Advanced Synthesis & Catalysis

Accepted Article

Title: n-Bu4NI/K2S2O8 Mediated Csp2-Csp2 Bond Cleavage – Transformylation from p-Anisaldehyde to Primary Amides

Authors: Xiaochen Liu, Samual Hee, Netanel Sapir, Alvin Li, Jianbo Liu, and Yu Chen

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202301505

Link to VoR: https://doi.org/10.1002/adsc.202301505

10.1002/adsc.202301505

COMMUNICATION

DOI: 10.1002/adsc.202((will be filled in by the editorial staff))

n-$Bu_4NI/K_2S_2O_8$ Mediated Csp^2-Csp^2 Bond Cleavage – Transformylation from *p*-Anisaldehyde to Primary Amides

Xiaochen Liu,[a,b] Samual Hee,[a,b] Netanel G. Sapir,[a] Alvin Li,[a] Jianbo Liu,[a,b,*] and Yu Chen[a,b,*]

[a] Department of Chemistry and Biochemistry, Queens College of the City University of New York, 65-30 Kissena Blvd., Queens, New York 11367, United States
[b] Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, 365 Fifth Ave., New York, New York 10016, United States
E-mail: yu.chen1@qc.cuny.edu; Jianbo.Liu@qc.cuny.edu

Received: ((will be filled in by the editorial staff))

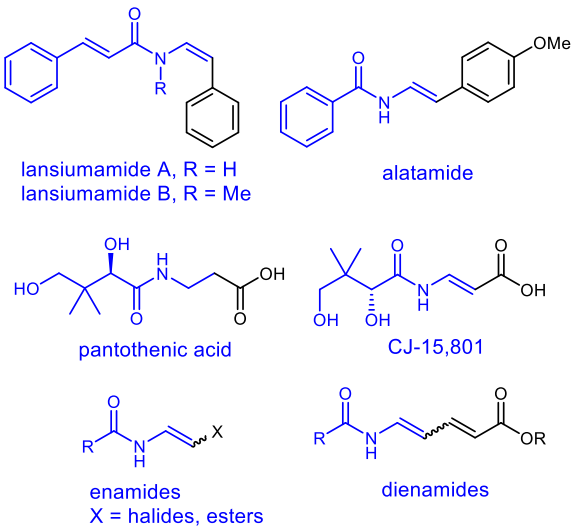
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. *n*-$Bu_4NI/K_2S_2O_8$ mediated transformylation from *p*-anisaldehyde to primary amides is reported. The mechanistic studies suggest the reaction occurs via a single electron transfer pathway. Based on the DFT electronic structure calculations of various reaction pathways, the most plausible mechanism involves the formation of a phenyl radical cation and an arenium ion as the key intermediates. It represents the first example where *p*-anisaldehyde is employed as a formyl source via a non-metal mediated Csp^2-Csp^2 bond cleavage.

Keywords: *n*-$Bu_4NI/K_2S_2O_8$ mediated; transformylation; single electron transfer reaction; *N*-formyl imide; Csp^2-Csp^2 bond cleavage

The cross dehydrogenative coupling reactions mediated by either iodine catalysts[1] or potassium persulfate[2] have attracted great attention from chemists. These metal free transformations are distinct from the traditional transition metal catalysis for their green chemistry features such as sustainability and environmental compatibility. Furthermore, these reactions in general take place via single electron transfer mechanism pathways which are distinct from the traditional transition metal catalysis, and often render novel chemical reactivities that the classical transition metal catalysis does not accommodate.

Formyl imides are the key intermediates in the synthesis of natural products such as lansiumamides A and B, alatamide,[3] pantothenic acid and CJ-15,801,[4] and pharmaceutical intermediates such as dienamides[5] and enamides[6] (Figure 1).



*** The portion of the target molecule originating from formyl imide is highlighted in blue.**

Figure 1. Natural Products and Pharmaceutical Intermediates Synthesized via Formyl Imides.

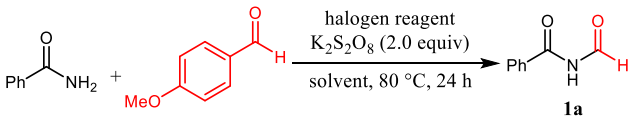
Many methods have been developed for the synthesis of formyl imides.[7-12] Most of them employ the strategy of direct *N*-formylation of amides, including direct treatment with acetic formic anhydride,[7] sequential treatment with *n*-butyl lithium and *N*-formylbenzotriazole,[3,6b] converting amides to amidines by *N*,*N*-dimethylformamide dimethyl acetal followed by propylphosphonic acid anhydride mediated hydrolysis,[8] transition metal[9] or *N*-heterocyclic carbene/carbene derivatives[10] catalyzed *N*-formylation of amides via hydrosilylative reduction of carbon dioxide, *N*-bromosuccinimide-mediated addition-elimination between amides and *N*,*N*-dimethylformamide,[11] and *N*-formylation by iodine and ammonium persulfate mediated activation of DMSO.[12]

10.1002/adsc.202301505

During the course of studying the non-metal mediated cross dehydrogenative coupling reaction of amides and aldehydes, we observed a *n*-$Bu_4NI/K_2S_2O_8$ mediated transformylation reaction from *p*-anisaldehyde to primary amides. The reaction involves a Csp^2-Csp^2 carbon-carbon bond cleavage between the aldehyde carbon and the phenyl ring of the *p*-anisaldehyde. It is worth noting that it differs from the well-known Dakin oxidation[13] process in terms of both the reaction mechanism and products. Inspired by the unprecedented reactivity, we have carried out a thorough study on the transformylation. Herein, we report the details of the new reaction.

At the beginning of the investigation, we attempted a cross dehydrogenative coupling between aldehydes and amides by iodine catalyzed oxidative acylation, expecting the formation of an imide. We chose *p*-anisaldehyde and benzamide as the model substrates. No reaction took place in the absence of either $K_2S_2O_8$ or *n*-Bu_4NI (Table 1, entries 1 and 2). On the other hand, a transformylation reaction occurred in the presence of 10 mol% of *n*-Bu_4NI and 2 equivalents of $K_2S_2O_8$, and *N*-formylbenzamide **1a** was obtained in a 67% yield in anhydrous CH_3CN (Table 1, entry 3). Other iodine reagents such as *n*-Et_4NI, I_2, KI, *N*-iodosuccinimide (NIS), PhI, phenyliodine(III) diacetate (PIDA), and Dess–Martin periodinane (DMP) either afforded mediocre yields or completely failed in the reaction (Table 1, entries 4 to 10). Other tetrabutylammonium halides (*n*-Bu_4NCl and *n*-Bu_4NBr) were also examined in the reaction and only resulted in a 13% and 29% yield of **1a** (Table 1, entries 11 and 12). The reaction failed in most of the solvents screened, except tetrahydrofuran (THF) which afforded **1a** in a 17% yield (Table 1, entry 13). An 80% yield of **1a** was obtained when 20 mol% of *n*-Bu_4NI was added (Table 1, entry 17). The yield of **1a** dropped to 41% when only one equivalent of $K_2S_2O_8$ was added (Table 1, entry 18). On the other hand, the yield was slightly enhanced to 82% when three equivalents of $K_2S_2O_8$ were added (Table 1, entry 19). In addition, **1a** was obtained in a 49% yield when $K_2S_2O_8$ was replaced by $(NH_4)_2S_2O_8$ (Table 1, entry 20). A similar chemical yield (52%) of **1a** was obtained even in the absence of *n*-Bu_4NI, when $(NH_4)_2S_2O_8$ was employed (Table 1, entry 21). The reaction time was not optimized, but we later found that the yield of **1a** reached a maximum after approximately 6 hours.

Table 1. Reaction Condition Optimization for the Transformylation from *p*-Anisaldehyde to Benzamide.[a]

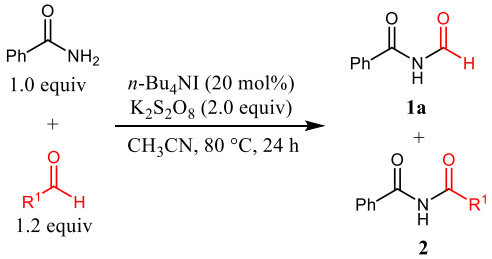


Entry	Halogen reagent (10 mol%)	Solvent	Yield[b]
1[c]	*n*-Bu_4NI	CH_3CN	NR
2	-	CH_3CN	NR
3	*n*-Bu_4NI	CH_3CN	67%
4	*n*-Et_4NI	CH_3CN	14%
5	I_2	CH_3CN	0%
6	KI	CH_3CN	0%
7	NIS	CH_3CN	0%
8	PhI	CH_3CN	0%
9	PIDA	CH_3CN	0%
10	DMP	CH_3CN	0%
11	*n*-Bu_4NCl	CH_3CN	13%
12	*n*-Bu_4NBr	CH_3CN	29%
13[d]	*n*-Bu_4NI	THF	17%
14	*n*-Bu_4NI	DMSO	0%
15	*n*-Bu_4NI	DCE	0%
16	*n*-Bu_4NI	DMAC	0%
17[e]	*n*-Bu_4NI	CH_3CN	80%
18[f]	*n*-Bu_4NI	CH_3CN	41%
19[g]	*n*-Bu_4NI	CH_3CN	82%
20[h]	*n*-Bu_4NI	CH_3CN	49%
21[h]	-	CH_3CN	52%

[a] General procedure: The iodine catalyst (0.1 mmol, 10 mol%), $K_2S_2O_8$ (2.0 mmol, 2.0 equiv), benzamide (1.0 mmol, 1.0 equiv), *p*-anisaldehyde (1.2 mmol, 1.2 equiv), and solvent (7 mL) were added to a 20 mL glass vial sealed with a pressure relief cap. The reaction mixture was stirred at 80 °C for 24 h. [b] Isolated yields after column chromatography. [c] No $K_2S_2O_8$ was added. [d] The reaction was carried out at 66 °C. [e] *n*-Bu_4NI (0.2 mmol, 20 mol%) was added. [f] One equivalent of $K_2S_2O_8$ (1.0 mmol) was added. [g] Three equivalents of $K_2S_2O_8$ (3.0 mmol) were added. [h] Two equivalents of $(NH_4)_2S_2O_8$ were added instead of $K_2S_2O_8$.

Inspired by the novel transformylation reaction, we further inspected the reaction between benzamide and various aromatic aldehydes employing the optimized reaction conditions listed in entry 17 of Table 1. All the aryl aldehydes containing an electron-donating group at either the *para* or the *ortho* position of the formyl group, such as *o*-anisaldehyde, *p*-tolualdehyde, 4-hydroxybenzaldehyde, 2-hydroxybenzaldehyde and thiophene-2-carbaldehyde, all exclusively led to the sole transformylation product **1a** (Table 2, entries 2-6). Among all the aryl aldehydes tested, *p*-anisaldehyde afforded the highest yield. On the other hand, *m*-anisaldehyde yielded a mixture of **1a** and the cross dehydrogenative coupling product imide **2a** (Table 2, entry 7). It is worth noting that benzaldehyde reacted with benzamide mainly afforded the imide **2b** (Table 2, entry 8) with only a trace amount of *N*-formylbenzamide **1a**.

Table 2. *n*-$Bu_4NI/K_2S_2O_8$ Mediated Transformylation from Electron-rich Aromatic Aldehydes to Benzamide.[a]



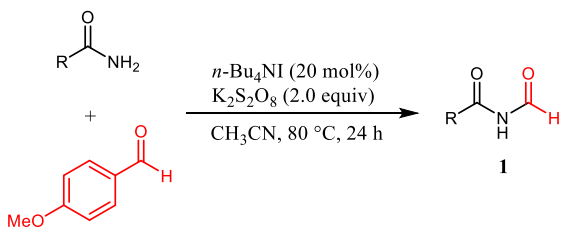
10.1002/adsc.202301505

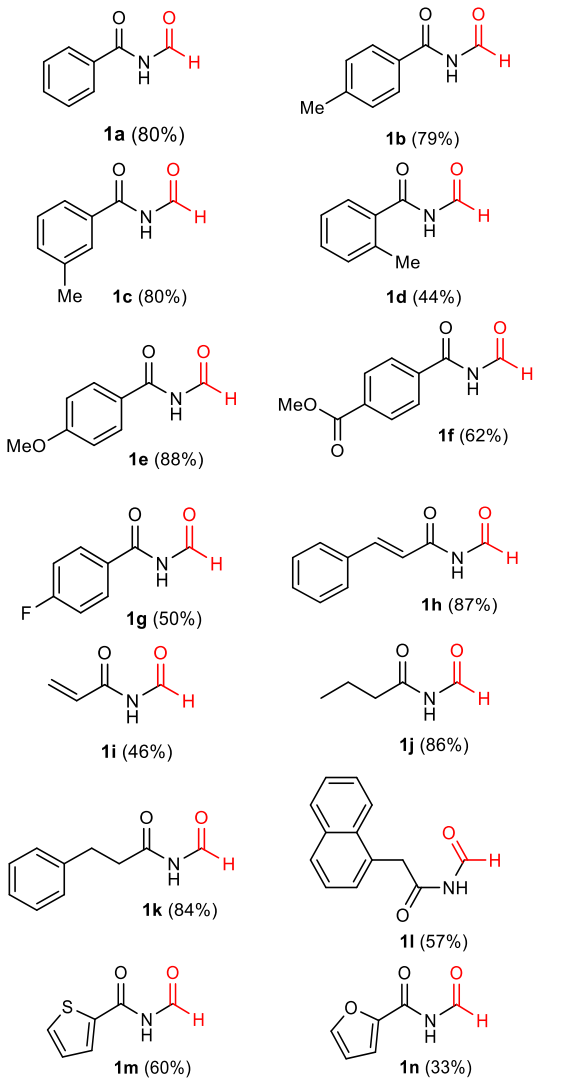
Entry	Aldehyde	Yield/**1a**[b]	Yield/**2**[b]
1	*p*-anisaldehyde	80%	0%
2	*o*-anisaldehyde	78%	0%
3	*p*-tolualdehyde	57%	0%
4	4-hydroxybenzaldehyde	22%	0%
5	2-hydroxybenzaldehyde	13%	0%
6	thiophene-2-carbaldehyde	26%	0%
7[c]	*m*-anisaldehyde	16%	21%/**2a**
8[c]	benzaldehyde	trace	79%/**2b**

[a] General procedure: *n*-Bu_4NI (0.2 mmol, 20 mol%), $K_2S_2O_8$ (2.0 mmol, 2.0 equiv), benzamide (1.0 mmol, 1.0 equivalent), aldehyde (1.2 mmol, 1.2 equiv), and CH_3CN (7 mL) were added in a 20 mL glass vial sealed with a pressure relief cap. The reaction mixture was stirred at 80 °C for 24 h. [b] Isolated yields after column chromatography. [c] *n*-Bu_4NI (0.1 mmol, 10 mol%) was added, while the amounts of the other reagents were the same as the general procedure.

The scope of the amide substrates in the transformylation was then examined employing *p*-anisaldehyde as the formyl source. The reaction displayed a good substrate compatibility and the corresponding formyl imides were obtained in moderate to good yields (Table 3). Aromatic amides bearing either electron-donating groups such as methyl (**1b-d**) and methoxy (**1e**) or electron-withdrawing groups such as ester (**1f**) and fluoro (**1g**) were all well accommodated, though in general higher yields were obtained in the former cases. Steric hindrance seemed to be detrimental to the transformylation as a much lower yield was obtained from *ortho*-methylbenzamide (**1d**), comparing to the *para*- or *meta*-methylbenzamide (**1b-c**). Aliphatic amides also gave excellent yields (**1j**, **1k**). In addition, α,β-unsaturated formyl imides were successfully synthesized (**1h**, **1i**) in moderate to good yields. The former (**1h**) was a key intermediate in the synthesis of lansiumamides A and B.[3] Subsequently, the scope was extended to heterocyclic amides, thiophene-2-carboxamide and furan-2-carboxamide. Both worked and gave the anticipated products in 60% (**1m**) and 33% yield **(1n)**, respectively. The transformylation to the secondary amide, *N*-methylbenzamide, however, failed under the reaction conditions and the amide starting material was fully recovered.

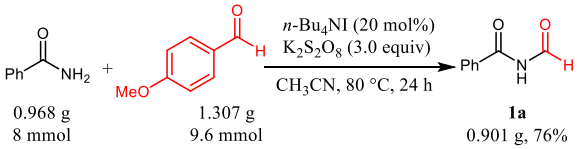
Table 3. *n*-$Bu_4NI/K_2S_2O_8$ Mediated Transformylation from *p*-Anisaldehyde to Various Primary Amides.[a],[b]





[a] General procedure: *n*-Bu_4NI (0.2 mmol, 20 mol%), $K_2S_2O_8$ (2.0 mmol, 2.0 equiv), amide (1.0 mmol, 1.0 equiv), *p*-anisaldehyde (1.2 mmol, 1.2 equiv), and CH_3CN (7 mL) were added in a 20 mL glass vial sealed with a pressure relief cap. The reaction mixture was stirred at 80 °C for 24 h. [b] Isolated yields after column chromatography.

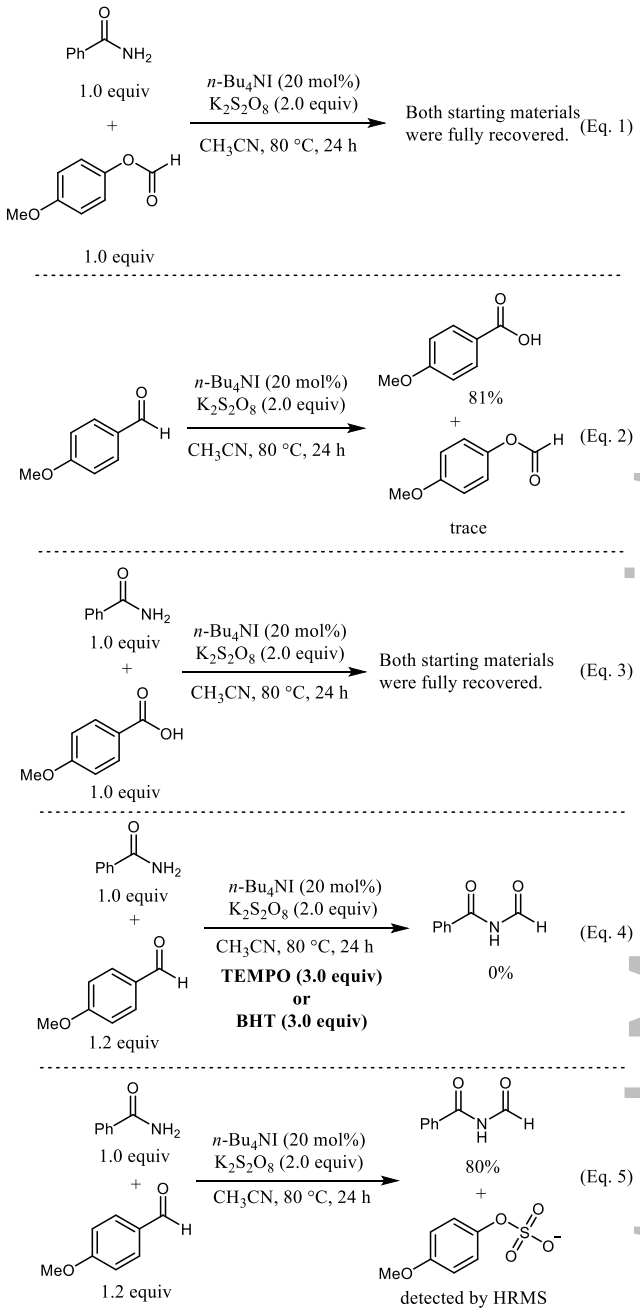
We also carried out a gram scale transformylation reaction between *p*-anisaldehyde and benzamide, and *N*-formylbenzamide (**1a**) was obtained in a 76% yield (Scheme 1; for the detailed experiment procedures, see the Supporting Information).



Scheme 1. *n*-$Bu_4NI/K_2S_2O_8$ Mediated Transformylation from *p*-Anisaldehyde to Benzamide on Gram Scale.

10.1002/adsc.202301505

In order to gain more insights into the transformylation, we conducted the following study. Considering phenyl formate was a known formylation reagent,[14] we therefore examined the reaction between benzamide and 4-methoxyphenyl formate. It turned out no reaction occurred under the optimized conditions and both starting materials were fully recovered after 24 hours (Scheme 2, Eq 1). In addition, we carried out the oxidation of *p*-anisaldehyde under the optimized conditions, which almost exclusively led to 4-methoxybenzoic acid (Scheme 2, Eq 2). We therefore ruled out the possibility for the formylation of benzamide by 4-methoxyphenyl formate. We further examined the coupling reaction between 4-methoxybenzoic acid and benzamide, but both starting materials were fully recovered after 24 hours (Scheme 2, Eq 3). Previous studies indicated that the combination of *n*-Bu_4NI and $K_2S_2O_8$ was a radical initiator.[15] In the presence of either three equivalents of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT), the transformylation reaction was completely suppressed (Scheme 2, Eq 4). Furthermore, the LC-MS analysis detected the formation of *p*-methoxyphenyl sulfate anion in the reaction mixture (Scheme 2, Eq 5). It is worth noting that in the presence of a stoichiometric amount of benzamide the transformylation takes place almost exclusively and only a trace amount of 4-methoxybenzoic acid, the oxidation product of *p*-anisaldehyde, was observed. The transformylation is probably kinetically more favorable than the oxidation under the current optimized conditions.

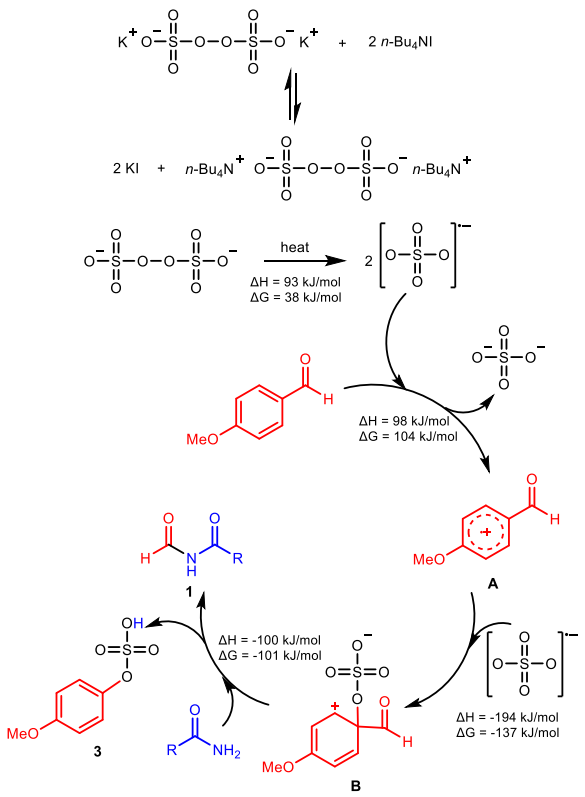


Scheme 2. Control Experiments Carried Out for the Mechanism Study.

In order to gain more insights into the reaction mechanism, we also completed DFT calculations (see the Supporting Information for details). The calculated DFT reaction enthalpies reflected the endo- and exothermicity for each elementary step, from which the probable rate-limiting step(s) may be singled out. The identified endothermic steps (i.e., the homolysis of peroxydisulfate anion, and the oxidation of *p*-anisaldehyde to a phenyl cation radical **A** by a sulfate anion radical, see Scheme 3) are consistent with the fact that the reactions only start at an elevated temperature (80 °C). Based on our experimental data, DFT calculations and the previous literature reports,[16] a plausible mechanism is depicted in Scheme 3. The reaction between *n*-Bu_4NI and $K_2S_2O_8$ results in the more soluble bis(tetrabutylammonium) peroxydisulfate,

10.1002/adsc.202301505

which undergoes homolytic cleavage generating sulfate anion radical at an elevated temperature. The sulfate anion radical is a well-known strong oxidant,[2] which oxidizes *p*-anisaldehyde to a phenyl cation radical (**A**). A second equivalent of sulfate anion radical adds to the *ipso* position of the formyl group forming an arenium ion (1-formyl-4-methoxycyclohexa-3,5-dien-2-ylium-1-yl sulfate) **B**, which is stabilized by the electron-donating *para*-methoxy group. A subsequent nucleophilic acyl substitution between **B** and amide takes place at the formyl group leading to the formyl imide (**1**) and 4-methoxyphenyl hydrogen sulfate (**3**).



Scheme 3. Proposed Mechanism for the *n*-$Bu_4NI/K_2S_2O_8$ Mediated Transformylation from *p*-Anisaldehyde to Primary Amides.

In summary, a transformylation from *p*-anisaldehyde to primary amides is developed with inexpensive and environmentally friendly reagents, *n*-Bu_4NI and $K_2S_2O_8$. A series of *N*-formyl imides were readily synthesized in moderate to good yields by the strategy. A sulfate radical anion initiated single electron transfer mechanism is proposed with a phenyl radical cation and a sigma complex as the key intermediates. DFT calculations support the thermodynamic analysis of the proposed mechanism. The novel Csp^2-Csp^2 bond cleavage via a single electron transfer mechanism reported herein may provide insights to the Csp^2-Csp^2 bond activation of similar aryl-Csp^2 bonds. Further investigation on how to make use of the 4-methoxyphenyl hydrogen sulfate and apply the transformylation strategy to the synthesis of new compounds via C-N and C-C bond coupling are undergoing in our group and will be reported in due course.

Experimental Section

General Procedure for the Preparation of Imides (1) via *N*-Acylation of Aldehydes with Amides.

An oven dried 20 mL glass reaction vials was charged with amide (1.0 mmol, 1.0 equiv), aldehyde (1.2 mmol, 1.2 equiv), tetrabutylammonium iodide (0.2 mmol, 73.8 mg), potassium persulfate (2.0 mmol, 540.6 mg), and anhydrous acetonitrile (7 mL). The reaction mixture was sealed with a pressure relief cap and stirred at 80 °C for 20 h. The reaction mixture was diluted with 20 mL of ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the corresponding product.

Acknowledgements

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number SC3GM144160. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We also thank Queens College and the City University of New York for their partial financial support. We thank Dr. Barney Yoo at Hunter College for his help in collecting the high-resolution mass spectrometry data of most of the new compounds. The high-resolution mass spectrometry measurements of a part of the new compounds were made in the Molecular Education, Technology, and Research Innovation Center (METRIC) at North Carolina State University.

References

[1] For reviews, see: a) P. Finkbeiner, B. J. Nachtsheim, *Synthesis* **2013**, *45*, 979-999; b) D. Liu, A. Lei, *Chem. Asian J.* **2015**, *10*, 806-823; c) P. T. Parvatkar, R. Manetsch, B. K. Banik, *Chem. Asian J.* **2019**, *14*, 6-30.

[2] For reviews, see: a) U. Wille, *Chem. Eur. J.* **2002**, *8*, 340-347; b) S. Mandal, T. Bera, G. Dubey, J. Saha, J. K. Laha, *ACS Catal.* **2018**, *8*, 5085-5144; c) S. Kumar, K. Padala, *Chem. Commun.* **2020**, *56*, 15101-15117.

[3] A. E. Pasqua, F. D. Ferrari, J. J. Crawford, R. Marquez, *Tetrahedron Lett.* **2014**, *55*, 6042-6043.

[4] A. L. Sewell, M. V. J. Villa, M. Matheson, W. G. Whittingham, R. Marquez, *Org. Lett.* **2011**, *13*, 800–803.

[5] J. E. Mathieson, J. J. Crawford, M. Schmidtmann, R. Marquez, *Org. Biomol. Chem.* **2009**, *7*, 2170-2175.

[6] a) A. E. Pasqua, J. J. Crawford, D.-L. Long, R. Marquez, *J. Org. Chem.* **2012**, *77*, 2149-2158; b) M. V. J. Villa, S. M. Targett, J. C. Barnes, W. G. Whittingham, R. Marquez, *Org. Lett.* **2007**, *9*, 1631-1633.

[7] A. E. Pasqua, L. H. Thomas, J. J. Crawford, R. Marquez, *Tetrahedron* **2011**, *67*, 7611-7617.

[8] M. Sambaiah, R. Gudipati, K. S. Kumar, S. Yennam, M. Behera, *Tetrahedron Lett.* **2016**, *57*, 403-406.

[9] a) Q. Zhang, X.-T. Lin, N. Fukaya, T. Fujitani, K. Sato, J.-C. Choi, *Green Chem.*, **2020**, *22*, 8414-8422; b) S. Chakraborty, A. Das, J. Ahmed, S. Barmana, S. K. Mandal, *Chem. Commun.* **2020**, *56*, 13788-13791.

[10] a) P. K. Hota, S. C. Sau, S. K. Mandal, *ACS Catal.* **2018**, *8*, 11999-12003; b) P. Sreejyothi, K. Bhattacharyya, S. Kumar, P. K. Hota, A. Datta, S. K. Mandal, *Chem. Eur. J.* **2021**, *27*, 11656–11662.

[11] Z. Niu, S. Lin, Z. Dong, H. Sun, F. Liang, J. Zhang, *Org. Biomol. Chem.* **2013**, *11*, 2460-2465.

[12] S. A. Bhat, M. Y. Bhat, S. A. Rather, I. Gani, K. A. Bhat, Q. N. Ahmed, *Org. Biomol. Chem.* **2022**, *20*, 8197-8202.

[13] For a recent review, see: P. Bora, B. Bora, U. Bora, *New J. Chem.* **2021**, *45*, 17077-17084.

[14] S. Batuta, N. A. Begum, *Synth. Commun.* **2017**, *47*, 137-147.

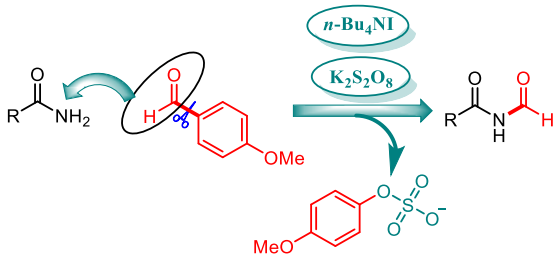
[15] a) M.-Z. Zhang, N. Luo, R.-Y. Long, X.-T. Gou, W.-B. Shi, S.-H. He, Y. Jiang, J.-Y. Chen, T.-Q. Chen, *J. Org. Chem.* **2018**, *83*, 2369-2375; b) X. Mi, C.-Y. Wang, M.-M. Huang, Y.-S. Wu, Y.-J. Wu, *J. Org. Chem.* **2015**, *80*, 148-155; c) X.-D. Yang, L.-B. Zhao, B.-X. Yuan, Z.-J. Qi, R.-L. Yan, *Adv. Synth. Catal.* **2017**, *359*, 3248-3253.

[16] a) Y.-F. Guo, S. Mahmood, B.-H. Xu, X.-Q. Yao, H.-Y. He, S.-J. Zhang, *J. Org. Chem.* **2017**, *82*, 1591-1599; b) C. Tong, B. Gan, Y. Yan, Y.-Y. Xie, *Synth. Commun.* **2017**, *47*, 1927-1933; c) F. Minisci, A. Citterio, C. Giordano, *Acc. Chem. Res.* **1983**, *16*, 1, 27–32.

10.1002/adsc.202301505

COMMUNICATION

n-$Bu_4NI/K_2S_2O_8$–Mediated Csp^2-Csp^2 Bond Cleavage – Transformylation from *p*-Anisaldehyde to Primary Amides



Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Xiaochen Liu, Samual Hee, Netanel G. Sapir, Alvin Li, Jianbo Liu,* Yu Chen*