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One-pot imine synthesis from methylarenes and anilines under air over heterogeneous Cu oxide-modified CeO₂ catalyst[†]

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Masazumi Tamura, 🕩 *a Yingai Li^b and Keiichi Tomishige 🕑 ^b

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Cu oxide-modified CeO_2 (CuO_x-CeO_2) with 2 wt% Cu loading amount was the most effective and reusable heterogeneous catalyst for selective one-pot imine synthesis from methylarenes and anilines *via* direct oxidation of the sp³ C-H bond in the methylarenes with atmospheric air (0.1 MPa) as an oxidant.

Direct, catalytic and selective aerobic oxidation of the sp³ C-H bond in alkylarenes to the corresponding oxygen-containing functional groups such as alcohols, aldehydes, ketones and carboxylic acids using O₂, particularly air, as an oxidant is an important and challenging reaction in organic syntheses.¹ Onepot reactions composed of partial aerobic oxidation of alkylarenes and C-N, C-O or C-C bond formation using alcohols, amines or other chemicals have attracted much attention as effective, economical and environmentally-benign methods for direct synthesis of more functionalized chemicals such as esters, amides, imines, and so on.²⁻⁴ Generally, for one-pot reactions, multiple functions (often multiple active sites) which can act without interference each other are required,⁵ and heterogeneous catalysts are a suitable candidate. However, effective heterogeneous catalyst systems enabling both sp³ C-H bond activation and one-pot reactions are very limited such as Au-Pd bimetallic catalysts³ and MnO₂:⁴ for examples, Hutchings and co-workers showed a seminal work that supported Au-Pd alloy nanoparticles on C or TiO₂ showed high activity for the oxidation of the sp³ C-H bond in toluene derivatives and the consecutive coupling to the corresponding esters.3a Mizuno and co-workers demonstrated that MnO2 was an effective heterogeneous catalyst for the oxidative amidation of methylarenes with urea to the corresponding amides.^{4a}

^a Research Center for Artificial Photosynthesis, Advanced Research Institute for Natural Science and Technology, Osaka City University, 3-3-138, Sugimoto, Sumiyoshi-ku, Osaka, 558-8585, Japan. E-mail: mtamura@osaka-cu.ac.jp

^b Department of Applied Chemistry, School of Engineering, Tohoku University,

6-6-07, Aoba, Aramaki, Aoba-ku, Sendai 980-8579, Japan † Electronic supplementary information (ESI) available. See DOI: 10.1039/

Imines are an important class of organic compounds due to the versatility for transformations, and conventionally synthesized by condensation of aldehydes or ketones and amines with an acid catalyst. Various effective methods have been investigated⁶ such as oxidation or dehydrogenation of secondary amines, dimerization of amines, hydroamination of alkynes with amines, and direct coupling of alcohols and amines and others. As more economical and greener methods, hydrogenative coupling of nitroarenes and aldehydes has been actively investigated because nitroarenes are more primitive chemicals than anilines.⁷ Similarly, aerobic oxidative coupling of alkylarenes and amines (Scheme 1) is also promising because alkylarenes are more primitive and cheap chemicals than other starting ones such as aldehydes, alcohols and alkynes. However, selective oxidative coupling of alkylarenes and anilines is generally difficult due to the reactions of oxidation of anilines and over-oxidation to carboxylic acids, which are often a poison for solid catalysts. Pd-Au/SiO2 was reported to be an effective heterogeneous catalyst for the oxidative coupling of alkylarenes and amines,^{3b} which provided high yields of the target imines but suffered from use of strong base (K_2CO_3), high pressure of pure oxygen (≥ 1 MPa), use of noble metals and cumbersome catalyst preparation. Combination of mesoporous MnO2 and tert-butyl hydroperoxide (THBP) was also effective,^{4b} however THBP, an organic oxidant, was necessary for high yield. Therefore, development of effective heterogeneous catalysts for the aerobic oxidative coupling of alkylarenes and amines under mild reaction conditions is highly desirable.

CeO₂ has been investigated in various research fields due to the unique physical and chemical properties.⁸ The prominent acid/base and redox properties have attracted much attention



Scheme 1 Direct imine formation from methylarenes and anilines.



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⁺ Electronic supplementary information (ESI) available. See DOI: 10.1039/ d0cc02969f

 Table 1
 Performance comparison of metal oxides in the direct imine formation from mesitylene and aniline^a



Reaction conditions: aniline 1 mmol, mesitylene 1.5 g, catalyst 50 mg, air, 393 K, 24 h. a Conversion and selectivity were calculated on aniline basis.

in liquid-phase organic reactions,^{9,10} and recently we firstly reported on the unique redox property of CeO₂ at low temperature, which can function as a heterogeneous catalyst for one-pot imine formation from benzyl alcohols and anilines under air at 333 K.¹⁰ Other researchers also vigorously investigated the redox property of CeO₂ with different morphologies or synthesis methods in the same reaction.¹¹ Herein, we found that Cu oxide-modified CeO₂ (CuO_x-CeO₂) was an effective and reusable heterogeneous catalyst for the selective oxidative imine formation from methylarenes and anilines under atmospheric air without any additives, giving high yields of the target imines.

At first, performance of metal oxides was compared in oxidative imination of mesitylene with aniline under air at 393 K as a model reaction (Table 1). Without metal oxides, no conversion was observed (entry 17). Metal oxides except CeO₂ and MnO₂ showed low conversion ($\leq 8\%$), and the yield of (3,5-dimethylbenzylidene)-phenyl-amine (1), the target imine, was $\leq 2\%$ (entries 4–16). CeO₂ showed higher conversion (25%) than other metal oxides, however, the selectivity to 1 was not so high (39%, entry 1), and the coupling products of anilines such as azobenzene and azoxybenzene were obtained. On the other hand, MnO₂ showed high selectivity to the target imine, although the conversion (12%) was half of that over CeO₂ (entry 2). In terms of the yield of 1, CeO₂ has a comparative potential to MnO₂ in the oxidation of the sp³ C-H bond. Therefore, CeO₂ was selected for further investigation.

Next, addition of various metal species (1 wt%) to CeO_2 was investigated (Fig. 1). The conversion was not improved by addition of any metal species, in contrast, addition of Cu, Hf,



Fig. 1 Performance comparison of metal oxide-modified CeO₂ in the direct imine formation from mesitylene and aniline. O: conversion, bars: selectivities (red: **1**, blue stripe: azobenzene, green dotted: azoxybenzene, black: others). Reaction conditions: aniline 1 mmol, mesitylene 1.5 g, MO_x -CeO₂ (M: 1 wt%, 873 K) 50 mg, air, 393 K, 24 h.

Co, W and Mn species increased the selectivity to **1**, and among these metal species Cu provided the highest selectivity of 75%, while the conversion slightly decreased in comparison with only CeO₂. In terms of the selectivity, Cu is the most effective additive for CeO₂ in the reaction.

The effect of Cu loading amount in CuO_x –CeO₂ catalysts was studied (Fig. 2). The conversion gradually decreased with increasing the Cu loading amount up to 2 wt% and became almost constant at over 2 wt%. On the other hand, the selectivity to **1** drastically increased from 39% to 85% with increasing the Cu loading amount up to 2 wt% and became almost constant (~87%) at more than 2 wt%. Therefore, 2 wt% CuO_x loaded CeO₂ is the optimum catalyst.

The calcination temperature dependence of CuO_x -CeO₂ was investigated in the range of 473–1073 K (Table S1, ESI†). The conversion increased from 10 to 15% with decreasing the calcination temperature from 1073 to 673 K and became almost constant at lower calcination temperature (473–673 K), while



Fig. 2 Effect of Cu loading amount in CuO_x – CeO_2 catalyst in the direct imine formation from mesitylene and aniline. \bigcirc : conversion, bars: selectivities (red: **1**, blue stripe: azobenzene, green dotted: azoxybenzene, black: others). Reaction conditions: aniline 1 mmol, mesitylene 1.5 g, CuO_x – CeO_2 50 mg, air, 393 K, 24 h.



Fig. 3 XRD patterns of CuO_x -CeO₂ catalysts (a) and STEM and STEM-EDX of CuO_x -CeO₂(Cu: 2 wt%, 673 K) (b).

the selectivity to **1** was not so changed. Therefore, lower calcination temperature (473–673 K) was preferable for high activity, and the calcination temperature was fixed at 673 K in the following study.

The CuO_x–CeO₂ catalysts were characterized by XRD and STEM analyses (Fig. 3). XRD analyses showed that CuO species were not detected up to 3 wt% Cu loading amount but were observed at higher Cu loading amount (Fig. 3(a), the expanded figure is in Fig. S1, ESI†). Therefore, CuO species can be highly dispersed on CeO₂ in CuO_x–CeO₂ catalysts with Cu loading amount below 3 wt%. In addition, STEM image of 2 wt% CuO_x-modified CeO₂ catalyst showed no particles assignable to CuO_x species over CeO₂ (Fig. 3(b)). STEM-EDX analysis showed Cu species is highly dispersed over CeO₂ (Fig. 3b), which is in good agreement with the result of XRD analyses.

The reaction temperature dependence was investigated (Table S2, ESI[†]) from 373 to 413 K. Higher reaction temperature provided higher conversion, and 51% conversion and 92% selectivity to 1 were obtained at 413 K and 24 h. It was also confirmed that the target imine was not formed without catalysts at 413 K. The time-course of the direct imine formation from mesitylene and aniline was studied with the optimized CuO_x -CeO₂ catalyst (Cu: 2 wt%, 673 K) at 413 K (Fig. 4(a) and the details are in Table S3, ESI[†]). The reaction



Fig. 4 Time-course of the direct imine formation from mesitylene and aniline over CuO_x - CeO_2 catalyst (a) (\bigcirc : conversion, \bullet : selectivity to **1**, \bullet : selectivity to azobenzene, \blacksquare : selectivity to azoxybenzene), and the reusability test (b). \bigcirc : conversion, bars: selectivities (red: **1**, blue stripe: azobenzene, green dotted: azoxybenzene, black: others). Reaction conditions of (a) aniline 1 mmol, mesitylene 1.5 g, CuO_x - CeO_2 (Cu: 2 wt%, 673 K) 50 mg, air, 413 K. (b) Aniline 1 mmol, mesitylene 1.5 g, CuO_x - CeO_2 (Cu: 2 wt%, 673 K), 50 mg, air, 393 K, 24 h.

smoothly proceeded to reach >99% conversion at 120 h. The selectivity to 1 increased at the low conversion level (<10%), and high selectivity ($\sim 93\%$) was maintained at the high conversion level. The maximum imine yield of 93% was obtained at 120 h. Focusing on the other products from mesitylene, formation of 3,5-dimethyl benzyl alcohol was not observed, but a small amount of 3,5-dimethyl benzaldehyde was detected (Table S3, ESI⁺). This result indicates that 3,5-dimethyl benzaldehyde is one possible intermediate, which may be formed from the corresponding benzyl alcohol. The catalyst reusability of CuO_x -CeO₂ was investigated (Fig. 4(b)). The conversion was not changed in all reuse tests and high selectivity to 1 was maintained during five-time reaction tests, although the selectivity increased at first reuse test. Moreover, the filtrate of the reaction mixture was measured by ICP-AES, showing no leaching of Ce and Cu species (below the detected level (<0.1%)). The XRD patterns of the catalysts before and after reactions were not changed (Fig. S2, ESI^{\dagger}). CuO_x-CeO₂ was a robust and reusable heterogeneous catalyst in this reaction.

The scope of anilines and methylarenes with CuO_x -CeO₂ catalyst is shown in Table S4 (ESI†). Various *p*-substituted anilines with electro-withdrawing groups such as halogens (entries 2–4) and an electron-donating methyl group (entry 5) were converted to the imines in high conversions and high selectivities. *o*-, *m*-, *p*-Xylenes also reacted to give the corresponding imines in high conversions and selectivities (entries 6–8).

The direct imine formation from mesitylene and aniline will proceed via two steps (Scheme 2): (i) oxidation of the methyl group in mesitylene to corresponding aldehyde. (ii) Imine formation from the produced aldehyde and aniline. Imine formation from aniline and benzaldehyde was conducted with CuOx-CeO2 catalyst (Scheme S1, ESI[†]) to estimate the reaction rate for the step (ii). The conversion was 10% at only 5 min, and the formation rate of the imine was calculated to be 48 mmol h^{-1} g⁻¹, which is about 440-fold higher than that of the direct imine formation from mesitylene and aniline over CuO_x -CeO₂ catalyst (0.11 mmol h⁻¹ g⁻¹). This result indicates that the rate-determining step is not step (ii) but step (i), which can explain the small detected amount of the aldehyde in the time-course. Moreover, imine formation from aniline and mesitylene was conducted under N2 (Scheme S2, ESI^{\dagger}), showing almost no conversion. Therefore, O₂ in air is essential for the reaction. As above, the rate-determining step is the step (i) and is catalyzed by CuO_x -CeO₂, and the step (i) proceeds with O_2 in air over CuO_x -CeO₂ catalyst. Moreover, oxidative coupling of aniline was conducted at 393 K for 6 h over CeO_2 and CuO_x -CeO₂ with *tert*-butylbenzene as an inert solvent because of no benzylic C-H bond (Scheme S3, ESI[†]). CuO_x-CeO₂ clearly suppressed formation of aniline coupling products such



Scheme 2 Plausible reaction route for the direct imine formation from mesitylene and aniline.

as azobenzene and azoxybenzene (0.6% aniline conversion) compared with CeO_2 (2.4% aniline conversion), indicating that CuO_x on CeO_2 will be effective for suppression of aniline coupling reactions.

Finally, to clarify the roles of CuO_x species and CeO_2 in CuO_x-CeO₂ catalyst, various reactions with only CuO, only Cu₂O, and physical mixture of CeO₂ and CuO or Cu₂O were conducted (Table S5, ESI⁺). Only CuO and only Cu₂O showed almost no conversion, indicating that Cu oxide species have no activity for the reaction (Table S5, ESI⁺, entries 5 and 6). The physical mixture of CeO_2 and CuO or Cu_2O (Table S5, ESI[†], entries 3 and 4) showed similar conversion to CeO₂ and a little improved selectivity compared with CeO₂. These results indicate that Cu species located on CeO2 is indispensable for the high selectivity. Considering that the yields with CuO_x-CeO₂, CeO₂ and the physical mixture of CeO₂ and Cu oxides are similar (10-14%, Table S5, ESI⁺, entries 1-4) and that no imine formation was observed over only Cu oxide species, the oxidation of mesitylene will proceed mainly by the redox property of CeO₂, and CuO_x species on CeO₂ will mainly contributed to improvement of the selectivity to the target imine by suppression of the oxidative coupling of aniline. According to our previous work,¹⁰ sp³ C-H activation of methylarenes will proceed by the lattice oxygen over CeO₂. On the other hand, according to the previous reports¹² on oxidative coupling of aniline over Ag nanoparticle, Cu-Mn spinel oxide and RuO₂/Cu₂O nanoparticle, superoxide (O²⁻) formed on the catalyst was proposed to be the active species for formation of aniline radical. It was also reported that superoxide can be formed on the defect site of CeO₂ by addition of O2.13 Based on them, one possible explanation for the suppression of the oxidative coupling of aniline is that the active species such as superoxide for formation of aniline radical was decreased by addition of CuO_x species because the imine formation amount was almost constant even by addition of Cu species (Fig. 1 and Table S5, ESI[†]), and CuO_x species may fill the defect site of CeO₂ or suppress the formation of superoxide by the redox property. Further investigations on characterization of the catalyst, kinetic studies and DFT calculations are necessary to clarify the detailed reaction mechanism over CuO_x-CeO₂ catalyst.

We found that CuO_x -CeO₂ acted as an effective and reusable heterogeneous catalyst for direct imine formation from methylarenes and anilines with air (0.1 MPa) as an oxidant, giving the aromatic imines in high yields (up to 94%). The high activity for the sp³ C–H bond oxidation of methylarenes will be mainly attributed to CeO₂ catalysis and high selectivity can be attributed to Cu oxide species on CeO₂.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) R. Vanjari and K. N. Singh, Chem. Soc. Rev., 2015, 44, 8062;
 (b) R. K. Grasselli and M. A. Tenhover, Ammoxidation, in Handbook of Heterogeneous Catalysis, ed. G. Ertl, H. Knözinger, F. Schüth and J. Weitkamp, Wiley-VCH, Weinheim, 2nd edn, 2008, pp. 3489–3517;
 (c) N. Dimitratos, J. A. Lopez-Sanchez and G. J. Hutchings, Chem. Sci., 2012, 3, 20; (d) Y. Ishii, S. Sakaguchi and T. Iwahama, Adv. Synth. Catal., 2001, 343, 305; (e) C. Limberg, Angew. Chem., Int. Ed., 2003, 42, 5932; (f) T. Punniyamurthy, S. Velusamy and J. Iqbal, Chem. Rev., 2005, 105, 2329; (g) Y.-F. Liang and N. Jiao, Acc. Chem. Res., 2017, 50, 1640; (h) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, Chem. Rev., 2013, 113, 6234; (i) L. Boisvert and K. I. Goldberg, Acc. Chem. Res., 2012, 45, 899.
- 2 Selected papers for homogeneous catalysts: (a) Y. Huang, T. Chen, Q. Li, Y. Zhou and S.-F. Yin, Org. Biomol. Chem., 2015, 13, 7289; (b) H. Xie, Y. Liao, S. Chen, Y. Chen and G.-J. Deng, Org. Biomol. Chem., 2015, 13, 6944; (c) J. Zhang, E. Khaskin, N. P. Anderson, P. Y. Zavalij and A. N. Vedernikov, Chem. Commun., 2008, 3625; (d) M. Liu, T. Chen and S.-F. Yin, Catal. Sci. Technol., 2016, 6, 690; (e) S.-i. Hirashima, T. Nobuta, N. Tada, T. Miura and A. Itoh, Org. Lett., 2010, 12, 3645; (f) Y.-F. Liang, X. Li, X. Wang, Y. Yan, P. Feng and N. Jiao, ACS Catal., 2015, 5, 1956; (g) J. Liu, X. Qiu, X. Huang, X. Luo, C. Zhang, J. Wei, J. Pan, Y. Liang, Y. Zhu, Q. Qin, S. Song and N. Jiao, Nat. Chem., 2019, 11, 71.
- (a) L. Kesavan, R. Tiruvalam, M. H. Ab Rahim, M. I. bin Saiman, D. I. Enache, R. L. Jenkins, N. Dimitratos, J. A. Lopez-Sanchez, S. H. Taylor, D. W. Knight, C. J. Kiely and G. J. Hutchings, *Science*, 2011, 331, 195;
 (b) X. Cui, F. Shi and Y. Deng, *Chem. Commun.*, 2012, 48, 7586.
- 4 (a) Y. Wang, K. Yamaguchi and N. Mizuno, Angew. Chem., Int. Ed., 2012, 51, 7250; (b) B. Dutta, S. Biswas, V. Sharma, N. O. Savage, S. P. Alpay and S. L. Suib, Angew. Chem., Int. Ed., 2016, 55, 2171.
- 5 M. J. Climent, A. Corma and S. Iborra, Chem. Rev., 2011, 111, 1072.
- 6 R. D. Patil and S. Adimurthy, Asian J. Org. Chem., 2013, 2, 726.
- 7 (a) L. L. Santos, P. Serna and A. Corma, *Chem. Eur. J.*, 2009, 15, 8196; (b) T. Schwob and R. Kempe, *Angew. Chem., Int. Ed.*, 2016, 55, 15175; (c) C. Bäumler and R. Kempe, *Chem. Eur. J.*, 2018, 24, 8989.
- 8 (a) L. Vivier and D. Duprez, *ChemSusChem*, 2010, 3, 654;
 (b) T. Montini, M. Melchionna, M. Monai and P. Fornasiero, *Chem. Rev.*, 2016, 116, 5987; (c) C. Sun, H. Li and L. Chen, *Energy Environ. Sci.*, 2012, 5, 8475; (d) T. Sahu, S. S. Brisht, K. R. Das and S. Kerkar, *Curr. Nanosci.*, 2013, 9, 588.
- 9 (a) Y. Wang, F. Wang, Q. Song, Q. Xin, S. Xu and J. Xu, J. Am. Chem. Soc., 2013, 135, 1506; (b) M. Tamura, H. Wakasugi, K.-I. Shimizu and A. Satsuma, Chem. - Eur. J., 2011, 17, 11428; (c) Y. Wang, F. Wang, C. Zhang, J. Zhang, M. Li and J. Xu, Chem. Commun., 2014, 50, 2438; (d) S. Zhang, Z.-Q. Huang, Y. Ma, W. Gao, J. Li, F. Cao, L. Li, C.-R. Chang and Y. Qu, Nat. Commun., 2017, 8, 15266; (e) A. Rapeyko, M. J. Climent, A. Corma, P. Concepcion and S. Iborra, ACS Catal., 2016, 6, 4564; (f) A. Leyva-Pérez, D. Cómbita-Merchán, J. R. Cabrero-Antonino, S. I. Al-Resayes and A. Corma, ACS Catal., 2013, 2, 250; (g) Z. Zhang, Y. Wang, M. Wang, J. Lu, C. Zhang, L. Li, J. Jiang and F. Wang, Catal. Sci. Technol., 2016, 6, 1693; (h) A. Bansode and A. Urakawa, ACS Catal., 2014, 4, 3877; (i) M. Honda, M. Tamura, Y. Nakagawa, S. Sonehara, K. Suzuki, K.-I. Fujimoto and K. Tomishige, ChemSusChem, 2013, 6, 1341; (j) L. Geng, J. Song, Y. Zhou, Y. Xie, J. Huang, W. Zhang, L. Peng and G. Liu, Chem. Commun., 2016, 52, 13495.
- 10 M. Tamura and K. Tomishige, Angew. Chem., Int. Ed., 2015, 54, 864.
- (a) Z. Zhang, Y. Wang, M. Wang, J. Lü, L. Li, Z. Zhang, M. Li, J. Jiang and F. Wang, *Chin. J. Catal.*, 2015, **36**, 1623; (b) H. Zhang, C. Wub, W. Wang, J. Bu, F. Zhou, B. Zhang and Q. Zhang, *Appl. Catal., B*, 2018, **227**, 209; (c) H. Ding, J. Yang, S. Ma, N. Yigit, J. Xu, G. Rupprechter and J. Wang, *ChemCatChem*, 2018, **10**, 4100.
- 12 (a) S. Cai, H. Rong, X. Yu, X. Liu, D. Wang, W. He and Y. Li, ACS Catal., 2013, 3, 478; (b) S. Sultan, M. Kumar, S. Devari, D. Mukherjee and B. A. Shah, ChemCatChem, 2016, 8, 703; (c) A. Saha, S. Payra, B. Selvaratnam, S. Bhattacharya, S. Pal, R. T. Koodali and S. Banerjee, ACS Sustainable Chem. Eng., 2018, 6, 11345.
- (a) J. Soria, A. Martínez-Arias and J. C. Conesa, *J. Chem. Soc., Faraday Trans.*, 1995, **91**, 1669; (b) G. Preda, A. Migani, K. M. Neyman, S. T. Bromley, F. Illas and G. Pacchioni, *J. Phys. Chem. C*, 2011, **115**, 5817.