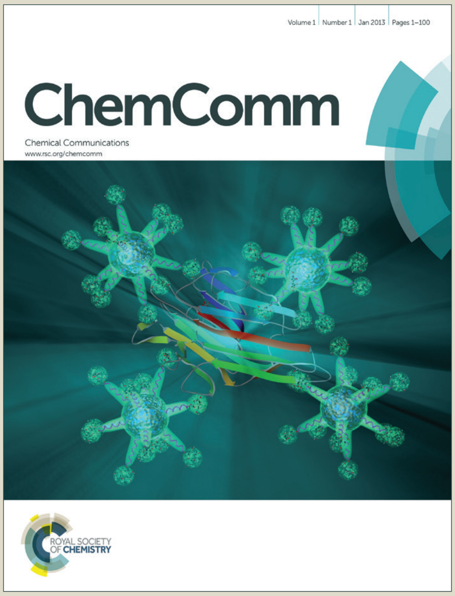
ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Guanidinium Iodide-Catalyzed Oxidative α-Nitroalkylation of β-Ketoamides **

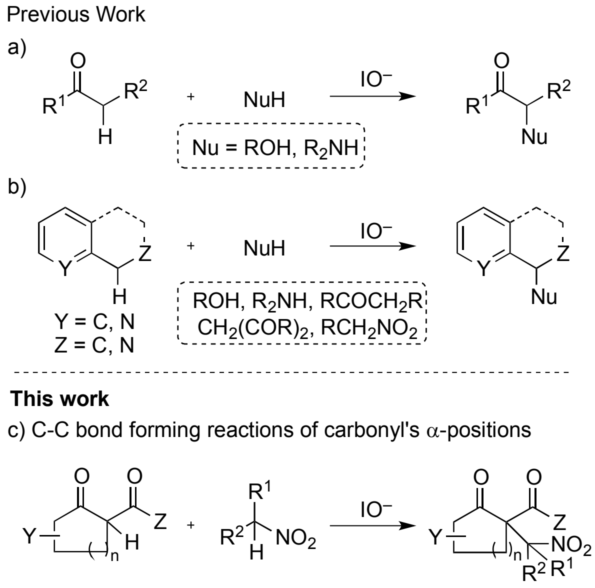
Koji Yasui,[a] Takanari Kato,[a] Kohei Kojima[a] and Kazuo Nagasawa[a] *

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Oxidative nitroalkylation of β-ketoamides and nitroalkanes, mediated by hypoiodide generated from *tert*-butyl hydrogen peroxide and a catalytic amount of guanidinium iodide, afforded the corresponding α-nitroalkyl-β-ketoamides in up to 97% yield.

Hypoiodite (represented by IOX or IO⁻) is easily generated in situ from a stoichiometric amount of iodine or iodide with oxidant, and has been used in a variety of oxidative coupling reactions.[1,2] Recently, Ishihara and co-workers found that hypoiodite could be effectively generated by using only a catalytic amount of iodide, and they reported oxidative α-phenoxyetherification[3a] or α-oxyacylation[3b] of carbonyl compounds with an equivalent amount of oxidant in the presence of a catalytic amount of quaternary ammonium iodide. Since then, various oxidative coupling reactions have been explored using this approach.[4] These oxidative reactions are mostly carbon-heteroatom (O or N) bond-forming reactions at the α-position of carbonyl compounds or at the benzylic position of aromatic groups (Schemes 1a and 1b).[5,6,7] However, carbon-carbon bond-forming reactions under these conditions have not been well explored, and the only reported reaction is that of tetrahydroisoquinoline bearing an activated benzylic moiety with carbon nucleophiles derived from nitroalkanes or 1,3-dicarbonyl compounds (Scheme 1b).[8,9] Therefore, we were interested in extending the scope of oxidative carbon-carbon bond-forming reactions mediated by hypoiodite. Among the possible combination of substrates, coupling of the α-position of carbonyls with nitroalkanes is especially attractive since the resulting β-nitrocarbonyls are very useful precursors for β-amino acid and their derivatives including spiro β-lactams.[10,11] Here, we describe an intermolecular oxidative coupling reaction of β-ketoamides with nitroalkanes mediated by hypoiodite generated from *tert*-butyl hydroperoxide (TBHP) and a catalytic amount of guanidinium iodide (Scheme 1c).

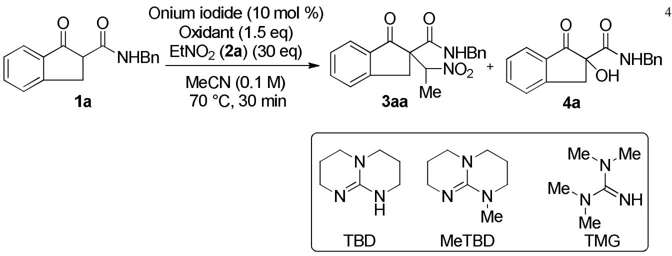
Initially, we screened onium iodide catalysts for the oxidative coupling reaction of β-ketoamide **1a**, derived from 2,3-dihydroindanone, and nitroethane (**2a**) (30 equiv.) in the presence of hydrogen peroxide (30%, 1.5 equiv.) in acetonitrile (Table 1).[12] Oxidative coupling reaction took place with ammonium iodide and phosphonium iodide as catalysts (0.1 equiv.), and **3aa** was obtained in moderate yield (38% in each case), together with hydroxylated **4a** in 37% and 46% yield, respectively (entries 1 and 2). On the other hand, pyridinium iodide was not effective (entry 3). Next, some guanidinium iodides were tested. In the case of acyclic tetramethylguanidinium iodide (TMG·HI), the coupling product **3aa** was obtained in 44% yield, accompanied with hydroxylated **4a** in 47% yield (entry 4). On the other hand, **3aa** was obtained in 60% yield by using the cyclic guanidinium salt triazabicyclodecene hydroiodide (TBD·HI) (entry 5). Interestingly, the yield of **3aa** fell to 33% when the methylated cyclic guanidinium salt MeTBD·HI was used (entry 6). Since the cyclic guanidinium iodide TBD·HI was effective with the onium iodides examined, the oxidative coupling reaction was further investigated with various oxidants. The yield of **3aa** was similar to, or worse than, that with hydrogen peroxide when urea hydrogen peroxide (UHP) and cumene hydroperoxide (CHP) were used (entries 7 and 8). In contrast, a drastic improvement was observed in the case of *tert*-butyl hydroperoxide (TBHP, 70% in water), and the coupling product of **3aa** was obtained almost exclusively in 94% yield (entry 9).[13,14] Under this condition, generation of hydroxylated **4a** was largely suppressed. Interestingly, TBHP was almost ineffective as an oxidant for methylated cyclic guanidinium iodide (entry 10). It is noteworthy that this reaction did not proceed at all with a stoichiometric



Scheme 1 Hypoiodite-mediated oxidative coupling reactions.

ChemComm Accepted Manuscript

Table 1 Screening of the onium salts of iodide for oxidative coupling of 2,3-dihydroindanone-derived β-ketoamide **1a** and nitroethane (**2a**).



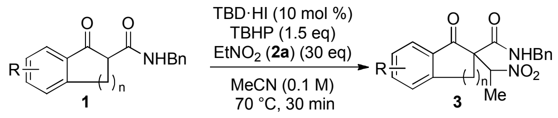
Entry	Onium iodide	Oxidant	**3aa** (%)[a]	**4a** (%)[a]
1	nBu$_4$NI	H_2O_2[b]	38	37
2	nBu$_4$PI	H_2O_2[b]	38	46
3	Py·HI	H_2O_2[b]	0	4
4	TMG·HI	H_2O_2[b]	44	47
5	TBD·HI	H_2O_2[b]	60	19
6	MeTBD·HI	H_2O_2[b]	33	27
7	TBD·HI	UHP	59	28
8	TBD·HI	CHP	42	14
9	TBD·HI	TBHP[c]	94	2
10	MeTBD·HI	TBHP[c]	2	18
11	PIDA[d]	—	0	0
12	PIFA[d]	—	0	0
13	PhI	TBHP[c]	0	0
14	PhI	*m*CPBA	0	0
15	TBD·HCl	TBHP[c]	0	0

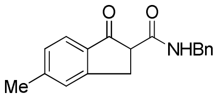
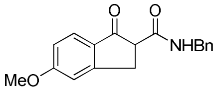
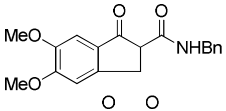
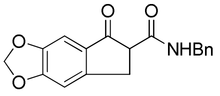
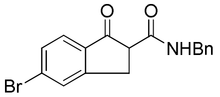
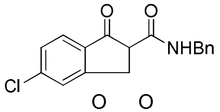
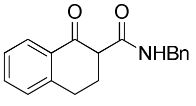
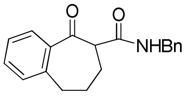
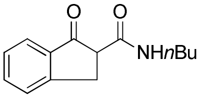
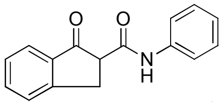
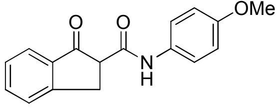
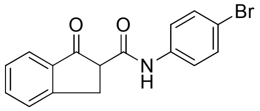
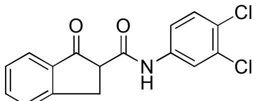
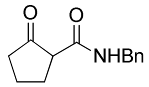
[a] Isolated yield. [b] 30% H_2O_2 was used. [c] 70% TBHP in H_2O was used. [d] One equivalent of reagent was used.

amount of hypervalent iodine reagent PIDA ($PhI(OAc)_2$) or PIFA ($PhI(OCOCF_3)_2$) (entries 11, 12), or with a catalytic amount of PhI in the presence of *m*CPBA or TBHP (entries 13, 14).[15] Since the hydrochloric acid salt of TBD, i.e., TBD·HCl, did not catalyze the reaction at all, iodine anion is mandatory for the reaction (entry 15).

With the optimized conditions in hand (Table 1, entry 9), the substrate scope for β-ketoamides **1** was examined with nitroethane (**2a**) (Table 2). Electron-donating methyl, methoxy, and dioxorane groups on the aromatic group did not affect the reactivity, and the corresponding oxidative coupling products **3ba-ea** were obtained in high yields (entries 1-4). Electron-withdrawing bromide and chloride afforded the oxidative coupling products **3fa** and **3ga** in 85% yield, using chloroform as the solvent and 20 mol% catalyst.[16] Tetralone- and benzosuberone-derived β-ketoamides **1h** and **1i** also underwent the coupling reaction (entries 7 and 8). Notably, in the case of tetralone-derived **1h**, which is labile under oxidation conditions due to aromatization,[17] the reaction proceeded smoothly in a mixed solvent of acetonitrile-chloroform (2:1), and the corresponding product **3ha** was obtained in 88% yield. An *N*-alkyl group, i.e., *n*-butyl-substituted amide **1j** was also available, affording **5ja** in 80% yield (entry 9). *N*-aryl group in amide was also varied (entry 10-13). Both of electron donating and

Table 2 Substrate scope for the β-ketoamides **1**.



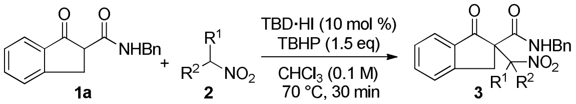
Entry		β-Ketoamide	Product	Yield (%)[e,f]
1	**1b**		**3ba**	88
2	**1c**		**3ca**	73
3	**1d**		**3da**	84
4	**1e**		**3ea**	93
5[a,b]	**1f**		**3fa**	85
6[a,b]	**1g**		**3ga**	85
7[c]	**1h**		**3ha**	88
8[d]	**1i**		**3ia**	84
9	**1j**		**5ja**	80
10[a]	**1k**		**5ka**	92
11[a]	**1l**		**5la**	97
12[a]	**1m**		**5ma**	95
13[a]	**1n**		**5na**	63
14[g]	**1o**		**5oa**	comp.

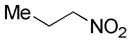
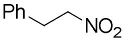
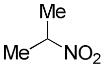
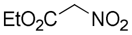
[a] $CHCl_3$ was used. [b] TBD·HI (20 mol%) was used. [c] MeCN-$CHCl_3$ (2:1) was used. [d] MeCN-ethyl acetate (1:7) was used. [e] Isolated yield. [f] diastereomeric ratios were shown in supporting information. [g] The reaction was carried out for 2 h.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry [year]

Table 3 Substrate scope for nitroalkanes **2**.[18]



Entry	Nitroalkane[a]		Product	Yield (%)
1	**2b**	$MeNO_2$	**3ab**	90
2	**2c**		**3ac**	82
3[b]	**2d**		**3ad**	81
4[b,c]	**2e**		**3ae**	90
5	**2f**		**3af**	87
6[b,d]	**2g**		**3ag**	79

[a] 30 equivalents of nitroalkanes were used. [b] 3 equivalents of nitroalkanes were used. [c] 5 equivalents of nitroalkanes were used. [d] The reaction was carried out at 50 °C for 1 h.

withdrawing groups were available, and corresponding products of **5ka**-**5na** were obtained in 63-97% yield. This reaction did not proceed to a simple cyclopentanone derived β-ketoamide **1o**, and complicated reaction products were obtained (entry 14).

Next, the nitroalkanes **2** were varied to examine the reaction with indanone-derived β-ketoamide **1a**. As shown in table 3, various nitroalkanes **2** were available, and oxidative coupling products **3ab**-**3ae** were obtained in good to high yields (entries 1-4). Interestingly, the reaction proceeded with 2-nitropropane, and the oxidative coupling product **3af** bearing quaternary carbon was obtained in 87% yield (entry 5). Moreover, ethyl nitroacetate also gave the coupling product **3ag** in 79% yield (entry 6).

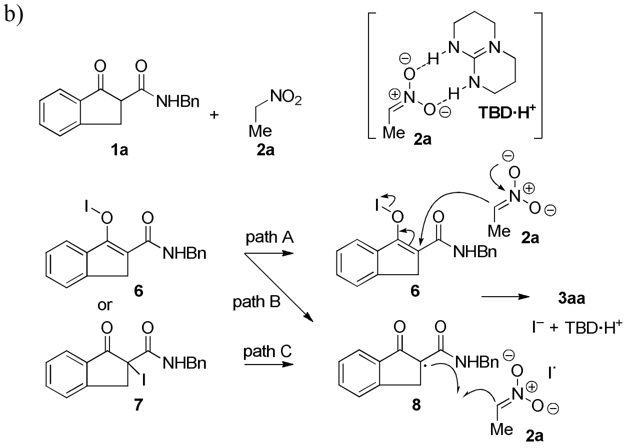
Then, the mechanism of this reaction was examined. Several pathways (A~C) can be considered based upon the recent studies by Ishihara and co-workers (Scheme 2).[19] Firstly, hypoiodite IO^- should be generated by reaction of I^- with TBHP (Scheme 2a). This hypoiodite species would react with β-ketoamide **1a** to form either iodoenolate **6** or α-iodo-β-ketoamide **7** (Scheme 2b). In the case of iodoenolate **6** as an intermediate, nitronate **2a** stabilized by TBD would react with **6** to generate **3aa** (path A).[20] On the other hand, radical-type coupling would proceed from intermediate **8** through homolytic cleavage of **6** or **7** followed by coupling with nitronate **2a** (paths B and C).

To verify these reaction pathways, oxidative coupling reaction of β-ketoamide **1a** and nitroethane (**2a**) was carried out in the presence of TEMPO, a radical scavenger, under optimized conditions (Scheme 3a). Only a trace amount of product **3aa** was obtained, and β-ketoamide **1a** was recovered almost quantitatively. Alternatively, we performed the oxidative coupling reaction in the presence of dibutylhydroxytoluene (BHT) (Scheme 3b). In this case, α-phenxylated **9** was obtained in 39% yield together with **3aa** (24%). Moreover, only hydroxylated **4a** was obtained in 97% yield under the oxygen atmosphere (Scheme 3c). Thus, the presence of radical intermediate **8** was suggested.[21,22]

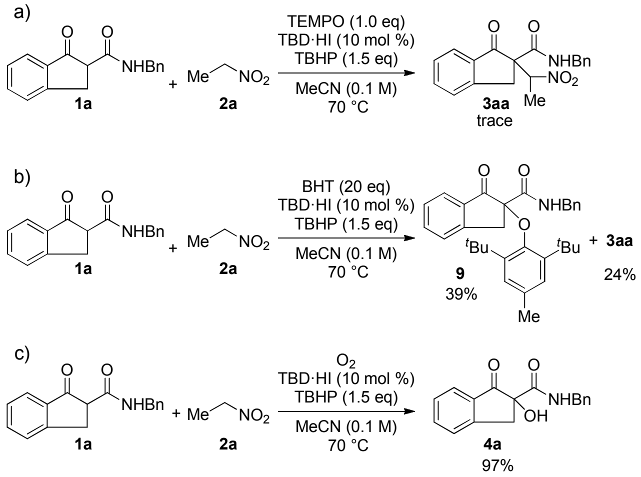
a)

$$\text{TBD·HI} + \textit{tert}\text{-BuOOH} \longrightarrow IO^- + \text{TBD·H}^+ + \textit{tert}\text{-BuOH}$$

b)



Scheme 2 (a) Oxidation of TBD·HI with TBHP. (b) Proposed mechanism for oxidative coupling reaction of β-ketoamide **1a** with nitroalkane **2a**.



Scheme 3 Oxidative α-nitroalkylation of β-ketoamide **1a** in the presence of TEMPO, b) dibutylhydroxytoluene (BHT), and c) oxygen.

Conclusions

In summary, we have developed an oxidative nitroalkylation of β-ketoamides in the presence of hypoiodite generated from TBHP as an oxidant and a catalytic amount of TBD·HI. A wide range of nitroalkanes and β-ketoamides was available for reaction under these conditions. This direct and simple oxidative catalytic reaction is expected to be a powerful and practically useful approach to obtain α-nitroalkyl-substituted carbonyl compounds. We are investigating the mechanism and further applications of guanidinium iodide-mediated oxidative coupling reactions.

We would like to dedicate this article to celebrate the 20th

ChemComm Accepted Manuscript

anniversary of the Department of Biotechnology and Life Science at Tokyo University of Agriculture and Technology. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (No. 23105013 and 23105005) from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

[a] *Department of Life Science and Biotechnology*
Tokyo University of Agriculture and Technology
2-24-16, Naka-cho, Koganei, Tokyo 184-8588 (Japan)
Fax: (+ 81) 42-388-7295
E-mail: knaga@cc.tuat.ac.jp

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1. J. L. Courtneidge, J. Lusztyk, D. Pagé, *Tetrahedron Lett.*, 1994, **35**, 1003.
2. a) J. Madsen, C. Viuf, M. Bols, *Chem. Eur. J.*, 2000, **6**, 1140; b) J. Barluenga, F. González-Bobes, J. M. González, *Angew. Chem.*, 2002, **114**, 2668; *Angew. Chem. Int. Ed.*, 2002, **41**, 2556; c) J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros, J. M. González, *Chem. Eur. J.*, 2004, **10**, 1677; d) S. Minakata, Y. Morino, Y. Oderaotoshi, M. Komatsu, *Chem. Commun.*, 2006, 3337; e) S. Minakata, Y. Morino, Y. Oderaotoshi, M. Komatsu, *Org. Lett.*, 2006, **8**, 3335; f) S. Minakata, Y. Morino, T. Ide, Y. Oderaotoshi, M. Komatsu, *Chem. Commun.*, 2007, 3279; g) T. Hu, K. Liu, M. Shen, X. Yuan, Y. Tang, C. Li, *J. Org. Chem.*, 2007, **72**, 8555; h) R. Fan, W. Li, D. Pu, L. Zhang, *Org. Lett.*, 2009**, 11**, 1425; i) S. Minakata, S. Okumura, T. Nagamachi, Y. Takeda, *Org. Lett.*, 2011, **13**, 2966; j) Y. Takeda, S. Okumura, S. Minakata, *Angew. Chem.*, 2012, **124**, 7924; *Angew. Chem. Int. Ed.* 2012, **51**, 7804; k) Y. Takeda, S. Enokijima, T. Nagamachi, K. Nakayama, S. Minakata, *Asian J. Org. Chem.*, 2013, **2**, 91; l) H. Kikui, K. Moriyama, H. Togo, *Synthesis,* 2013, 791; m) Y. Takeda, S. Okumura, S. Minakata, *Synthesis*, 2013, 1029.
3. a) M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science*, 2010, **328**, 1376; b) M. Uyanik, D. Suzuki, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.*, 2011, **50**, 5331;
4. Reviews, see: a) M. Uyanik, K. Ishihara, *ChemCatChem*, 2012, **4**, 177; b) X. F. Wu, J. L. Gong, X. Qi, *Org. Biomol. Chem.*, 2014, **12**, 5807.
5. C-O bond-forming reactions at the α-position of carbonyls, see: a) W. Wei, Y. Wang, J. Yin, J. Xue, Y. Li, *Org. Lett.,* 2012, **14**, 1158; b) L. Wei, J. Xue, H. Liu, W. Wang and Y. Li, *Org. Lett.,* 2012, **14**, 5302; c) S. Guo, J. T. Yu, Q. Dai, H. Yang, J. Cheng, *Chem. Commun.*, 2014, **50**, 6240; d) S. S. K. Boominathan, W. P. Hu, G. C. Senadi, J. K. Vandavasi, J. J. Wang, *Chem. Commun.*, 2014, **50**, 6726; Benzylic position, see: e) J. Huang, L. T. Li, H. Y. Li, E. Husan, P. Wang, B. Wang, *Chem. Commun.*, 2012, **48**, 10204; f) L. Niu, H. Yang, D. Yang, H. Fu, *Adv. Synth. Catal.*, 2012, **354**, 2211; g) G. Majji, S. Guin, A. Gogoi, S. K. Rout, B. K. Patel, *Chem. Commun.*, 2013, **49**, 3031; h) L. Liu, L. Yun, Z. Wang, X. Fu, C. H. Yan, *Tetrahedron Lett.*, 2013, **54**, 5383; Other examples, see: i) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu, X. Wan, *Chem. Eur. J.*, 2011, **17**, 4085; j) Q. Xue, J. Xie, P. Xu, K. Hu, Y. Cheng and C. Zhu, *ACS Catal.*, 2013, **3**, 1365; k) H. Yu, J. Shen, *Org. Lett.,* 2014, **16**, 3204.
6. C-N bond-forming reaction at the α-position of carbonyls, see: a) J. Zhang, J. Jiang, Y. Li, Y. Zhao and X. Wan, *Org. Lett.,* 2013, **15**, 3222; b) Y. Lv, Y. Li, T. Xiong, Y. Lu, Q. Liu, Q. Zhang, *Chem. Commun.*, 2014, **50**, 2367; Benzylic position, see: c) Q. Xue, J. Xie, H. Li, Y. Cheng, C. Zhu, *Chem. Commun.*, 2013, **49**, 3700; Other examples, see: d) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *Org. Lett.,* 2011, **13**, 3754; e) A. Yoshimura, K. R. Middleton, C. Zhu, V. N. Nemykin, V. V. Zhdankin, *Angew. Chem. Int. Ed.*, 2012, **51**, 8059; f) Z. J. Cai, S. Y. Wang and S. J. Ji, *Org. Lett.*, 2013, **15**, 5226; g) R. Wang, H. Liu, L. Yue, X. Zhang, Q. Tan, R. Pan, *Tetrahedron Lett.*, 2014, **55**, 2233; h) X. Zhang, M. Wang, P. Li, L. Wang, *Chem. Commun.*, 2014, **50**, 8006;
7. Cycloaddition reactions, see: a) Y. C. Wong, C. T. Tseng, T. T. Kao, Y. C. Yeh and K. S. Shia, *Org. Lett.*, 2012, **14**, 6024; b) J. Xie, H. Jiang, Y. Cheng, C. Zhu, *Chem. Commun.*, 2012, **48**, 979; c) U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *J. Org. Chem.*, 2013, **78**, 2751; d) A. Yoshimura, C. Zhu, K. R. Middleton, A. D. Todora, B. J. Kastern, A. V. Maskaev, V. V. Zhdankin, *Chem. Commun.*, 2013, **49**, 4800; e) H. M. Huang, Y. J. Li, Q. Ye, W. B. Yu, L. Han, J. H. Jia, J. R. Gao, *J. Org. Chem.*, 2014, **79**, 1084.
8. C-C bond-forming reaction at the benzylic position, see: a) A. Rodríguez, W. J. Moran, *Org. Lett.* 2011, **13**, 2220; b) T. Nobuta, A. Fujiya, T. Yamaguchi, N. Tada, T. Miura and A. Itoh, *RSC Adv.*, 2013, **3**, 10189; c) T. Nobuta, N. Tada, A. Fujiya, A. Kariya, T. Miura and A. Itoh, *Org. Lett.*, 2013, **15**, 574; d) J. Dhineshkumar, M. Lamani, K. Alagiri and K. R. Prabhu, *Org. Lett.*, 2013, **15**, 1092; The other example, see: e) C. Zhang, C. Liu, Y. Shao, X. Bao and X. Wan. *Chem. Eur. J.*, 2013, **19**, 17917.
9. Fan and co-workers reported intramolecular oxidative coupling reactions of β-dicarbonyl compounds with nitroalkanes in the presence of stoichiometric amounts of tetrabutylammonium iodide and iodobenzene diacetate; R. Fan, Y. Ye, W. Li, L. Wang, *Adv. Synth. Catal.*, 2008, **350**, 2488.
10. a) J. A. Ma, *Angew. Chem., Int. Ed.* 2003, **42**, 4290; b) E. Juaristi, V. A. Soloshonok, *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2005; c) B.Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev*. 2010, **39**, 1656.
11. a) A. Bhalla, P. Venugopalan, S. S. Bari, *Eur. J. Org. Chem.* 2006, 4943; b) M. Hatano, T. Horibe and K. Ishihara, *J. Am. Chem. Soc.* 2010, **132**, 56.
12. Acetonitrile (solvent) was used after purging with argon.
13. The use of anhydrous TBHP (3 M in dichloroethane) did not affect the results, and **3aa** was obtained in 89% yield.
14. We tested the α-nitroalkylation of **1a** with **2a** using TBHP in the presence of *n*-Bu$_4$NI, *n*BuPI, or TMG·HI. In all cases, reaction did not proceed very well. See supporting information in Table SI-1.
15. a) M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda, K. Miyamoto, *J. Am. Chem. Soc.*, 2005, **127**, 12244; b) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita, *Angew. Chem.*, 2005, **117**, 6349; *Angew. Chem. Int. Ed.*, 2005, **44**, 6193;
16. Formation of α-hydroxylated products **4a** was effectively suppressed by using 20 mol% of catalyst and CHCl$_3$ as a solvent.
17. a) L. Engman, *J. Org.Chem.*, 1988, **53**, 4031; b) A. Cordero-Vargas, I. Perez-Martin, B. Quiclet-Sire, S. Z. Zard, *Org. Biomol. Chem.*, 2004, **2**, 3018; c) T. F. Yang, K. Y. Wang, H. W. Li, Y. C. Tseng, T. C. Lien, *Tetrahedron Lett.*, 2012, **53**, 585; d) D. Niculescu-Duvaz, I. Niculescu-Duvaz, B. M. Suijkerbuijk, D. Ménard, A. Zambon, L. Davies, J. F. Pons, S. Whittaker, R. Marais, C. J. Springer, *Bioorg. Med. Chem.*, 2013, **21**, 1284.
18. Chloroform was used as a solvent for these nitroalkanes.
19. M. Uyanik, H. Hayashi, K. Ishihara, *Science*, 2014, **345**, 291.
20. We currently consider that the TBD is effective for stabilization of nitronates **2** through interaction of the two parallel bonds. To support this structure, we performed the ^{1}H NMR studies. See supporting information in Figure SI-1.
21. Reactions in the presence of TEMPO and BHT as radical scavengers, see: a) Y. Y. Yu, A. R. Ranade and G. I. Georg, *Adv. Synth. Catal.* 2014, **356**, 3510; b) F. Zhang, P. Du, J. Chen, H. Wang, Q. Luo and X. Wan, *Org. Lett.* 2014, **16**, 1932.
22. Reactions under oxygen atmosphere, see: a) R. Lin, F. Chen, N. Jiao, *Org. Lett.* 2012, **14**, 4158; b) T. Wang, N. Jiao, *J. Am. Chem. Soc.* 2013, **135**, 11692; c) Y. Su, X. Sun, G. Wu, N. Jiao, *Angew. Chem. Int. Ed.* 2013, **52**, 9808.

ChemComm Accepted Manuscript