**) in the presence of a catalytic amount of MSA (methanesulfonic acid). By using 1 mol% of the catalyst almost full conversion with 73% yield of 2,3-dimethylindole (**3b**) and 10% of 1,2-dimethyl indoline (**2b**) was obtained (Table 1, entry 4). The critical combination using a facial tridentate ligand was verified, while other ligands, including some tridenate ligands and a ruthenium pincer complex, showed almost no reactivity (Table 1, entries 1–3 and 5–6; see Table S1). Acid additives are also necessary for the reactivity, and several other (Lewis) acids, including $Al(OTf)_3$, lead to **3b** in 20–26% yields (Table 1, entries 7–9). When using $HNTf_2$ high reactivity and almost full conversion to give the undesired reduction product was observed (Table 1, entry 10). Apart from the effect of the acid, the combination of the ruthenium(III) precursor and triphos was proven to be critical for the desired C methylation (Table S1). For example, when using the Shvo ruthenium complex, again only the reduced 2-methylindoline **6** was obtained with a yield of 27%. Surprisingly, in this case MSA suppressed even the hydrogenation reactivity, and the yield of **6** increased to 49% in the absence of MSA. When $[Ru(2\text{-methylallyl})_2(cod)]$ was used as a pre-catalyst, similar reactivity was observed, albeit with lower selectivity, thus giving 17% yield of **3b** and 45% yield of **2b**.

The temperature as high as 140°C is critical for reaction efficiency, as the yield of **3b** decreased to 9% at 120°C. Other than THF, the desired transformation takes place in toluene (Table 1, entry 11). Protic solvents, however, are not suitable, as they result in low yields of **3b** (Table 1, entry 12) and several by-products. Finally, it is worth noting that water which is generated during the reaction does not decrease the reactivity. Thus, in the presence of 1 equivalent of H_2O, the efficiency is almost retained. The yield decreased to 46% when molecular sieves were used (Table S1).

Next, control experiments were performed to elucidate the key steps during the transformation of CO_2. As shown in Scheme 2a, three possible indole-type intermediates were tested under the standard reaction conditions. Compared to the parent model substrate, similar results were obtained using the 3-formyl- and 3-hydroxymethyl-2-methylindole (**7b** and **7c**, respectively). However, only low conversion and trace amounts of the desired product were observed for the carboxylic acid derivative **7a**. Additionally, the reaction of **1b** under standard conditions, did not yield either **7a**, **7b**, or **7c** as monitored by GC-MS, and is explained by the higher reactivity of **7b** and **7c**. Besides, under the standard reaction conditions, CO_2 is reduced to MeOH.[17] Hence, the benchmark reaction was performed in the presence of other potential C1 intermediates such as CO, HCOOH, and

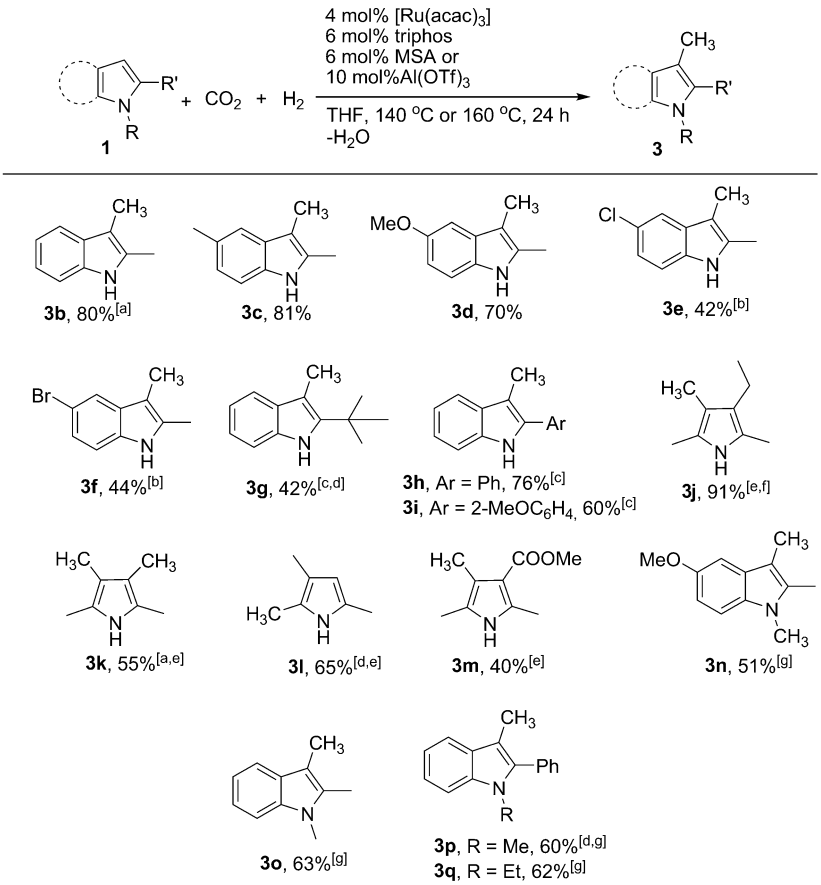


Scheme 2. Control experiments and the proposed reaction pathway.

MeOH (Scheme 2b). Firstly, blank reactions of **1b** with CO, paraformaldehyde, and MeOH in the presence of 3 mol% MSA were tested and no desired product (formylated, hydroxymethylated, or methylated product, respectively) was observed (see Scheme S3 in the Supporting Information). Under standard reaction conditions, apart from formic acid (3% of **3b**), no product was formed either of these reactions. In contrast, reaction of paraformaldehyde with **1b** under standard reaction conditions led to the desired product in 80% yield. Nevertheless, no free HCOOH, CO, or HCHO could be detected in the reaction of **1b**.

Based on these results, we propose that in the presence of acid the cationic $[Ru\text{-}H]^+$ species is generated.[18] The presence of the triphos ligand allows a stable coordination and subsequent reduction of CO_2 by the Ru–H bond (Scheme 2c). Next, the formate complex **A** undergoes attacked by the carbon nucleophile to form the corresponding acetal **B**. Finally, hydrogenolysis of the C–OH bond and C–OX bond of the key acetal intermediate (**B**) produces the C-methylated product.[19] Notably, in this proposal the property of the carbon nucleophile is critical for the C–C bond formation step. Efforts to obtain or observe this acetal intermediate are still ongoing.

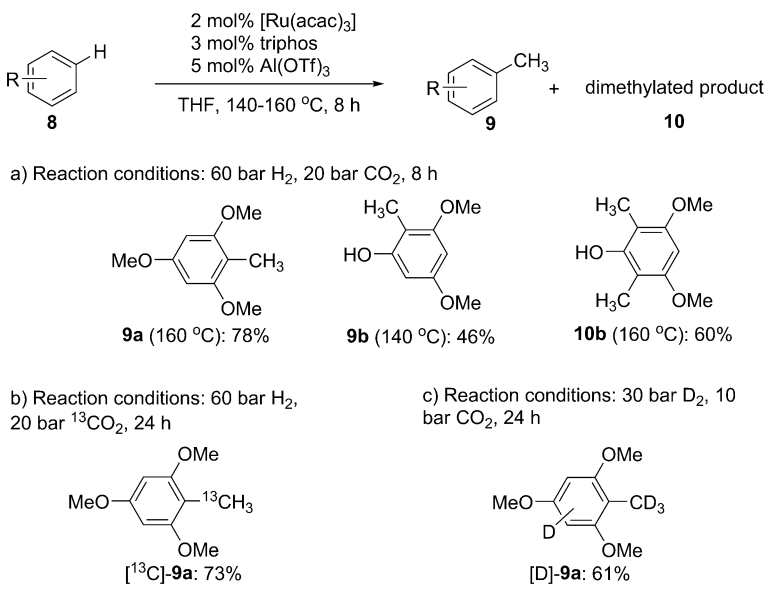
With good reactivity for 2-methylindole in hand, the methylation of different types of heteroaromatic substrates was studied in more detail (Scheme 3). A variety of substituted indoles with different electron-donating groups can be smoothly methylated, thus producing the 3-methylated indoles with good yields (**3c**,**d**; 70–81% yield). Also notable is that halide-substituted indoles underwent this transformation, albeit in moderate yields (**3e**,**f**; 42–44% yields). Related heteroarenes, for example, pyrroles were also tested. In contrast to the indoles, the use of MSA caused lower selectivity for the desired C-methylation products. However, to our delight improved chemoselectivity and moderate to excellent yields were obtained (**3j**–**m**; 40–91% yields) by simply changing the additive to diphenyl phosphate. Here, the stable 3-ethyl-2,5-dimethyl pyrrole gave the best result with the full conversion and 91% yield upon isolation. When the 1-substituted indoles were used, only trace amounts of product were obtained regardless of whether MSA or diphenyl phosphate was used. Notably, for such substrates using the Lewis-acidic $Al(OTf)_3$ offers the possibility of C methylation, too. In the presence of $Al(OTf)_3$, moderate yields of the corresponding methylated indoles were obtained (**3o**–**q**; 60–63% yields). The reaction with 1-*H*-5-MeO-indole in the presence of $Al(OTf)_3$ gave the 1,3-dimethylated product **3n** in 51% yield and derives from a sequential N-methylation/C-methylation reaction.



Scheme 3. C methylation of heteroarenes. Reaction conditions: 0.5 mmol substrate, 20 atm CO_2, 60 atm H_2, 2 mL THF, 140°C, 24 h. Yields are those of the isolated products. [a] Determined by GC using *n*-hexadecane as an internal standard. [b] Reaction time of 36 h. [c] Used 10 mol% of $[Ru(acac)_3]$, 12 mol% triphos, and 15 mol% MSA at 160°C. [d] Yield determined by NMR analysis. [e] Used 6 mol% $(PhO)_2(OH)PO$ at 160°C. [f] Reaction time of 5 h. [g] Used 5 mol% $[Ru(acac)_3]$, 7.5 mol% triphos, 7.5 mol% $Al(OTf)_3$ at 160°C for 24 h.

Finally, apart from heteroarenes a few electron-rich benzenes were tested. Gratifyingly, good reactivity and monomethylation are obtained for 1,3,5-trimethoxybenzene (**8a**) in the presence of the product (Scheme 4). An additional increase in the catalyst loading to 10 mol% led to a slightly higher yield of **9a** (from 78% to 83%) along with 16% of **10a**. Notably, trimethoxytoluene is used for the synthesis of natural or bioactive flavanones, which are often synthesized through methylation of trimethoxybenzene using either RLi/MeI or formyl chloride/reductant conditions.[20] Surprisingly, mono- or dimethylation can be achieved even for the phenol derivative **8b**, thus giving the corresponding product **9b** and **10b** with yields of 46–60% (Scheme 4a). Notably, the methylation here proceeds at C and not at O.

Additionally, the preparation of the isotopically labelled derivatives of **9** was tested using $^{13}CO_2$ and D_2. Under similar reaction conditions, [^{13}C]-**9a** was obtained in 73% yield (Scheme 4b). For the use of D_2, H–D exchange on the aromatic ring was observed.[21] As a whole, a yield of 61% was observed with a ratio of 85:15 for $[D_4]$-**9a** $[D_5]$-**9a** (Scheme 4c).



Scheme 4. Methylation of arenes.

In summary, the first examples for catalytic methylation of C–H bonds using CO_2 and hydrogen are disclosed. Key to the success of this novel methylation of aromatic C–H bonds is the use of an in situ formed ruthenium triphos catalyst in the presence of specific (Lewis) acids. Moderate to excellent yields were obtained for the C methylation of indoles, pyrroles, and activated benzene derivatives. Preliminary mechanistic studies suggest the formation of formylated (hetero)arenes as intermediates. As a new method for catalytic C–C bond formation from CO_2, it will be inspiring for chemists to explore practical methodologies involving CO_2. Studies into the mechanism are underway.

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[1] a) G. A. Olah, *Chem. Eng. News* **2003**, *81*, 42; b) G. A. Olah, G. K. S. Prakash, A. Goeppert, *J. Org. Chem.* **2009**, *74*, 487.

[2] a) H. Arakawa, et al. *Chem. Rev.* **2001**, *101*, 953; b) T. Sakakura, J.-C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365; c) Z. Han, L. Rong, J. Wu, L. Zhang, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 13218; *Angew. Chem. Int. Ed.* **2012**, *51*, 13041; d) G. Ménard, D. W. Stephan, *J. Am. Chem. Soc.* **2010**, *132*, 1796.

[3] a) M. Takimoto, Y. Nakamura, K. Kumura, M. Mori, *J. Am. Chem. Soc.* **2004**, *126*, 5956; b) M. North, *Angew. Chem.* **2009**, *121*, 4166; *Angew. Chem. Int. Ed.* **2009**, *48*, 4104; c) T. Ohishi, M. Nishiura, Z. Hou, *Angew. Chem.* **2008**, *120*, 5876; *Angew. Chem. Int. Ed.* **2008**, *47*, 5792; d) C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2008**, *130*, 7826; e) O. Vechorkin, N. Hirt, X. Hu, *Org. Lett.* **2010**, *12*, 3567; f) B. Miao, S. Ma, *Chem. Commun.* **2014**, *50*, 3285; g) T. León, A. Correa, R. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 1221; h) A. Correa, R. Martin, *Angew. Chem.* **2009**, *121*, 6317; *Angew. Chem. Int. Ed.* **2009**, *48*, 6201; i) T. Mita, J. Chen, M. Sugawara, Y. Sato, *Angew. Chem.* **2011**, *123*, 1429; *Angew. Chem. Int. Ed.* **2011**, *50*, 1393; j) T. Mita, Y. Higuchi, Y. Sato, *Org. Lett.* **2014**, *16*, 14; k) T. Mita, J. Chen, Y. Sato, *Org. Lett.* **2014**, *16*, 2200.

[4] a) I. I. F. Boogaerts, S. P. Nolan, *J. Am. Chem. Soc.* **2010**, *132*, 8858; b) L. Zhang, J. Cheng, T. Ohishi, Z. Hou, *Angew. Chem.* **2010**, *122*, 8852; *Angew. Chem. Int. Ed.* **2010**, *49*, 8670; c) D. Yu, Y. Zhang, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20184.

[5] a) K. Huang, C.-L. Sun, Z.-J. Shi, *Chem. Soc. Rev.* **2011**, *40*, 2435; b) M. Aresta, A. Dibenedetto, A. Angelini, *Chem. Rev.* **2014**, *114*, 1709.

[6] L. Wu, Q. Liu, I. Fleischer, R. Jackstell, M. Beller, *Nat. Commun.* **2014**, *5*, 3091.

[7] a) Y. Li, X. Fang, K. Junge, M. Beller, *Angew. Chem.* **2013**, *125*, 9747; *Angew. Chem. Int. Ed.* **2013**, *52*, 9568; b) Y. Li, I. Sorribes, T. Yan, K. Junge, M. Beller, *Angew. Chem.* **2013**, *125*, 12378; *Angew. Chem. Int. Ed.* **2013**, *52*, 12156.

[8] H. Schönherr, T. Cernak, *Angew. Chem.* **2013**, *125*, 12480; *Angew. Chem. Int. Ed.* **2013**, *52*, 12256.

[9] A. Solladié-Cavallo, J. Schwarz, C. Mouza, *Tetrahedron Lett.* **1998**, *39*, 3861.

[10] J. G. Rodríguez, A. Urrutia, *J. Heterocycl. Chem.* **1999**, *36*, 129.

[11] For ruthenium/triphos-catalyzed reductions, see: a) H. T. Teunissen, C. J. Elsevier, *Chem. Commun.* **1998**, 1367; b) M. C. van Engelen, H. T. Teunissen, J. G. de Vries, C. J. Elsevier, *J. Mol. Catal. A* **2003**, *206*, 185; c) F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer, W. Leitner, *Angew. Chem.* **2010**, *122*, 5642; *Angew. Chem. Int. Ed.* **2010**, *49*, 5510; d) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin, D. J. Cole-Hamilton, *Chem. Eur. J.* **2013**, *19*, 11039; For other selected examples of CO_2 reduction, see: e) W. Leitner, *Angew. Chem.* **1995**, *107*, 2391; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2207; f) J. F. Hull, Y. Himeda, W.-H. Wang, B. Hashiguchi, R. Periana, D. J. Szalda, J. T. Muckerman, E. Fujita, *Nat. Chem.* **2012**, *4*, 383; g) P. G. Jessop, T. Ikariya, R. Noyori, *Nature* **1994**, *368*, 231; h) O. Jacquet, C. D. N. Gomes, M. Ephritikhine, T. Cantat, *J. Am. Chem. Soc.* **2012**, *134*, 2934; S. N. Riduan, Y. Zhang, J. Y. Ying, *Angew. Chem.* **2009**, *121*, 3372; *Angew. Chem. Int. Ed.* **2009**, *48*, 3322; i) S. Park, D. Bézier, M. Brookhart, *J. Am. Chem. Soc.* **2012**, *134*, 11404; j) C. Federsel, A. Boddien, R. Jackstell, R. Jennerjahn, P. J. Dyson, R. Scopelliti, G. Laurenczy, M. Beller, *Angew. Chem.* **2010**, *122*, 9971; *Angew. Chem. Int. Ed.* **2010**, *49*, 9777; for reduction of carboxylic acid derivatives, see: k) D. Addis, S. Das, K. Junge, M. Beller, *Angew. Chem.* **2011**, *123*, 6128; *Angew. Chem. Int. Ed.* **2011**, *50*, 6004; l) K. Junge, B. Wendt, F. A. Westerhaus, A. Spannenberg, H. Jiao, M. Beller, *Chem. Eur. J.* **2012**, *18*, 9011; m) Y. Motoyama, K. Mitsui, T. Ishida, H. Nagashima, *J. Am. Chem. Soc.* **2005**, *127*, 13150; n) K. Matsubara, T. Iura, T. Maki, H. Nagashima, *J. Org. Chem.* **2002**, *67*, 4985.

[12] K. Beydoun, T. vom Stein, J. Klankermayer, W. Leitner, *Angew. Chem.* **2013**, *125*, 9733; *Angew. Chem. Int. Ed.* **2013**, *52*, 9554.

[13] For details, see the Supporting Information.

[14] A. H. Jackson, N. Prasitpan, P. V. R. Shannon, A. C. Tinker, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2543.

[15] Recent examples show the reduction of CO_2 to formaldehyde by boranes. See: a) S. Bontemps, S. Sabo-Etienne, *Angew. Chem.* **2013**, *125*, 10443; *Angew. Chem. Int. Ed.* **2013**, *52*, 10253; b) S. Bontemps, L. Vendier, S. Sabo-Etienne, *J. Am. Chem. Soc.* **2014**, *136*, 4419.

[16] Under reduction conditions, benzyl-alcohol-type compounds ($ArCH_2OH$) can be easily transformed into the deoxygenation product Ar-CH_3. See: a) T. Gu, L. Liu, C. Zhao, *Mod. Res. Catal.* **2013**, *2*, 9; b) H.-G. Cheng, L.-Q. Lu, T. Wang, Q.-Q. Yang, X.-P.

Liu, Y. Li, Q.-H. Deng, J.-R. Chen, W.-J. Xiao, *Angew. Chem.* **2013**, *125*, 3332; *Angew. Chem. Int. Ed.* **2013**, *52*, 3250.

[17] After the reaction up to 8.6 mmol of MeOH were obtained with a TON of up to 430, which indicates the highest efficiency for homogeneous catalytic hydrogenation of CO_2 to MeOH. The study using specific indoles as the additives for this transformation is underway.

[18] F. M. A. Geilen, B. Engendahl, M. Hölscher, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* **2011**, *133*, 14349.

[19] The reaction may also proceed via formic acid or formaldehyde. However, both possibilities can be excluded as the major reaction pathway. When using formic acid, the product was obtained only in 3% yield (Scheme 2b). Further, if free formaldehyde were the main intermediate, the reactivity should be much less influenced by the electronic/steric properties of the carbon nucleophiles compared to the results obtained in Schemes 3 and 4.

[20] L. Pouységu, M. Marguerit, J. Gagnepain, G. Lyvinec, A. J. Eatherton, S. Quideau, *Org. Lett.* **2008**, *10*, 5211.

[21] H–D exchange of THF was also observed. When [D_8]THF was used as the solvent in the reaction of **1b** under standard reaction conditions in the presence of H_2, significant amounts of THF were produced and detected by ^{1}H NMR spectroscopy.