ChemPubSoc Europe

DOI: 10.1002/ejoc.201600226

EurJOC European Journal of Organic Chemistry

Communication

Formylation

Microwave-Assisted Formylations of Weakly Basic Anilines with Methyl Formate Catalyzed by Calcium and Hydrogen Triflimides

Eric Tan,[a] Sosthène Ung,[a] and Matthieu Corbet*[a]

Abstract: Catalytic amounts of calcium and hydrogen triflimides [$Ca(NTf_2)_2$, $HNTf_2$] were found to be efficient for the solvent-free formylation of a variety of weakly basic anilines by using cheap and widely available methyl formate as the formylating agent under microwave irradiation. Initial investigations showed that in the case of calcium triflimide, Brønsted acid catalysis was most likely operating. Remarkably, the corresponding calcium triflate and triflic acid were significantly less active.

Introduction

N-Formylation is a very important and ubiquitous transformation in organic synthesis.[1] It is traditionally used as an effective strategy to protect amines,[2] especially in the field of peptide chemistry, and as the first step toward the rich chemistry of isocyanides,[3] isocyanates,[4] and amidines.[5] Interestingly, the resulting formamides have not only been reported to be intermediates in the manufacture of some pharmaceuticals, but have also been reported to possess biological activities themselves.[1] Today, their main uses remain as industrial solvents and formylating agents.[6]

Historically, toxic reagents such as chloral were routinely employed, which generated stoichiometric amounts of chloroform as a byproduct.[7] Later on, alternative *N*-formylating agents appeared in the literature but were not necessarily deemed safer.[1] Today, *N*,*N*-dimethylformamide (DMF)[6c,6d] and formic acid are commonly used because of their wide availability and low cost.[8,9] However, their lack of reactivity usually calls for harsh reaction conditions together with stoichiometric amounts of activating agents, especially if amines of low nucleophilicity (e.g., aromatic) are involved. In addition, the high toxicity of DMF and the corrosive nature of formic acid can preclude the development of industrial processes. Recently, tremendous research on the chemical valorization of carbon dioxide has led to the disclosure of efficient catalytic *N*-formylation reactions involving CO_2 and a stoichiometric reducing reagent such as hydrogen, hydrosilanes, or hydroboranes.[10] Even though these strategies bring the undeniable advantage of using a cheap and widely available feedstock, they suffer from the necessity of using expensive catalysts as well as excess amounts of bases at elevated pressures of CO_2 and H_2 for extended reaction times if formanilides are targeted (weakly basic anilines usually do not react under these conditions).[10a]

Although formic acid alkyl esters (alkyl formates) are usually nontoxic and noncorrosive substitutes for DMF and formic acid, only a few catalytic syntheses of formamides from aromatic amines have been disclosed. The catalysts reported range from Brønsted and Lewis acids to organic bases, as well as heterogeneous catalysts.[11] For instance, *p*-toluenesulfonic acid,[11a] trifluoroacetic acid,[11b] formic acid,[11g] as well as an excess amount of sodium hexamethyldisilazane have been described.[11e] Nevertheless, in most cases, the catalysts are too costly or corrosive (or both), the yields could still be improved, and the use of expensive alkyl formates such as ethyl,[11a,11c,11e–11i] *n*-propyl,[11d] and *n*-butyl[11b] is the rule, not the exception. Given that methyl formate is a more cost-effective *N*-formylating agent,[9] the development of eco-efficient strategies for the synthesis of formanilides with it, especially substituted with electron-withdrawing groups, is highly desirable. In this respect, some recent patents described the use of methyl formate for the formylation of aniline derivatives, but examples were limited to substrates bearing electron-donating groups only.[12] Whereas no catalyst was used in these instances, extended reaction times along with huge excess amounts of methyl formate were needed to achieve moderate yields of the products, except under microwave heating.[12a] Strikingly, in another example, 4 days at reflux was required to obtain *p*-tolylformamide in only 56 % yield.[13a] The addition of catalytic amounts (5 mol-%) of strong organic bases such as bicyclic guanidines were shown to give better results at room temperature in reasonable time spans (8–48 h).[13b] Unfortunately, the formylation of *p*-nitroaniline was very difficult (30 % yield), despite the higher temperature and longer reaction time (4 d). Sodium hydride and sodium methoxide were also shown to give acceptable yields with electron-rich substrates.[13c,13d] Reactions with phosphoric acid as well as zinc and ytterbium salts were also devised for the *N*-formylation of aromatic amines under autogenous pressures in good yields, but the use of toxic *N*,*N*-dimethylacetamide as the solvent and the lack of generality

[a] *Eco-Efficient Products & Processes Laboratory (E2P2L), Solvay/CNRS UMI 3464, Solvay Research & Innovation Center Shanghai,*
3966 Jindu Road, Xinzhuang Industrial Zone, Shanghai 201108, P. R. China
E-mail: matthieu.corbet@solvay.com
http://www.e2p2l.com

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600226.

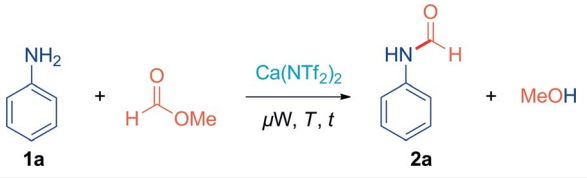
represented clear drawbacks – only diaminotoluene derivatives and aniline were reported as examples.[14]

We sought to develop an eco-efficient *N*-formylation method for anilines of reduced nucleophilicity by using a catalyst based on an inexpensive, nontoxic, and abundant metal. The high affinity of calcium for oxygen coupled with the increasing popularity of related catalysts led us to select calcium triflimide [$Ca(NTf_2)_2$] as a Lewis acid candidate with high potential.[15] In fact, it was only recently that the catalytic ability of calcium-based catalysts was assessed and recognized in a wide range of transformations: they include, but are not limited to, Friedel–Crafts reactions, Luche-type reductions, multicomponent reactions, cyclopropanations, cycloadditions, hydroaminations, and even enantioselective reactions.[15,16] To the best of our knowledge, *N*-formylation reactions with the use of calcium triflimide have not yet been reported, despite the tremendous work of Niggemann and co-workers in the field.[15]

Results and Discussion

We initiated our investigations with aniline (**1a**) as the model substrate (Table 1).

Table 1. Initial screening with aniline (**1a**).[a]

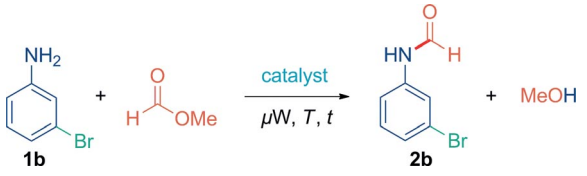


Entry	$Ca(NTf_2)_2$ [mol-%]	HCO_2Me [equiv.]	*T* [°C]	*t* [h]	Conversion [%][b]
1	10	10	115	1	>99
2	10	5	115	1	>99 (49)
3	5	10	115	1	>99
4	3	5	90	2	>99[c] (46)
5	2	10	115	1	93
6	1	10	115	1	79

[a] Reaction conditions: a 0.5–2 mL microwave vial was charged successively with $Ca(NTf_2)_2$ (1–10 mol-%), **1a** (2 mmol), methyl formate (*n* equiv.), and a magnetic stir bar. The vial was then sealed, placed in a microwave reactor, and heated at the set temperature for the noted time. [b] Conversion was determined by ^1H NMR spectroscopy. Conversion of control experiments without catalyst is given in parentheses. [c] Conditions reported in ref.[14]

We found that **1a** (pK_{aH} = 4.6)[17] could be efficiently converted into desired formanilide **2a** with calcium triflimide (5–10 mol-%) as the catalyst and methyl formate (5–10 equiv.) as the formyl source without additional solvent (Table 1, entries 1–4). Surprisingly, the presence of the catalyst was not mandatory to reach about half conversion after 2 h at 90 °C by using microwave heating following the published conditions (Table 1, entry 4).[14,18] Hence, we changed our model substrate to less basic **1b** (pK_{aH} = 3.5) (Table 2). As expected, the absence of calcium triflimide did not allow the reaction to proceed at reasonable rates (Table 2, entries 1–4; numbers in parentheses), but high conversions into 3-bromoanilide (**2b**) were observed if different catalyst loadings and amounts of methyl formate were used (Table 2, entries 1–6).[19] At a lower temperature (e.g. 90 °C), the reaction became rather sluggish (Table 2, entry 7), whereas no product was obtained at 50 °C, even in the presence of the catalyst (Table 2, entry 8). Notably, the amounts of calcium triflimide and methyl formate could be decreased to 5 mol-% and 5 equiv., respectively, without affecting the conversion (Table 2, entry 9). Control experiments with thermal heating (Table 2, entry 10) or the addition of Bu_4NPF_6 (Table 2, entry 11) under otherwise identical reaction conditions did not lead to any improvements,[20] and substituting calcium triflate for calcium triflimide gave poorer results (Table 2, entries 12 and 13).[21] We thus selected the conditions from entry 9 (Table 2) to study the scope and limitations of the reaction.

Table 2. Optimization of the reaction conditions with 3-bromoaniline (**1b**).[a]

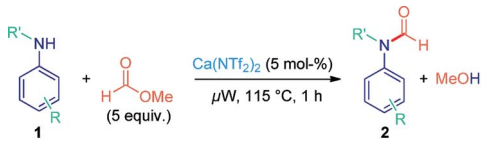


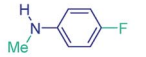
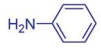
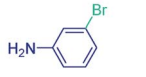
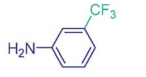
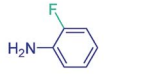
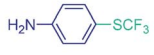
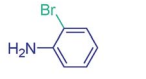
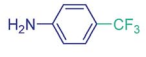
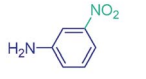
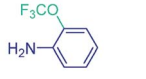
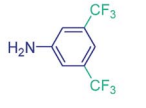
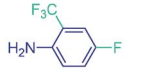
Entry	Catalyst [mol-%]	HCO_2Me [equiv.]	*T* [°C]	*t* [h]	Conversion [%][b]
1	10	10	115	0.5	71 (9)
2	10	10	115	1	>99 (10)
3	10	5	115	1	89 (9)
4	5	10	115	1	87
5	2	10	115	1	44
6	1	10	115	1	33
7	10	10	90	1	33 (9)
8	10	10	50	1	0 (0)
9	5	5	115	1	>99 (9)
10	5	5	115	1	84[c]
11	5	5	115	1	97[d]
12	10	10	115	1	66[e] (10)
13	5	10	115	1	56[e] (10)

[a] Reaction conditions: a 0.5–2 mL microwave vial was charged successively with the catalyst (1–10 mol-%), **1b** (2 mmol), methyl formate (*n* equiv.), and a magnetic stir bar. The vial was then sealed, placed in a microwave reactor, and heated at the set temperature for the noted time. [b] Conversion was determined by ^1H NMR spectroscopy. Conversion of control experiments without catalyst is given in parentheses. [c] Oil bath heating. [d] With Bu_4NPF_6 (5 mol-%). [e] With $Ca(OTf)_2$ as catalyst.

Different substituted anilines were chosen to assess the activity of the calcium salt in this transformation further (Table 3). Anilines endowed with electron-donating groups such as ethoxy and ethyl reacted smoothly (quantitative conversions) to give the desired formanilides in excellent yields (Table 3, entries 1 and 2). Substrates with pK_{aH} values falling between 4.6 and 3.5 were also fully converted into the corresponding products, and excellent yields were obtained (Table 3, entries 4–7). Even secondary aniline **1e** reacted rather efficiently (Table 3, entry 3). Importantly, the reaction of **1b** with methyl formate could be easily scaled up (3 g of starting material) without affecting the reaction rate or yield (Table 3, entry 6). Upon employing weakly basic anilines (pK_{aH} < 3.5), moderate to very good yields were still obtained under identical conditions (Table 3, entries 8–15). The rather low yield obtained for compound **2o** (48 %; Table 3, entry 15) could be explained by the low reactivity of its precursor (i.e., compound **1o**), which is the

Table 3. Scope of the reaction with substituted anilines.[a]

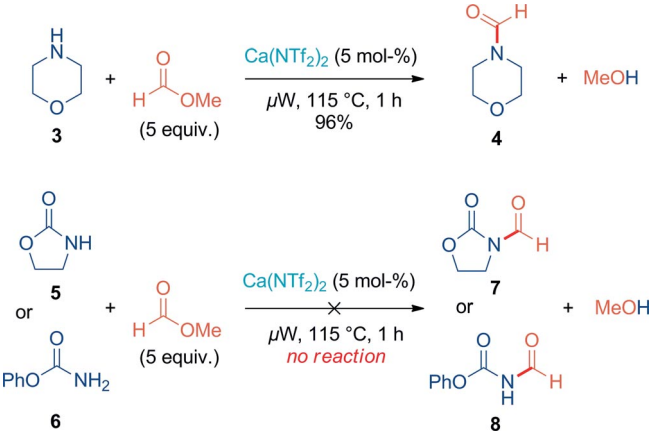


Entry	Substrate		pK_{aH}[b]	Product	Yield [%][c]
1		**1c**	5.3	**2c**	98
2[d]		**1d**	5.1	**2d**	98
3		**1e**	4.8[e]	**2e**	61
4		**1a**	4.6	**2a**	92
5		**1f**	4.5	**2f**	97
6		**1b**	3.5	**2b**	97[f]
7		**1g**	3.5	**2g**	96
8		**1h**	3.0	**2h**	86
9		**1i**	2.8	**2i**	87
10		**1j**	2.6	**2j**	65
11		**1k**	2.6	**2k**	66
12		**1l**	2.5	**2l**	83
13		**1m**	2.4[g]	**2m**	63
14		**1n**	1.8	**2n**	63
15		**1o**	1.8[e]	**2o**	48
16		**1p**	1.0	**2p**	15[h]

[a] Reaction conditions: a 0.5–2 mL microwave vial was charged successively with $Ca(NTf_2)_2$ (5 mol-%), **1a**–**p** (2 mmol), methyl formate (5 equiv.), and a magnetic stir bar. The vial was then sealed, placed in a microwave reactor, and heated at 115 °C for 1 h. [b] Values from ref.[17c] and reduced by one decimal place. [c] Yield of isolated product after purification by flash chromatography. [d] Value from ref.[17d] [e] Simulated value by using MarvinSketch Software. [f] Result on a 14 mmol scale. [g] Value from ref.[17b] [h] 40 % conversion.

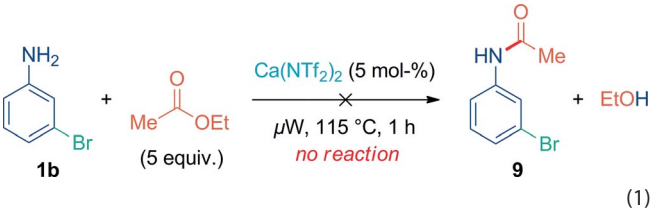
result of both the steric hindrance exerted by the trifluoromethyl group at the *ortho* position and the low nucleophilicity of the nitrogen atom induced by the presence of two electron-withdrawing groups on the aromatic ring. Finally, despite 40 % conversion of **1p**, the low solubility of *p*-nitroformanilide (**2p**) during chromatography only allowed its isolation in 15 % yield (Table 3, entry 16). Overall, the reactivity of anilines **1a**–**p** roughly followed their respective pK_{aH} values: the more basic the aniline, the higher the conversion.

Other N-nucleophiles were also examined (Scheme 1). As anticipated, aliphatic morpholine (**3**) reacted efficiently, even in the absence of a catalyst. However, no reaction was observed with carbamates **5** and **6**.



Scheme 1. Reaction with other N-nucleophiles.

To evaluate the performance of this catalytic system in *N*-acylation reactions, methyl formate was replaced with ethyl acetate. Unfortunately, only the starting material was recovered under the same conditions [Equation (1)].[22]



(1)

Given that it is now well established that some metal triflates and triflimides can be readily hydrolyzed to release triflic acid (HOTf) and triflimidic acid ($HNTf_2$), respectively,[21] we decided to investigate this eventuality under our reaction conditions. Hence, we repeated some experiments with 2 mol-% of triflimidic acid and compared the conversions of anilines **1a**–**o** into corresponding products **2a**–**o** with those obtained previously (Table 4).

We found that the conversions obtained with $HNTf_2$ were in the same range as those reached with calcium triflimide as the catalyst. Furthermore, thermogravimetric analysis of a sample of $Ca(NTf_2)_2$ showed that it was in the form of a tetrahydrate [$Ca(NTf_2)_2 \cdot 4H_2O$, see the Supporting Information], which is consistent with the structure reported by DesMarteau and co-workers.[23] In light of these results, we cannot exclude the involve-

Table 4. Comparison of the activities of $Ca(NTf_2)_2$ (5 mol-%) and $HNTf_2$ (2 mol-%).[a]

Entry	Aniline	Conversion with $Ca(NTf_2)_2$ [%][b]	Conversion with $HNTf_2$ [%][b]
1	**1a**	>99	96
2	**1b**	>99	>99
3	**1b**	>99	80[c] (55)[d]
4	**1c**	>99	>99
5	**1d**	>99	95
6	**1e**	63	43
7	**1f**	>99	97
8	**1g**	>99	89
9	**1h**	90	90
10	**1i**	90	85
11	**1j**	67	57
12	1**k**	70	68
13	**1l**	85	80
14	**1m**	65	65
15	**1n**	70	70
16	**1o**	50	45

[a] Reaction conditions: methyl formate (5 equiv.) was added to a 2 mL microwave vial equipped with a magnetic stir bar and a mixture of **1a**–**o** (2 mmol) and $Ca(NTf_2)_2$ (5 mol-%) or $HNTf_2$ (2 mol-%). The vial was then capped, placed in a microwave reactor, and heated at 115 °C for 1 h. [b] Conversion was determined by ^1H NMR spectroscopy. [c] $HNTf_2$ (1 mol-%). [d] HOTf (1 mol-%).

ment of Brønsted acid catalysis in this reaction if $Ca(NTf_2)_2$ is used alone. Worthy of note, the use of triflic acid (1 mol-%) as the catalyst (Table 4, entry 3; number in parentheses) was less effective than the use of an identical loading of $HNTf_2$, which is reminiscent of the differences in activity observed between calcium triflate and calcium triflimide (Table 2, entries 2 and 12).

Conclusions

In summary, we uncovered that calcium triflimide was an efficient catalyst for the solvent-free microwave-assisted *N*-formylation of different weakly basic anilines by using a noncorrosive and cheap formylating agent. On the other hand, calcium triflate showed lower performance under the same reaction conditions. This was attributed to the superior Lewis acidity of metal triflimides relative to that of their triflates counterparts.[21] Additional control experiments showed that formylations of weakly basic anilines could also be achieved with $HNTf_2$. However, in practice the use of $Ca(NTf_2)_2$ as the catalyst was preferred, as its handling was much easier: no special precautions to exclude air or moisture were required. Although an excess amount of the formylating agent was used in this transformation, no additional (toxic) solvents were required and unreacted methyl formate should be easily recovered together with the methanol formed. The recycling of calcium triflimide is currently the object of further investigations.

Experimental Section

General Procedure for the Synthesis of Formanilides: A 0.5–2 mL microwave vial was charged successively with $Ca(NTf_2)_2$ (60 mg, 0.1 mmol, 5 mol-%), aniline **1a**–**p** (2 mmol), methyl formate (0.6 mL, 10 mmol, 5 equiv.), and a magnetic stir bar. The vial was then sealed, placed in a microwave reactor, and heated at 115 °C for 1 h in high absorption mode. The volatiles were then removed under reduced pressure, and the crude residue was purified by automated flash chromatography on silica gel to give **2a**–**p**.

Keywords: Synthetic methods · Microwave chemistry · Formylation · Anilines · Brønsted acids

[1] For a recent review on the formylation of amines, see: C. J. Gerack, L. McElwee-White, *Molecules* **2014**, *19*, 7689–7713.
[2] P. G. M. Wuts, *Greene's Protective Groups in Organic Synthesis*, 5th ed., Wiley, Hoboken, NJ, **2014**, p. 991–993.
[3] a) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, K. Offermann, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 472–484; *Angew. Chem.* **1965**, *77*, 492–504; b) F. Millich, *Chem. Rev.* **1972**, *72*, 101–113; c) U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339–348; *Angew. Chem.* **1977**, *89*, 351–360; d) F. E. Hahn, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 650–665; *Angew. Chem.* **1993**, *105*, 681–696; e) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; f) L. El Kaim, L. Grimaud, *Tetrahedron* **2009**, *65*, 2153–2171; g) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331; h) A. V. Lygin, A. de Meijere, *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124; *Angew. Chem.* **2010**, *122*, 9280–9311.
[4] a) R. H. Riecheter, R. D. Priester Jr., *Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, Hoboken, NJ, **1993**, vol. 14, p. 902–934; b) C. Six, F. Richter, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, Germany, **2012**, vol. 20, p. 63–82.
[5] a) G. Haflinger, F. K. H. Kuske, *The Chemistry of Amidines and Imidates*, Wiley, Chichester, UK, **1991**; b) J. Barker, M. Kilner, *Coord. Chem. Rev.* **1994**, *133*, 219–300; c) J. Y. Quek, T. P. Davis, A. B. Lowe, *Chem. Soc. Rev.* **2013**, *42*, 7326–7334.
[6] a) V. I. Minkin, G. N. Dorofeenko, *Russ. Chem. Rev.* **1960**, *29*, 599–618; b) G. A. Olah, L. Ohannesian, M. Arvanaghi, *Chem. Rev.* **1987**, *87*, 671–686; c) W. Kantlehner, *Eur. J. Org. Chem.* **2003**, 2530–2546; d) J. Muzart, *Tetrahedron* **2009**, *65*, 8313–8323; e) H.-J. Arpe, *Industrial Organic Chemistry*, 5th ed., Wiley-VCH, Weinheim, Germany, **2010**; f) S. Ding, N. Jiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 9226–9237; *Angew. Chem.* **2012**, *124*, 9360–9371.
[7] a) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 240–248; b) G. B. L. Smith, M. Silver, E. I. Becker, *J. Am. Chem. Soc.* **1948**, *70*, 4254; c) F. F. Blicke, C.-J. Lu, *J. Am. Chem. Soc.* **1952**, *74*, 3933–3934.
[8] Industrially, DMF is synthesized either from dimethylamine and carbon monoxide in methanol with sodium methoxide as the catalyst or directly from dimethylamine and methyl formate without a catalyst. The former one-step process is believed to generate methyl formate in situ, see: a) H. Bipp, H. Kieczka, *Formamides*, in: *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, Germany, **2011**, vol. 16, p. 1–12; b) J. A. Marsella, *Dimethylformamide*, in: *Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, Hoboken, NJ, **2013**, p. 1–9.
[9] Today, most of the worldwide production of formic acid relies on the hydrolysis of methyl formate, see: a) W. Reutemann, H. Kieczka, *Formic Acid*, in: *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, Germany, **2011**, vol. 16, p. 13–33; b) D. J. Drury, *Formic Acid*, in: *Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, Hoboken, NJ, **2013**, p. 1–9.
[10] a) A. Tlili, E. Blondiaux, X. Frogneux, T. Cantat, *Green Chem.* **2015**, *17*, 157–168, and references cited therein; b) L. Zhang, Z. Han, X. Zhao, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2015**, *54*, 6186–6189; *Angew. Chem.* **2015**, *127*, 6284–6287; c) T. V. Q. Nguyen, W.-J. Yoo, S. Kobayashi, *Angew. Chem. Int. Ed.* **2015**, *54*, 9209–9212; *Angew. Chem.* **2015**, *127*, 9341–9344; d) C.-C. Chong, R. Kinjo, *Angew. Chem. Int. Ed.* **2015**, *54*, 12116–12120; *Angew. Chem.* **2015**, *127*, 12284–12288.
[11] a) J. Casanova Jr., N. D. Werner, R. E. Schuster, *J. Org. Chem.* **1966**, *31*, 3473–3482; b) Z. Daszkiewicz, A. Domański, J. B. Kyzioł, *Chem. Pap.* **1993**, *47*, 109–113; c) D. H. R. Barton, S. I. Parekh, M. Tajbakhsh, E. A. Theodorakis, C.-L. Tse, *Tetrahedron* **1994**, *50*, 639–654; d) Y. Ishii, M. Takeno, Y. Kawasaki, A. Muromachi, Y. Nishiyama, S. Sakaguchi, *J. Org. Chem.* **1996**, *61*, 3088–3092; e) J. Wang, M. Rosingana, R. P. Discordia, N. Soundararajan, R. Polniaszek, *Synlett* **2001**, 1485–1487; f) F. Maya, J. M. Tour, *Tetrahe-*

dron **2004**, *60*, 81–92; g) A. H. Lewin, J. Szewczyk, J. W. Wilson, F. I. Carroll, *Tetrahedron* **2005**, *61*, 7144–7152; h) N. Iranpoor, H. Firouzabadi, A. Jamalian, *Tetrahedron Lett.* **2005**, *46*, 7963–7966; i) K. Niknam, D. Saberi, *Tetrahedron Lett.* **2009**, *50*, 5210–5214.

[12] a) R. Ducray, C. D. Jones, F. H. Jung, I. Simpson, AstraZeneca AB, US 2010/0105655, **2010**; b) H. C. Hansen, Resverlogix Corp., WO 2010/079431, **2010**.

[13] a) B. Janza, A. Studer, *Org. Lett.* **2006**, *8*, 1875–1878; b) J. Deutsch, R. Eckelt, A. Köckritz, A. Martin, *Tetrahedron* **2009**, *65*, 10365–10369; c) A. E. Sheshenev, E. V. Boltukhina, K. K. Hii, *Chem. Commun.* **2013**, *49*, 3685–3687; d) M. S. Yalfani, G. Lolli, T. E. Müller, A. Wolf, L. Mleczko, *ChemSusChem* **2015**, *8*, 443–447.

[14] A. Franzke, T. Mattke, J. Leschinski, R. Abdallah, M. Bock, R. Baumann, E. Stroefer, BASF SE, US Patent 8,680,333, **2014**.

[15] a) J.-M. Begouin, M. Niggemann, *Chem. Eur. J.* **2013**, *19*, 8030–8041, and references cited therein; b) T. Haven, G. Kubik, S. Haubenreisser, M. Niggemann, *Angew. Chem. Int. Ed.* **2013**, *52*, 4016–4019; *Angew. Chem.* **2013**, *125*, 4108–4111; c) M. Hut'ka, T. Tsubogo, S. Kobayashi, *Organometallics* **2014**, *33*, 5626–5629; d) C. C. Dulin, K. L. Murphy, K. A. Nolin, *Tetrahedron Lett.* **2014**, *55*, 5280–5282; e) D. Leboeuf, E. Schulz, V. Gandon, *Org. Lett.* **2014**, *16*, 6464–6467; f) L. Fu, M. Niggemann, *Chem. Eur. J.* **2015**, *21*, 6367–6370; g) V. J. Meyer, C. Ascheberg, M. Niggemann, *Chem. Eur. J.* **2015**, *21*, 6371–6374; h) T. Stopka, M. Niggemann, *Org. Lett.* **2015**, *17*, 1437–1440; i) D. Leboeuf, M. Presset, B. Michelet, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Chem. Eur. J.* **2015**, *21*, 11001–11005; j) M. Rauser, S. Schroeder, M. Niggemann, *Chem. Eur. J.* **2015**, *21*, 15929–15933; k) H. Damsen, M. Niggemann, *Eur. J. Org. Chem.* **2015**, 7880–7883.

[16] a) S. Harder, *Chem. Rev.* **2010**, *110*, 3852–3876; b) M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, *49*, 3823–3826; *Angew. Chem.* **2010**, *122*, 3911–3914; c) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* **2011**, *133*, 3339–3341; d) A. Alix, C. Lalli, P. Retailleau, G. Masson, *J. Am. Chem. Soc.* **2012**, *134*, 10389–10392; e) C. Lalli, A. Dumoulin, C. Lebée, F. Drouet, V. Guérineau, D. Touboul, V. Gandon, J. Zhu, G. Masson, *Chem. Eur. J.* **2015**, *21*, 1704–1712.

[17] In this communication, we use the pK_{aH} values of substituted anilines to account for their nucleophilicity, although this is a rough approximation that is often deemed inaccurate, see: a) T. Kanzian, T. A. Nigst, A. Maier, S. Pichl, H. Mayr, *Eur. J. Org. Chem.* **2009**, 6379–6385, and references cited therein. For a compilation of pK_{aH} values of substituted anilines, see: b) W. A. Sheppard, *J. Am. Chem. Soc.* **1963**, *85*, 1314–1318; c) K. C. Gross, P. G. Seybold, Z. Peralta-Inga, J. S. Murray, P. Politzer, *J. Org. Chem.* **2001**, *66*, 6919–6925; d) J. Zabicky, *Analytical Aspects of Aromatic Amines*, in: *Patai's Chemistry of Functional Groups*, Wiley, **2009**, Chichester, UK, p. 5.

[18] Microwave heating was initially chosen for better practicability, as the reactions were heated above the boiling point of methyl formate (32 °C), which thus generated pressures as high as 1.0 MPa (with 10 equiv. of methyl formate).

[19] Control experiments without catalyst were systematically performed to ascertain the effectiveness of the catalyst. During preliminary work, we were indeed surprised to see that the solvent-free formylation of morpholine at 70 °C with formic acid without a catalyst gave better results than if ZnO (50 mol-%) or $ZnCl_2$ (10 mol-%) was used under otherwise identical conditions, see: a) M. Hosseini-Sarvari, H. Sharghi, *J. Org. Chem.* **2006**, *71*, 6652–6654; b) A. C. Shekhar, A. R. Kumar, G. Sathaiah, V. L. Paul, M. Sridhar, P. S. Rao, *Tetrahedron Lett.* **2009**, *50*, 7099–7101.

[20] Most of the time, calcium triflimide is used in combination with a PF_6^- salt to promote the desired reaction. The active catalytic species is then a calcium cation endowed with one triflimide and one hexafluorophosphate anion, see: a) ref.[15]; b) J. Davies, D. Leonori, *Chem. Commun.* **2014**, *50*, 15171–15174.

[21] S. Antoniotti, V. Dalla, E. Duñach, *Angew. Chem. Int. Ed.* **2010**, *49*, 7860–7888; *Angew. Chem.* **2010**, *122*, 8032–8060.

[22] $Yb(OTf)_3$ was reported to catalyze the acylation of some anilines with ethyl acetate, see: W. Su, H. Cai, *J. Chem. Res.* **2004**, 414–415.

[23] L. Xue, D. D. DesMarteau, W. T. Pennington, *Solid State Sci.* **2005**, *7*, 311–318.

Received: February 28, 2016
Published Online: March 21, 2016

