Chemoselective acylation of *N*-acylglutarimides with *N*-acylpyrroles and aryl esters under transition-metal-free conditions

Jie Li,[1,3] Jiaqi Yao,[1,3] Lingfeng Chen,[1] Dong Zou,[3] Patrick J. Walsh,*[,2] Guang Liang*[,1]

ABSTRACT: The imide moiety is a well-known structural motif in bioactive compounds and a useful building block in a variety of processes. Using *N*-acylglutarimides with $MN(SiMe_3)_2$ and either *N*-acylpyrroles or aryl esters, an operationally convenient method to produce a wide array of diaryl- and alkyl arylimides is presented. Symmetric imides are also accessible when *N*-acylglutarimides are employed as acylation reagent under similar reaction conditions. A unique feature of this method stems from the use of two different electrophilic acylating reagents leading to the formation of the unsymmetrical imides with excellent chemoselectivity.

Imides are key structural motifs found extensively in natural products[1] and pharmaceuticals.[2] They are also fundamental building blocks in industrial materials.[3] Traditionally, imides are prepared by two routes: (1) acylation of amides with acyl chlorides, carboxylic esters, and anhydrides (Scheme 1a)[4] and (2) Mumm rearrangement of isoimides (Scheme 1b).[5] Despite the utility of these methods, both have shortcomings. The acylation method usually suffers from limited substrate scope because of the high reactivity of the activated carboxylic acid derivatives. The Mumm rearrangement requires prefunctionalization and often gives moderate yields. Recently, substantial effort has been dedicated to the synthesis of imides and several methods were developed, including: (1) metal catalyzed carbonylation of amides (Scheme 1c);[6] (2) oxidation of amides (Scheme 1d);[7] and (3) oxidative decarboxylation of amino acids (Scheme 1e),[8] among others.[9] It is noteworthy that most of these methods have drawbacks, such as use of prefunctionalized substrates, use of sophisticated reagents, need for excess oxidants, or tedious procedures. Therefore, the development of greener and more straightforward methods for the synthesis of imides from readily available substrates is highly desirable, especially those conducted under additive-, transition metal-, and oxidant-free conditions.

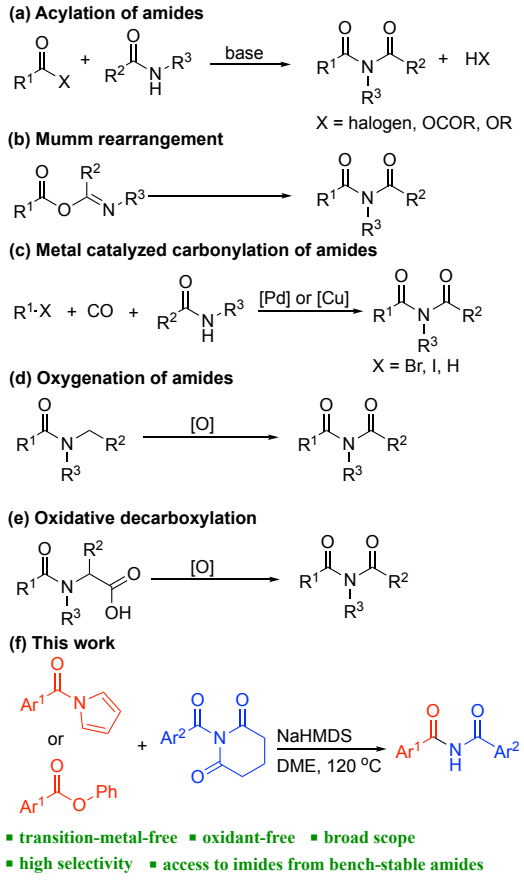
Recently *N*-acylglutarimides, popularized by Szostak's group,[10] have been successfully employed as activated amide acyl transfer reagents through N–C activation. Due to the electronic activation and twisted geometric nature of the amide bond in these species,[11] these bench-stable amides have proven to be excellent electrophilic partners in metal-catalyzed cross-coupling reactions, such as the Suzuki-Miyaura,[12] Heck,[13] Negishi,[14] Hiyama,[15] and Sonogashira reactions.[16] Based on the utility of *N*-acylglutarimides, we aimed to develop a simple and highly efficient transition metal-free method for the synthesis of unsymmetrical imides from *N*-acylglutarimides. The unique aspect of our approach is the *simultaneous use of two acyl electrophiles that leads to exquisite selectivity for unsymmetrical imides*. As outlined in Scheme 1f, *N*-acylglutarimides can be coupled with either *N*-acylpyrroles and O-aryl esters in the presence of silylamide bases to provide high yields of unsymmetrical imides. Interestingly, symmetric imides can be prepared from *N*-acylglutarimides and silyl amide base without additional external electrophilic reagents.

Scheme 1. Methods for the synthesis of imides.

[1] *School of Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang 311399, China*

[2] *Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, USA*

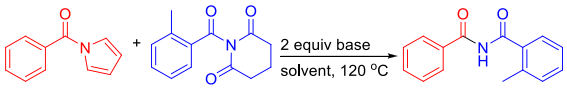
[3] *Department of Pharmacy, School of Medicine, Zhejiang University City College, No. 48, Huzhou Road, Hangzhou 310015, P. R. China*



We began our investigation by using *N*-benzoylpyrrole **1a** and *N*-2-methylbenzoylglutarimide **2a** as model substrates to test various reaction conditions (Table 1). Among the solvents tested [toluene, 1,4-dioxane, CPME (cyclopentyl methyl ether) and DME], DME turned out to be the top hit, providing the product in 80% yield (entries 1–5). Further screening of different bases, including $MN(SiMe_3)_2$ (M = Li, Na, K), MO^tBu (M = Li, Na, K), LDA and ^{n}BuLi indicated that silylamides [$MN(SiMe_3)_2$, M = Li, Na, K], are suitable bases for this transformation (entries 5–7), while other bases such as LiO^tBu, NaO^tBu, and KO^tBu resulted in recovered starting material (entries 8–10). The stronger bases LDA and ^{n}BuLi resulted in decomposition of the starting materials (entries 11–12). The high reaction temperature (120 °C) was also essential for this transformation; only 55% and 30% yield were observed when the temperature was lowered to 100 °C and 80 °C respectively (entries 13–14).

The observation that only silyl amide bases were viable in this reaction supports the notion that it is the nitrogen of the silyl amide base that unites the two acyl groups together in the product.

Table 1. Reaction Optimization[a]



1a 2a 3a

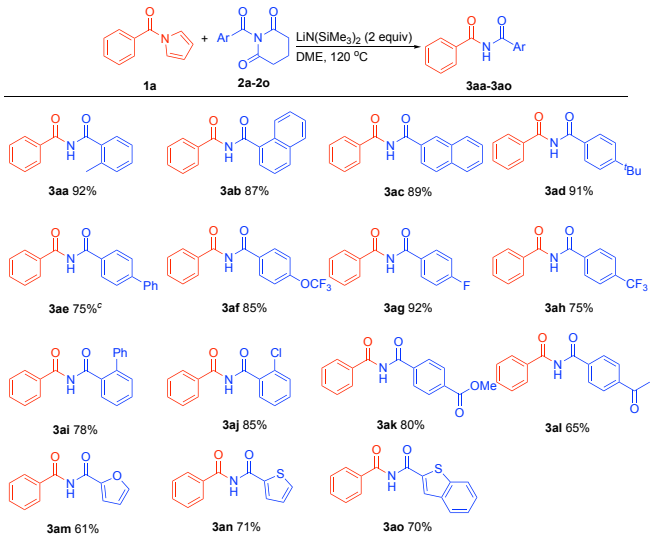
entry	solvent	base	Temp	Yield[b]
1	toluene	$NaN(SiMe_3)_2$	120 °C	75
2	dioxane	$NaN(SiMe_3)_2$	120 °C	trace
3	THF	$NaN(SiMe_3)_2$	120 °C	35
4	CPME	$NaN(SiMe_3)_2$	120 °C	trace
5	DME	$NaN(SiMe_3)_2$	120 °C	80
6	DME	$KN(SiMe_3)_2$	120 °C	40
7	DME	$LiN(SiMe_3)_2$	120 °C	92
8	DME	KO^tBu	120 °C	–
9	DME	NaO^tBu	120 °C	–
10	DME	LiO^tBu	120 °C	–
11	DME	LDA	120 °C	–
12	DME	BuLi	120 °C	–
13	DME	$LiN(SiMe_3)_2$	100 °C	60
14	DME	$LiN(SiMe_3)_2$	80 °C	30

[a]Reactions were conducted with **1a** (0.1 mmol), **2a** (0.1 mmol), base (0.2 mmol), solvent (1 mL), 12 h. [b] Isolated yields.

With the optimized conditions in hand, we examined the substrate scope of the *N*-acylglutarimides components. As presented in Table 2, a wide variety of *N*-acylglutarimides were well-tolerated, giving the desired products in good to excellent yields. Replacing the phenyl moiety with 1-naphthyl or 2-naphthyl groups did not influence the reaction, providing the imide **3ab** and **3ac** in 87% and 89% yield, respectively. Various substituents, including 4-*tert*-butyl and 4-Ph groups (**3ad** and **3ae**, 91 and 75%) and electron-withdrawing and electronegative groups, including 4-OCF_3, 4-F, and 4-CF_3 (**3af**, **3ag**, **3ah**) were well-tolerated in this transformation (75–92%).

In addition, this protocol worked well with sterically hindered *N*-acylglutarimides substrates bearing 2-Ph or 2-Cl, affording products **3ai** and **3aj** in 78–85% yield . Substrates containing ester and acetyl moieties, which may be sensitive to silylamide bases, were also tolerated in this reaction, providing the corresponding products in 80% (**3ak**) and 65% (**3al**) yields. Notably, this acylation reaction proceeded smoothly with various *N*-acylglutarimides bearing heteroaromatic rings, such as furan (**3am**), thiophene (**3an**), and benzothiophene (**3ao**).

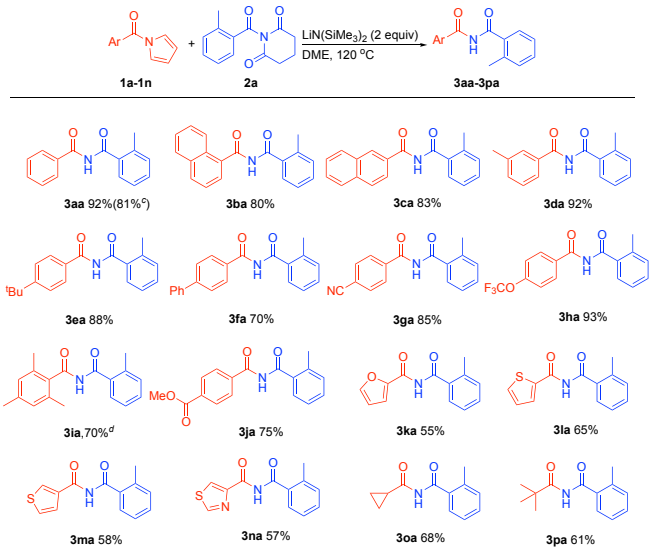
Table 2. Scope of *N*-acylglutarimides [a,b]



[a]Reaction conditions: *N*-acylglutarimides (0.1 mmol), **1a** (0.1 mmol), $LiN(SiMe_3)_2$ (1.0 mol/L in THF, 0.2 mL, 0.2 mmol), DME (0.1 M), 120 °C, 12 h. [b]Isolated yield. [c]2 Equiv of $NaN(SiMe_3)_2$.

The scope of *N*-acylpyrroles was next explored with *N*-2-methylbenzoylglutarimide **2a** (Table 3). *N*-1-Naphthyl- and *N*-2-naphthylpyrrole furnished **3ba** and **3ca** in 80% and 83% yield, respectively. Electronically neutral aryl *N*-acylpyrroles bearing 3-Me, 4-*tert*-Bu, or 4-Ph (**3da**, **3ea**, **3fa,** 70–92% yield) or electron withdrawing 4-OCF_3 or 4-CN (**3ga**, **3ha**) provided products in 58 and 93% yields, respectively. A sterically hindered *N*-acylpyrrole derived from mesitylene furnished product **3ia** in 70% yields when $KN(SiMe_3)_2$ was used as the base. An aryl *N*-acylpyrrole bearing a methyl ester reacted under the standard conditions to provide the imide product **3ja** in 75% yield. Heteroaryl-containing *N*-acylpyrroles were also found to be suitable substrates, giving the desired products (**3ka**, **3la**, **3ma**, **3na**) in 55–65% yields. Furthermore, it is important to note that aliphatic substrates bearing cyclopropyl (**1o**) and *tert*-butyl (**1p**) groups were both suitable, affording the desired imides **3na** and **3oa** in 68 and 61% yield, respectively. To test the scalability of our method, 4 mmol of *N*-benzoylpyrrole (**1a**) was reacted with *N*-2-methylbenzoylglutarimide (**2a**) and the aroylation product **3aa** was isolated in 81% yield.

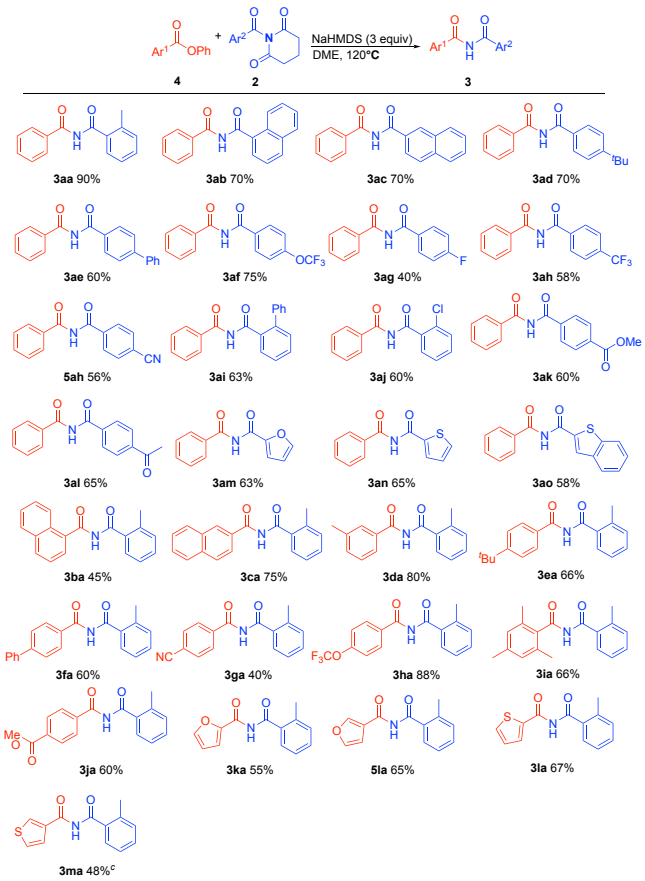
Table 3. Scope of *N*-acylpyrroles [a,b]



[a]Reaction conditions: *N*-acylpyrroles (0.1 mmol), **2a** (0.1 mmol), $LiN(SiMe_3)_2$ (1.0 mol/L in THF, 0.2 mL, 0.2 mmol), DME (0.1 M), 120 °C, 12 h. [b]Isolated yield. [c]Reaction conducted on 4 mmol scale. [d]2 Equiv of $KN(SiMe_3)_2$.

To expand on the acylation method above, we examined the acylation with aryl benzoates in place of the aryl *N*-acyl pyrroles. We were pleased to find that the acylation could be extended to phenyl benzoate with very high chemoselectivity (Table 4). The main change in reaction conditions was swapping $NaN(SiMe_3)_2$ for $LiN(SiMe_3)_2$, which led to higher yields. Most of the *N*-acylglutarimides used with phenyl *N*-acylpyrrole in Table 2 were also successful with phenyl benzoate in Table 4 (40–90% yield, 16 examples). In comparison with the results using phenyl *N*-acylpyrrole (Table 2), the yields were slightly diminished with phenyl benzoate. When substrates with different substituents on the benzoate aryl were employed with the parent phenyl *N*-acylglutarimide, similar results were obtained (Table 4, 40–88% yield, 14 examples). These yields were slightly lower than those observed with *N*-acylpyrroles in Table 3.

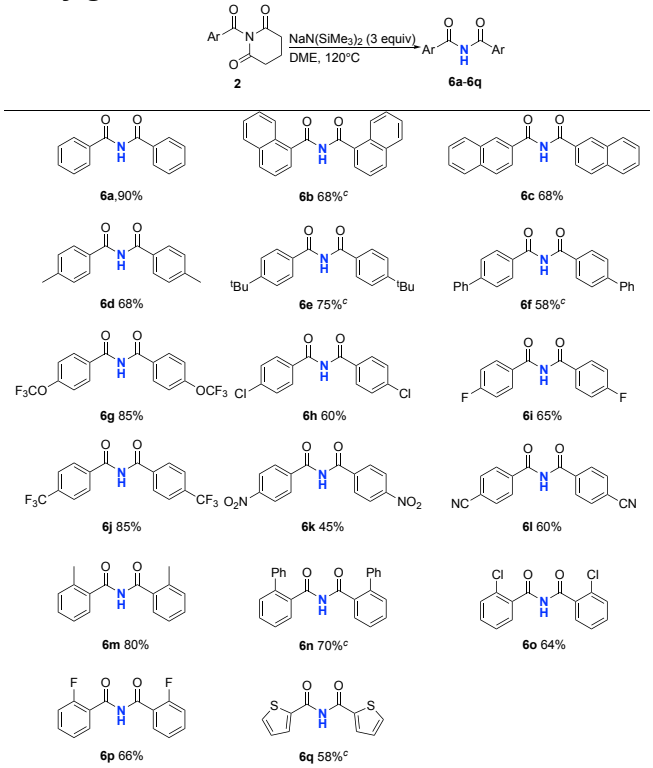
Table 4. Acylation with *N*-acylglutarimides and phenyl benzoate derivatives[a,b]



[a]Reaction conditions: **2** (0.1 mmol), **4** (0.1 mmol), $NaN(SiMe_3)_2$ (2.0 mol/L in THF, 0.15 mL, 0.3 mmol), DME (0.1 M), 120 °C, 12 h. [b]Isolated yield. [c]3 Equiv of $LiN(SiMe_3)_2$.

Given the utility of the *N*-acylglutarimides in these imide syntheses, we were curious if the *N*-acylglutarimides could be used as both acyl components of the coupling process. This would lead to symmetric diimides. In the event, we were please to find that symmetric imides could be obtained under similar reaction conditions. In these reactions, $NaN(SiMe_3)_2$ proved to be the better base. Examination of the scope indicated that a range of *N*-acylglutarimides are suitable for this self-coupling protocol (Table 5). Aryl *N*-acylglutarimides possessing extended aryl groups such as 1-naphthyl and 2- naphthyl were well-accommodated, giving **6a** and **6b** in 68% yield. Moreover, aryl *N*-acylglutarimides bearing alkyl or Ph substituents on the aryl provided products **6d**, **6e** and **6f** in 58–75% yield. When the aryl group contained electron-withdrawing or electronegative groups at the 4-position imides **6g–6l** could be isolated in 45–85%. Furthermore, *N*-acylglutarimides with 2-substituted aryl groups bearing Ph, Me, Cl or F provided the expected products in 64–80% yield (**6m**, **6n**, **6o**, **6p**). Substrates with strongly electron-donating substituents on the aryl were not viable. For example, the 4-methoxy derivative did not react, leaving recovered starting material. A substrate bearing a hydroxyl group failed to furnish the desired product and led to decomposition. The incompatibility of these substrates may result from the reduced electrophilicity of the carbonyl group. The heterocyclic substrate thienylglutarimide was tolerated in this transformation, providing the product **6q** in 58% yield.

Table 5. Synthesis of symmetrical imides from *N*-acylglutarimides[a,b]

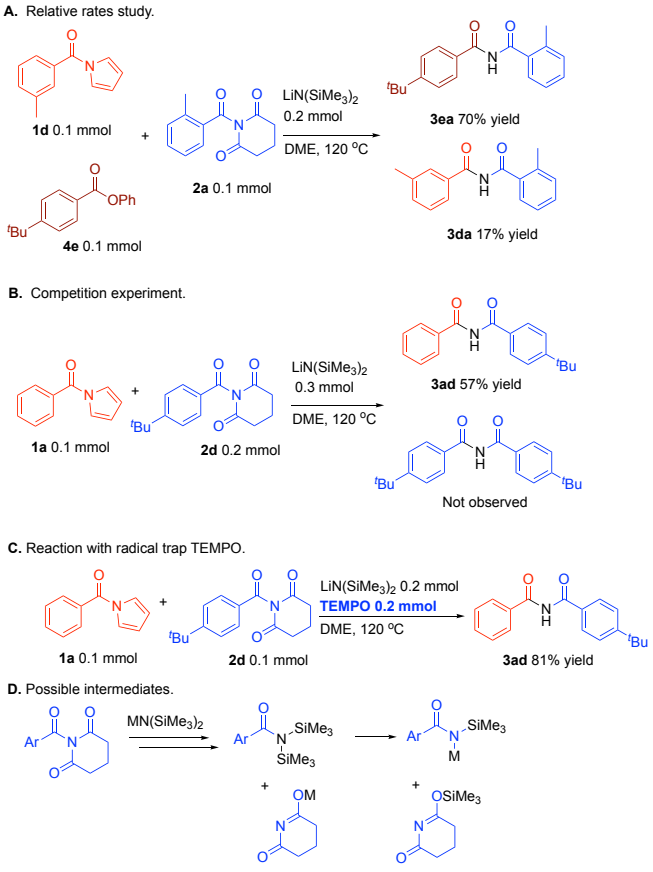


[a]Reaction conditions: **2** (0.1 mmol), $NaN(SiMe_3)_2$ (0.3 mmol), DME (0.1 M), 120 °C, 12 h. [b]Isolated yield. [c]3 Equiv of $LiN(SiMe_3)_2$.

To probe the reaction mechanism and relative rates of reactions of the different acyl electrophiles, several control experiments were performed. We conducted a competitive reaction between 3-methylbenzoylpyrrole (**1d**) and 4-*tert*-butylphenyl benzoate (**4e**) with *N*-2-methylbenzoylglutarimide (**2a**) under the optimized conditions with $LiN(SiMe_3)_2$. As shown in Scheme 2A, the *N*-2-methylbenzoylglutarimide 2-tolyl group was found in all the products, suggesting that the *N*-acylglutarimide reacts first with the base. The benzoyl group from the phenyl benzoate was found in 70% of the product (based on the theoretical yield). The unsymmetrical product derived from the *N*-acylpyrrole was found in 17% (based on the theoretical yield). These observations suggest that the phenyl benzoate is more reactive than the *N*-acylpyrrole in reacting with the intermediate formed from the *N*-acylglutarimide. When 2 equiv 4-*tert*-butylbenzoylglutarimide was reacted with *N*-acylpyrrole **1a**, only the unsymmetrical product was obtained (Scheme 2B). This result suggest that the intermediate formed from reaction of the base with

the *N*-acylglutarimide reacts faster with the *N*-acylpyrrole than with the second equivalent of *N*-acylglutarimide. These observations are consistent with the results presented in Tables 2–4, in which there is no symmetric imide products observed. Finally, we found the radical scavenger TEMPO did not negatively affect the reaction between *N*-acylglutarimide and *N*-acylpyrrole, which gave the unsymmetrical imide product in 81% yield (Scheme 2C). This result is consistent with the reaction proceeding by a 2-electron pathway. We speculate that the intermediate formed on reaction of the silyl amide bases with the *N*-acylglutarimide is the anion ArC(=O)NM($SiMe_3$) (M = Li or Na), derived from attack of M$N(SiMe_3)_2$ on the *N*-acylglutarimide carbonyl to expel glutarimide and give ArC(=O)N($SiMe_3$)$_2$ (Scheme 2D). This is followed by removal of one of the *N*-$SiMe_3$ groups, possibly by the deprotonated glutarimide.

Scheme 2. Control experiments



In conclusion, we have advanced a general, efficient, and highly chemoselective method for acylation of *N*-acylglutarimides with amides, esters, or even *N*-acylglutarimides themselves. The broad scope and high functional group compatibility of the results outlined herein make this method an attractive alternative to classical acylation chemistry. This work avoids the use of expensive transition metals and it is operationally simple. Mechanistic studies to understand how the base promotes the reaction are currently underway. We presently favor a mechanism wherein the silylamide is the nitrogen donor that serves to link the two acyl units, with preliminary attack on the *N*-acylglutarimide.

Conflicts of interest

There are no conflicts to declare

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Notes and references

1.(a) L. Raj, T. Ide, A. U. Gurkar, M. Foley, M. Schenone, X. Li, N. J. Tolliday, T. R. Golub, S. A. Carr, A. F. Shamji, A. M. Stern, A. Mandinova, S. L. Schreiber and S. W. Lee, Selective killing of cancer cells by a small molecule targeting the stress response to ROS, *Nature*, 2011, **475**, 231-234; (b) H. B. Maruyama, Y. Suhara, J. Suzuki-Watanabe, Y. Maeshima, N. Shimizu, M. Ogura-Hamada, H. Fujimoto and K. Takano, A new antibiotic, fumaramidmycin*I, production, biological properties and characterization of producer strain, *J. Antibiot.*, 1975, **28**, 636-647; (c) M. Prudhomme, Rebeccamycin analogues as anti-cancer agents, *Eur. J. Med. Chem.*, 2003, **38**, 123-140.

2.(a) Y. Takeuchi, T. Shiragami, K. Kimura, E. Suzuki and N. Shibata, (*R*)- and (*S*)-3-Fluorothalidomides: isosteric analogues of thalidomide, *Org. Lett.*, 1999, **10**, 1571-1573; (b) D. M. Robinson, M. P. Curran and K. A. Lyseng-Williamson, A review of its use in essential hypertension, type 1 diabetic nephropathy and chronic heart failure, *Drugs*, 2007, **67**, 1359-1378; (c) T. Ishiyama, K. Tokuda, T. Ishibashi, A. Ito, S. Toma and Y. Ohno, Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test, *Eur. J. Pharmacol.*, 2007, **572**, 160-170.

3.(a) J. Lawrence, A. B. Patel and J. G. Brisson, The thermal conductivity of Kapton HN between 0.5 and 5 K, *Cryogenics*, 2000, **40**, 203-207; (b) E. S. Kim, K. Y. Park, J. M. Heo, B. J. Kim, K. D. Ahn and J. G. Lee, Effect of reactive distillation on the yield of tetraacetylethylenediamine (TAED), *Ind. Eng. Chem. Res.*, 2010, **49**, 11250–11253.

4.(a) A. Giovannini, D. Savoia and A. Umani-Ronchi, Organometallic ring-opening reactions of JV-acyl and JV-alkoxycarbonyl lactams. Synthesis of cyclic imines, *J. Org. Chem.*, 1989, **54**, 228-233; (b) D. Savoia, V. Concialini, S. Roffia and L. Tarsi, Organometallic reactions of -heterosubstituted JV-acyl lactams. A new route to 7-keto aldehydes from 5-rthoxy-2-pyrrolidinone, *J. Org. Chem.*, 1991, **56**, 1822-1827; (c) M. B. Andrus, W. Li and R. F. Keyes, Synthesis of mixed acyclic imides using pentafluorophenyl esters, *Tetrahedron Lett.*, 1998, **39**, 5465-5468.

5.(a) O. Mumm, H. Hesse and H. Volquartz, Otto mumm, hugo heese und hans volquarta: zur kenntnis der diacylamide, *Chem. Ber.*, 1915, **48**, 379-391; (b) J. S. P. Schwarz, Preparation of acyclic isoimides and their rearrangement rates to imides, *J. Org. Chem.*, 1972, **37**, 2906-2908; (c) K. Brady and A. F. Hegarty, The isoimide-imide rearrangement, *J. Chem. Soc., Perkin Trans. 2*, 1980, 121-126.

6.(a) A. Schnyder and A. F. Indolese, Synthesis of unsymmetrical aroyl acyl imides by aminocarbonylation of aryl bromides, *J. Org. Chem.*, 2002, **67**, 594-597; (b) L. Ran, Z. H. Ren, Y. Y. Wang and Z. H. Guan, Palladium-catalyzed aminocarbonylation of aryl iodides with amides and N-alkyl anilines, *Chem. Asian J.*, 2014, **9**, 577-583; (c) H. Li, K. Dong, H. Neumann and M. Beller, Palladium-catalyzed hydroamidocarbonylation of olefins to imides, *Angew. Chem., Int. Ed.*, 2015, **54**, 10239-10243; (d) Y. Li, K. Dong, F. Zhu, Z. Wang and X. F. Wu, Copper-catalyzed carbonylative coupling of cycloalkanes and amides, *Angew. Chem., Int. Ed.*, 2016, **55**, 7227-7230.

7.(a) L. Xu, S. Zhang and M. L. Trudell, Novel chromium(VI) catalyzed oxidation of *N*-alkylamides to imides with periodic acid, *Chem. Comm.*, 2004, 1668-1669; (b) K. C. Nicolaou and C. J. Mathison, Synthesis of imides, *N*-acyl vinylogous carbamates and ureas, and nitriles by oxidation of amides and amines with Dess-Martin periodinane, *Angew. Chem., Int. Ed.*, 2005, **44**, 5992-5997; (c) J. Sperry, The oxidation of amides to imides: a powerful synthetic transformation, *Synthesis*, 2011, **2011**, 3569-3580; (d) H. Yu, Y. Chen and Y. Zhang, TBHP/TEMPO-mediated oxidative synthesis of imides from amides, *Chin. J. Chem.*, 2015, **33**, 531-534.

8.(a) A. Itoh, T. Kodama, S. Inagaki and Y. Masaki, New synthetic method of imides through oxidative photodecarboxylation reaction of *N*-Protected α-amino acids with FSM-16, *Chem. Lett.*, 2000, **29**, 542-543; (b) A. Itoh, T. Kodama, Y. Masaki and S. Inagaki, Oxidative photo-decarboxylation in the presence of mesoporous silicas, *Chem. Pharm. Bull.*, 2006, **54**, 1571-1575; (c) W. Huang, M. Wang and H. Yue, Conversion of *N*-Acyl amino acids into imides via oxidative decarboxylation induced by $Ag+/Cu^{2+}/S_2O_8^{2-}$ in Water, *Synthesis*, 2008, **2008**, 1342-1344.

9.(a) D. A. Evans, P. Nagorny and R. Xu, Cericammonium nitrate promoted oxidation of oxazoles, *Org. Lett.*, 2006, **8**, 5669-5671; (b) L. Wang, H. Fu, Y. Jiang and Y. Zhao, Highly efficient copper-catalyzed amidation of aldehydes by C-H activation, *Chem. Eur. J.*, 2008, **14**, 10722-10726; (c) F. Wang, H. Liu, H. Fu, Y. Jiang and Y. Zhao, Highly efficient iron(II) chloride/*N*-Bromosuccinimide-mediated synthesis of imides and acylsulfonamides, *Adv. Synth. Catal.*, 2009, **351**, 246-252; (d) J. Wang, C. Liu, J. Yuan and A. Lei, Fe-Catalysed oxidative C-H/N-H coupling between aldehydes and simple amides, *Chem. Commun.*, 2014, **50**, 4736-4739; (e) H. Yu and Y. Zhang, Copper-catalyzed synthesis of imides from aldehydes or alcohols and amine hydrochloride salts, *Eur. J. Org. Chem.*, 2015, 1824–1828; (f) C. S. Digwal, U. Yadav, P. V. S. Ramya, S. Sana, B. Swain and A. Kamal, Vanadium-catalyzed oxidative C(CO)-C(CO) bond cleavage for C-N bond formation: one-pot domino transformation of 1,2-diketones and amidines into imides and amides, *J. Org. Chem.*, 2017, **82**, 7332-7345; (g) K. Kataoka, K. Wachi, X. Jin, K. Suzuki, Y. Sasano, Y. Iwabuchi, J. Y. Hasegawa, N. Mizuno and K. Yamaguchi, CuCl/TMEDA/nor-AZADO-catalyzed aerobic oxidative acylation of amides with alcohols to produce imides, *Chem. Sci.*, 2018, **9**, 4756-4768; (h) A. O. Galvez, C. P. Schaack, H. Noda and J. W. Bode, Chemoselective acylation of primary amines and amides with potassium acyltrifluoroborates under acidic conditions, *J. Am. Chem. Soc.*, 2017, **139**, 1826-1829; (i) X. Zhang, T. Cui, X. Zhao, P. Liu and P. Sun, Electrochemical difunctionalization of alkenes by a four-component reaction cascade Mumm rearrangement: rapid access to functionalized imides, *Angew. Chem., Int. Ed.*, 2020, **59**, 3465-3469.

10.(a) G. Meng and M. Szostak, Sterically controlled Pd-catalyzed chemoselective ketone synthesis via N-C cleavage in twisted amides, *Org. Lett.*, 2015, **17**, 4364-4367; (b) G. Meng and M. Szostak, Palladium-catalyzed Suzuki-Miyaura coupling of amides by carbon-nitrogen cleavage: general strategy for amide N-C bond activation, *Org. Biomol. Chem.*, 2016, **14**, 5690-5707.

11.(a) V. Pace, W. Holzer, G. Meng, S. Shi, R. Lalancette, R. Szostak and M. Szostak, Structures of highly twisted amides relevant to amide N-C cross-coupling: evidence for ground-state amide destabilization, *Chem. Eur. J.*, 2016, **22**, 14494-14498; (b) R. Szostak, S. Shi, G. Meng, R. Lalancette and M. Szostak, Ground-state distortion in *N*-acyl-tert-butyl-carbamates (Boc) and *N*-acyl-tosylamides (Ts): twisted amides of relevance to amide N-C cross-coupling, *J. Org. Chem.*, 2016, **81**, 8091-8094; (c) S. Shi, G. Meng and M. Szostak, Synthesis of biaryls through Nickel-catalyzed Suzuki–Miyaura coupling of amides by carbon–nitrogen bond cleavage, *Angew. Chem., Int. Ed.*, 2016, **55**, 6959 –6963.

12.(a) C. L. Ji and X. Hong, Factors controlling the reactivity and chemoselectivity of resonance destabilized amides in Ni-catalyzed decarbonylative and nondecarbonylative Suzuki-Miyaura coupling, *J. Am. Chem. Soc.*, 2017, **139**, 15522-15529; (b) P. Lei,

G. Meng and M. Szostak, General method for the Suzuki–Miyaura cross-coupling of amides using commercially available, air- and moisture-stable Palladium/NHC (NHC = N-Heterocyclic carbene) complexes, *ACS Catal.*, 2017, **7**, 1960-1965; (c) Y. Osumi, C. Liu and M. Szostak, *N*-Acylsuccinimides: twist-controlled, acyl-transfer reagents in Suzuki-Miyaura cross-coupling by N-C amide bond activation, *Org. Biomol. Chem.*, 2017, **15**, 8867-8871; (d) P. Lei, G. Meng, Y. Ling, J. An and M. Szostak, Pd-PEPPSI: Pd-NHC Precatalyst for Suzuki-Miyaura cross-coupling reactions of amides, *J. Org. Chem.*, 2017, **82**, 6638-6646.

13. G. Meng and M. Szostak, General olefin synthesis by the Palladium-catalyzed Heck reaction of amides: sterically controlled chemoselective N-C activation, *Angew. Chem., Int. Ed.*, 2015, **54**, 14518-14522.
14. M. Szostak and S. Shi, Nickel-catalyzed Negishi cross-coupling of *N*-acylsuccinimides: stable, amide-based, twist-controlled acyl-transfer reagents via N–C activation, *Synthesis*, 2017, **49**, 3602-3608.
15. M. A. Idris and S. Lee, Palladium-catalyzed amide N-C Hiyama cross-coupling: synthesis of ketones, *Org. Lett.*, 2020, **22**, 9190-9195.
16. W. Srimontree, A. Chatupheeraphat, H. H. Liao and M. Rueping, Amide to alkyne interconversion via a Nickel/Copper-catalyzed deamidative cross-coupling of aryl and alkenyl amides, *Org. Lett.*, 2017, **19**, 3091-3094.