Direct alkylation of \(N, N\)-dialkyl benzamides with methyl sulfides under transition metal-free conditions

Can-Can Bao\(^1\), Hui-Zhen Du\(^1\), Yan-Long Luo\(^1\) & Bing-Tao Guan\(^2\)

Amides are a fundamental and widespread functional group, and are usually considered as poor electrophiles owing to resonance stabilization of the amide bond. Various approaches have been developed to address challenges in amide transformations. Nonetheless, most methods use activated amides, organometallic reagents or transition metal catalysts. Here, we report the direct alkylation of \(N, N\)-dialkyl benzamides with methyl sulfides promoted by the readily available base LDA (lithium diisopropylamide). This approach successfully achieves an efficient and selective synthesis of \(\alpha\)-sulfenylated ketones without using transition-metal catalysts or organometallic reagents. Preliminary mechanism studies reveal that the deprotonative arylation of methyl sulfides is promoted by the directed ortho-lithiation of the tertiary benzamide with LDA.
Amide as one of the most fundamental structural units exists widely and performs significantly in various proteins, natural products, pharmaceuticals, and synthetic materials. The stability and planarity of the amide group originating from the resonance stability guarantees for their particular functions. Yet simultaneously, the decreased electrophilicity of the carbonyl group and the enhanced C–N bond energy become the main obstacle for the transformations of the inert amide group. The strongly nucleophilic organolithium and organomagnesium reagents could undergo the direct nucleophilic acyl substitution reaction with some amides. However, the reactions must be carried out under harsh conditions with a precise amount of the organometallic reagent to prevent the possible side reactions, for instance, reduction, deprotonation, and over addition reactions. Therefore, the selective ketone synthesis from amides under mild conditions here comes as another great challenge. Thus, various activated amides have been particularly designed for the nucleophilic acyl substitution reactions. As early as 1981, Weinreb reported a clean and effective acylation of organolithium and organomagnesium reagents by using N-methoxy-N-methyl amides. Moreover, N-Boc amides have also been developed as the direct acylating reagents for the strong nucleophilic organometallic ketone synthesis. Very recently, a fast and general ketone synthesis from amides and organolithium compounds was achieved by the stabilization of tetrahedral intermediate in CPME solution. In 2015, Garg and co-workers reported the nickel-catalyzed carboxylation of amides, making a great breakthrough in amide transformations. Soon later, Zou, Szostak, Garg, and Huang further reported the cross-coupling reactions of amides with organoboron or organozinc reagents by using palladium or hydrosilanes by a yttrium metallocene catalyst. We earlier found that some relatively weak base catalysts could not undergo the complete deprotonation of a weakly acidic C–H bond but form a deprotonative equilibrium. Thanks to the deprotonative equilibrium, the in-situ formed carbanion intermediate was reactive but in a low concentration, helping to avoid side reactions and achieving the reaction selectively. In particular, we recently

![Fig. 1 Amides transformations.](image-url)
discovered the benzylic arylation of toluene with tertiary benzoamides promoted by directed ortho-lithiation of benzamides with LDA. Here we show that N, N-dialkyl benzamides can be directly alkylated with methyl sulfides using LDA as the base.

**Results and discussion**

**Reaction discovery.** We first conducted our attempt in the reaction between N, N-diisopropyl benzamide, and thioanisole with several bases (1.2 equiv.) in THF at 60 °C (Table 1). Alkali bis(trimethylsilyl)amides failed to start the nucleophilic acyl substitution reaction (entries 1 and 2). LDA and LiTMP, as expected, smoothly drove on the reaction and selectively afforded the desired substituted product α-(phenylthio)acetophenone (3aa) in good yields (entries 3 and 4). It is worth noting that LDA and LiTMP generally could not deprotonate thioanisole for their relatively weak basicity. However, the direct deprotonative benzoylation of thioanisole was simply achieved with these bases. Strong basic n-BuLi and TMSCH2Li in the reaction completely consumed the amide but gave the ketone products in low yields of 21 and 58% (entries 5 and 6). The direct substitution reaction between benzamide and butyl lithium took place to give butyl phenyl ketone (30% yield) and 5-phenylnonan-5-ol (14% yield) as by-products (entry 5). These results suggested that the strongly basic but slim butyl lithium worked not only as a base but also as a nucleophile, leading to side reactions. LDA, a readily available base, displayed less nucleophilicity and thus behaved better than the strong bases. We found the reaction to be a stoichiometric reaction (see Supplementary Table 1 in Supplementary Methods) and finally revealed the optimized conditions: lower loading of thioanisole (1.4 equiv.) and LDA (1.1 equiv.) and lower temperature (40 °C, entry 7; for more condition screening, see Table 1.

### Table 1 Alkylation of N, N-diisopropylbenzamide with Thioanisolea.

| entry | base      | x   | 1a Conv. (%)b | 3aa yield (%)b |
|-------|-----------|-----|---------------|----------------|
| 1     | LiHMDS    | 1.2 | <5            | <5             |
| 2     | KHMDS     | 1.2 | <5            | <5             |
| 3     | LiTMP     | 1.2 | >95           | 76             |
| 4     | LDA       | 1.2 | >95           | 94             |
| 5     | n-BuLiC   | 1.2 | >95           | 21             |
| 6     | LiCH2TMS  | 1.2 | >95           | 58             |
| 7e    | LDA       | 1.1 | >95           | 98 (93)        |

*Reaction Conditions: benzamide 1a (0.5 mmol), thioanisole 2a (1.0 mmol), base, THF (1.0 mL), 60 °C, 24 h. HMDS: bis(trimethylsilyl)amide; LDA: lithium diisopropylamide; LiTMP: lithium 2,2,6,6-tetramethylpiperidide. bNMR yields and conversions with 2-methyloxynaphthalene as an internal standard, isolated yield in parenthesis. c1.6 M in hexane. dButyl phenyl ketone (30% yield) and 5-phenylnonan-5-ol (14% yield) were obtained as by-products. eLDA (0.55 mmol), 2a (0.7 mmol), 40 °C.

**Fig. 2 Scope of Methyl Sulfinides.** Conditions: for thioanisoles, benzamide 1a (0.5 mmol), 2 (0.7 mmol), LDA (0.55 mmol), THF (1 mL), 40 °C, 24 h; for alkyl methyl sulfoxides, benzamide 1a (0.5 mmol), 4 (1.25 mmol), LDA (0.75 mmol), THF (1 mL), 40 °C, 24 h. Di-benzoylation product 3ana was obtained as by-product (26% yield). Benzamide 1a (0.9 mmol), 1,4-bis(methylthio)benzene 2n (0.3 mmol), LDA (0.66 mmol), yield based on 2n.  e60 °C.
Supplementary Table 2 and 3). Several other tertiary benzamides were also tested in this reaction. The steric bulky \( \text{N, N-dicyclohexyl benzamide} \) smoothly underwent the reaction and afforded a comparable yield of 95%, while the less steric benzamides afforded lower yields (for additional substrates, see Supplementary Table 4). In addition, a high yield of 92% for the gram-scale reaction positively demonstrated the reliability of this protocol (1.1 g, see 4.3 in Supplementary Information).

With this optimized condition in hand, we carried the reactions between \( \text{N, N-diisopropyl benzamide} \) and various aryl methyl sulfides (Fig. 2). 4-Ethylthio thioanisole smoothly underwent the reaction with benzamide and afforded the methyl benzoylation product in a high yield of 96% (3ab), but leaving the methylene group intact. It is worth noting that the reaction displayed excellent selectivity of the thiomethyl group over the thiomethylene group and the ortho phenyl C–H bond. 4-N, N-Dimethyl thioanisole, 4-isopropoxyl thioanisole, and methoxy thioanisoles were allowed to react with benzamide and the benzoylation products were obtained in good to high yields (3ac–ag). The slightly lower yield of 2-methoxythioanisole relative to its 4-methoxy and 3-methoxy isomers suggested that the coordination or steric repulsion from the 2-methoxyl group made the thioanisole a bit sluggish in the substitution reaction. Phenyl, alkenyl, alkyl-substituted thioanisoles, and methyl naphthyl sulfides are also suitable substrates to give the substitution products in good to high yields (3ah–am). For 1,4-bis(methylthio)benzene, we could control the ratio of the reactants to selectively get the mono-benzoylation product (3an) and the di-benzoylation product (3ana). Some methyl sulfides bearing heteroaromatic rings were subjected in the reaction with benzamide but failed to give the desired products (see Supplementary Table 4). It was possible that the strong coordinating groups would inhibit the deprotonation and substitution reaction.

To explore the generality of this reaction, we further carried out the reactions of isopropyl methyl sulfide and got the expected benzamide substitution product 5aa in a high yield of 85% under a slightly enhanced condition (2.5 equiv. of sulfide and 1.5 equiv. of LDA; for detail condition screening, see Supplementary Table 5). We then explored the nucleophilic acyl substitution reactions of benzamide with a series of alkyl methyl sulfides under this condition (Fig. 2). The reaction displays excellent selectivity on the methyl group over the methylene and methine groups. Interestingly, we found that the methyl sulfides bearing isopropyl, tert-butyl, cyclohexyl, and cycloheptyl groups gave better yields than the ones with other alkyl groups (5aa–ad vs. 5ae–al). It seems that the steric hindrance from the other side of the sulfide could increase its reactivity. Trimethylsilyl, tertiary amine, ether, and silyl ether groups were well tolerated in the reaction, giving the corresponding \( \alpha \)-sulfenylated ketones in moderate to good yields (5am–ap).

We further investigated the scope of substituted benzamides with either thioanisole or isopropyl methyl sulfide (Fig. 3). 4-Tert-butyl benzamide, 4-isopropyl benzamide, and 4-cyclohexyl...
benzamide successfully reacted with thioanisole and gave the substitution products in high yields (3ba–da). 4-Butyl benzamide, however, yielded the corresponding products in lower yields (3ea 74%), which could be attributed to the side reactions of an alkyl group. Phenyl, N, N-dimethyl, phenoxyl, and methoxy benzamides were also allowed to react with thioanisole and corresponding α-sulfenylated ketone products were obtained in good to high yields (3fa–la). 2-Naphthamide gave the desired product in 83% yield (3ma), while 1-naphthamide afforded a low yield of 14%. 2-Phenyl benzamide failed to react with thioanisole. It seems that the steric hindrance from benzamides would greatly inhibit the substitution reaction. Isopropyl methyl sulfide smoothly reacted with the benzamides but gave the products in a bit lower yields than those of thioanisole (5ba–ma).

Mechanistic studies. We are quite interested in the deprotonation of thioanisole with LDA, which is the key step in alkylation of the tertiary benzamide. LDA failed to deprotonate thioanisole for its weak acidity. The tertiary benzamide must play an essential role in the deprotonation process. The nucleophilic acyl substitution reaction of benzamide with alkyl lithium would generate ketone intermediate and a new LDA. The enolization of the ketone with LDA could take place easily and provide the driving force. The direct quench of the reaction with benzyl bromide could take place easily and provide the driving force of the reaction. The direct quench of the reaction with benzyl bromide could take place easily and provide the driving force of the reaction. The direct quench of the reaction with benzyl bromide could take place easily and provide the driving force of the reaction.

In summary, we have developed a direct alkylation reaction of N, N-dialkyl benzamides with methyl sulfides, which provides a direct and efficient approach for the synthesis of α-sulfenylated ketones. This reaction features selective methyl C–H bond deprotonative functionalization of methyl sulfides with LDA, a relatively weaker base than lithium alkyls. Preliminary mechanism studies revealed that the ortho-lithiation of the tertiary benzamide promoted the deprotonation of methyl sulfides and triggered the nucleophilic acyl substitution reaction of the benzamide. Distinct from the amide activation strategies by either
enhancing the amide reactivity or stabilizing the tetrahedral intermediates, the low concentration of the reactive carbanion intermediates arising from the deprotonation equilibrium of methyl sulfides with LDA could be the key factor for restraining side reactions and improving the selectivity.

**Methods**

A general procedure for the alkylation of benzamide with thianisoles. To a 25 mL Schlenk tube equipped with a Teflon septum and magnetic stir bar were added benzamides 1 (0.50 mmol, 1.0 equiv.), thianisoles 2 (0.70 mmol, 1.4 equiv.), THF (1.0 mL) and LDA (80.3 mg, 0.55 mmol, 1.1 equiv., solid). The tube was sealed and stirred at 40 °C for 24 h. The mixture was then cooled to room temperature, quenched by adding five drops of H2O and then diluted by ethyl acetate (EtOAc, 30 mL). The obtained solution was dried over anhydrous Na2SO4. After filtration and concentration by rotary evaporation, the residue was purified by silica gel column chromatography to afford the desired products 3.

A general procedure for the alkylation of benzamide with alkyl methyl sulfides. To a 25 mL Schlenk tube equipped with a Teflon septum and magnetic stir bar were added benzamides 1 (0.50 mmol, 1.0 equiv.), alkyl methyl sulfides 4 (1.25 mmol, 2.5 equiv.), THF (1.0 mL) and LDA (80.3 mg, 0.55 mmol, 1.1 equiv., solid). The tube was sealed and stirred at 40 °C for 24 h. The mixture was then cooled to room temperature, quenched by adding five drops of H2O and then diluted by ethyl acetate (EtOAc, 30 mL). The obtained solution was dried over anhydrous Na2SO4. After filtration and concentration by rotary evaporation, the residue was purified by silica gel column chromatography to afford the desired products 5.

**Data availability**

For additional condition screening, see Supplementary Tables. 1–6; for 1H and 13C spectra of compound 3 and 5, see Supplementary Fig. 12–13.

Received: 10 March 2021; Accepted: 19 August 2021; Published online: 27 September 2021

**References**

1. Greenberg, A., Breneman, C. M. & Liebman, J. F. The amide linkage: selected structural aspects in chemistry, biochemistry, and materials science; Wiley-Interscience: New York, 2000.

2. Jin, Z. Amaryllidaceae and Sceletium alkaloids. Tetrahedron Lett. 26, 657–660 (1985).

3. Giovannini, A., Savoia, D. & Umani-Ronchi, A. Organometallic ring-opening reactions of N-acyl and N-alkoxyacylcarbonyl lactams. Synth. Cycl. Imines. J. Org. Chem. 54, 228–234 (1989).

4. Rudolph, A. C., Machauer, R. & Martin, S. F. Synthesis of cis-2,5-disubstituted pyrroldiones via diastereoselective reduction of N-acyliminium ions. Tetrahedron Lett. 45, 4895–4898 (2004).

5. Sureshbabu, P., Azeea, S., Muniyappan, N., Nabiah, S. & Kandasamy, I. Chemoselective synthesis of ary ketones from amides and grignard reagents via C(O)-N bond cleavage under catalyst-free conditions. J. Org. Chem. 84, 11823–11838 (2019).

6. Evans, D. A., Borg, G. & Scheidt, K. A. Remarkably stable tetrahedral intermediates: carbinols from nucleophilic additions to α,ω-pyrrolidines. Angew. Chem. Int. Ed. 41, 3188–3191 (2002).

7. Heller, S. T., Newton, J. N., Fu, T. & Sarpong, R. One-pot unsymmetrical ketone synthesis employing a pyrrole-bearing formal carbonyl dication linchpin reagent. Angew. Chem. Int. Ed. 54, 9839–9843 (2015).

8. Szostak, M. & Aubé, J. Chemistry of bridged lactams and related heterocycles. Chem. Rev. 113, 5701–5765 (2013).

9. Adachi, S., Kumagai, N. & Shibasaki, M. Conquering amide planarity: structural distortion and its hidden reactivity. Tetrahedron Lett. 59, 1147–1158 (2018).

10. Adachi, S., Komarov, I. V. & Feeder, N. Spontaneous, nullisecond formation of a twisted amide from the amino acid, and the crystal structure of a tetrahedral intermediate. J. Am. Chem. Soc. 120, 7101–7102 (1998).

11. Szostak, M., Yao, L. & Aubé, J. Proximity effects in nucleophilic addition reactions to medium-bridged twisted lactams: remarkably stable tetrahedral intermediates. J. Am. Chem. Soc. 132, 20878–20878 (2010).

12. Szostak, M. & Aubé, J. Medium-bridged lactams: a new class of non-planar amides. Org. Biomol. Chem. 9, 27–35 (2011).

13. Liu, C., Achtenhagen, M. & Szostak, M. Chemoselective ketone synthesis by the addition of organometallics to N-acylazetidines. Org. Lett. 18, 2375–2378 (2016).

14. Ghinato, S. et al. A fast and general route to ketones from amides and organolithium compounds under aerobic conditions: synthetic and mechanistic aspects. Chem. - Eur. J. 22, 2868–2874 (2014).

15. Hie, L. et al. Conversion of amides to esters by the nickel-catalysed activation of amide C-N bonds. Nature 524, 79–83 (2015).

16. Li, X. & Zou, G. Acylative Suzuki coupling of amides: α-acyl-nitrogen activation via synergy of independently modifiable activating groups. Chem. Commun. 51, 5089–5092 (2015).

17. Meng, G. & Szostak, M. Sterically controlled Pd-catalysed chemoselective ketone synthesis via N-C cleavage in twisted amides. Org. Lett. 17, 4364–4367 (2015).

18. Weires, N. A., Baker, E. L. & Garg, N. K. Nickel-catalysed Suzuki–Miyaura coupling of amides. Nat. Chem. 8, 75–79 (2016).

19. Huang, P. & Chen, H. Ni-Catalyzed cross-coupling reactions of N-acylpyrrole-type amides with organoboron reagents. Chem. Commun. 53, 12584–12587 (2017).

20. Meng, G., Szostak, M. & Aubé, J. Pd-catalysed cross-coupling of N-acylpyrroles and pyrazoles: planar, electronically activated amides in catalytic N-C cleavage. Org. Lett. 19, 3596–3599 (2017).

21. Simmons, B. J., Weires, N. A., Dander, J. E. & Garg, N. K. Nickel-catalyzed alkylation of amide derivatives. ACS Catal. 6, 3176–3179 (2016).

22. Bechara, W. S., Pelletier, G. & Charette, A. B. Chemoselective synthesis of ketones and ketimines by addition of organometallics to secondary amides. Nat. Chem. 4, 228 (2012).

23. Xiao, K., Wang, A., Huang, Y. & Huang, P. Versatile and direct transformation of secondary amides into ketones by deaminative alkylation with organocopper reagents. Asian. Asian J. Org. Chem. 1, 130–132 (2012).

24. Huang, P., Wang, Y., Xiao, K. & Huang, Y. A general method for the direct transformation of common tertiary amides into ketones and amines by addition of Grignard reagents. Tetrahedron 71, 4248–4254 (2015).

25. Huang, P., Huang, Y., Geng, H. & Ye, J. Metal-free C=H alklymination and acylation of alkenes with secondary amides. Sci. Rep. 6, 28801 (2016).

26. Huang, P., Huang, Y. & Xiao, K. Metal-free intermolecular coupling of amines with secondary amides: chemoselective synthesis of aromatic ketimines and ketones, and N-deacylation of secondary amides. J. Org. Chem. 81, 9020–9027 (2016).

27. Huang, P., Huang, Y. & Wang, S. One-pot synthesis of N-heterocycles and enmino carbocycles by tandem dehydroative coupling–reductive cyclization of halo-sec-amides and dehydroative cyclization of olefinic sec-amides. Org. Chem. Front. 4, 431–444 (2017).

28. Huang, P. & Huang, Y. Further studies on the direct synthesis of α,β-unsaturated ketimines and α,β-enoynes by chemoselective dehydroative addition
of functionalized alkenes to secondary amides. Chin. J. Chem. 35, 613–620 (2017).

42. Winterr, S. & Huang, P. Cross-coupling of secondary amides with tertiary amides: the use of tertiary amides as surrogates of alkyl carbamions for ketone synthesis. Chin. J. Chem. 37, 887–891 (2019).

43. Geng, H. & Huang, P. Ketone synthesis by direct, orthogonal chemoselective hydrocyanation of alkenes with amides: use of alkenes as surrogates of alkyl carbamions. Chin. J. Chem. 37, 811–816 (2019).

44. Wu, D., He, Q., Chen, D., Ye, J. & Huang, P. A stepwise annulation for the transformation of cyclic ketones to fused 6 and 7-membered cyclic enimines and enones. Chin. J. Chem. 37, 315–322 (2019).

45. Li, J., Oost, R., Maryasin, B., González, L. & Maulide, N. A redox-neutral synthesis of ketones by coupling of alkenes and amides. Nat. Commun. 10, 2327 (2019).

46. Sun, W. et al. Chemodivergent transformations of amides using gem-diborylalkanes as pro-nucleophiles. Nat. Commun. 11, 3113 (2020).

47. Trost, B. M., Salzmann, T. N. & Hiroi, K. New synthetic reactions. Sulfenylation and dehydrosulfenylation of esters and ketones. J. Am. Chem. Soc. 98, 4887–4902 (1976).

48. Zou, L., Pribiškow, D. L., Wang, L., Mottweiler, J. & Bolm, C. Copper-catalyzed synthesis of a-thiaryl carbonyl compounds through S-S and C-C bond cleavage. Adv. Synth. Catal. 355, 2558–2563 (2013).

49. Biswas, S., Wattle, R. A. & Samec, J. S. M. Tandem Pd/Au-catalyzed route to α-sulfenylated carbonyl compounds from terminal propargylic alcohols and thiols. Chin. J. Chem. 29, 2159–2163 (2014).

50. Wang, H. et al. Catalyst-free difunctionalization of activated alkenes in water: efficient synthesis of β-Keto sulfinides and sulfoxones. Chem. Eur. J. 22, 14489–14493 (2016).

51. Dias, R. M. P. & Burutolo, A. C. B. Catalyst-free insertion of sulfonoximes ylides into aryl thiolis. A direct preparation of β-Keto thioethers. Org. Lett. 18, 3034–3037 (2016).

52. Siddaraju, Y. & Prabhhu, K. R. Iodine promoted regioselective α-sulfenylation of carbonyl compounds using dimethyl sulfoxide as an oxidant. Org. Lett. 18, 6090–6093 (2016).

53. Poirier, D., Auger, S., Merand, Y., Simard, J. & Labrie, F. Synthesis and dehydration of chiral α-thiocarbonyl compounds. J. Org. Chem. 78, 10344–10347 (2013).

54. Strebe, N. & Shi, Z. Weak bases display better: kinetic deprotonative transformations of sulfonamides as pro-nucleophiles. Angew. Chem. Int. Ed. 57, 6056–6059 (2018).

55. Nakano, M. & Takimiya, K. Sodium sulfinates and 1,3-Dithianes. J. Am. Chem. Soc. 120, 7796–7799 (1998).

56. Fraser, R. R., Bresse, M. & Mansour, T. S. α-PKa Measurements in tetrahydrofuran. J. Am. Chem. Soc. 130, 7838–7841 (2008).

57. Silvestre, S. & Shi, Z. Synthetic methods using α-heterosubstituted organometallics. Tetrahedron 56, 2531–2640 (1990).

58. Nakamura, S., Nakagawa, R., Watanabe, Y. & Toru, T. Highly enantioselective transformations of configurationally labile α-thioorganolithiums using chiral bis(oxazolines) via two different enantiometermination steps. J. Am. Chem. Soc. 122, 11340–11347 (2000).

59. Smith, A. B., Pitram, S. M., Gaunt, M. J. & Kozmin, S. A. Dithiane additions to vinyl epoxides: steric control over the SN2 and SN2′ mandatories. J. Am. Chem. Soc. 124, 14516–14517 (2002).
