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# Squaramide-Catalyzed Synthesis of Enantioenriched Spirocyclic Oxindoles via Ketimine Intermediates with Multiple Active Sites

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***Abstract:*** *A new method for the construction of five-membered spirocyclic oxindoles is based on a Michael–Mannich cascade reaction of a ketimine intermediated catalyzed by a bifunctional quinine-derived squaramide. The desired products were obtained in excellent yields (up to 94%) and stereoselectivities (up to >20:1 d.r., >99% ee). A scaled-up variant also proceeded smoothly showing that the one-pot reaction might find application in the synthesis of bioactive-compound libraries.*

The spirocyclic oxindole architecture is prevalent in both natural products and synthetic bioactive molecules (Figure 1).[1] In particular, enantiopure five-membered spirocyclic oxindoles have attracted tremendous attention owing to their diverse bioactivities and structural complexity. The key challenge for the construction of such structures lies in the formation of multiple stereocenters, particularly for those containing two adjacent quaternary centers. Therefore, new strategies for the synthesis of such spirocyclic oxindoles[2] with high levels of efficiency and selectivity from readily available starting materials are always in great demand.

In the past few years, elegant advances have been made in the development of enantioselective syntheses of five-membered spirocyclic oxindoles.[3] In 2007, Trost[4] and co-workers disclosed a palladium-catalyzed [3+2] cycloaddition for the assembly of such compounds. Aside from transition-metal catalysis, organocatalytic cascade reactions provide an alternative powerful strategy for the preparation of spirocyclic oxindoles. After [3+2] cycloadditions catalyzed by chiral tertiary phosphines[5] or amines[6] had been reported, hydrogen bond donor catalyzed cascade reactions,[7] Michael–Michael reactions promoted by primary[8] or secondary amines,[9] NHC-catalyzed processes,[10] as well as alkylations mediated by phase transfer catalysts (PTCs)[11] were developed. More recently, synergistic catalysis[12] and C–H bond oxygenation[13] were also applied to the asymmetric construction of five-membered spirocyclic oxindoles.

Inspired by our ongoing interest in the development of reactions towards spirocyclic oxindoles[14] and previous work on nitrosoarenes,[15] we hypothesized that the addition of β-dicarbonyl compounds to nitrosoarenes followed by a Michael–Mannich sequence in the presence of a bifunctional catalyst would be an appropriate strategy to prepare enantioenriched spirocyclic oxindoles (Scheme 1d). As an interesting electrophile, nitrosobenzene can react with ketones/aldehydes to form either the α-aminooxylation[16] or the α-oxyamination products[17] (Scheme 1a). However, very few methods for the addition of β-dicarbonyl compounds[18] to nitrosoarenes to generate α-imino-β-dicarbonyl compounds have been reported thus far, and they all suffer from low yields (Scheme 1b). These products are very useful synthons that bear multiple nucleophilic and electrophilic sites. To the best of our knowledge, the application of these novel ketimines in asymmetric synthesis has not been reported thus far.

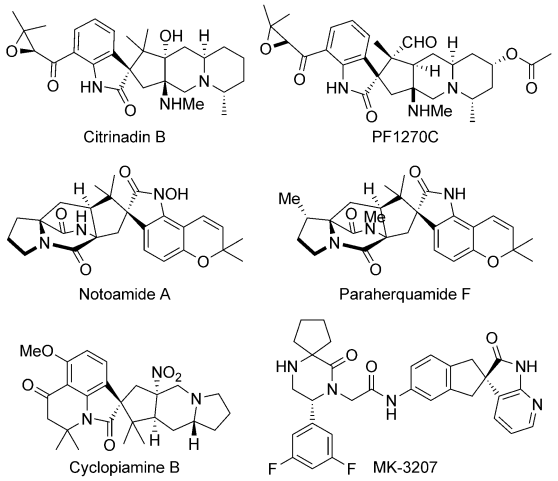


***Figure 1.*** Bioactive five-membered spirocyclic oxindoles.

At the outset of this study, a method for the preparation of α-imino-β-dicarbonyl compounds was developed. We were pleased to find that such a compound could be isolated in nearly quantitative yield when acetylacetone (**1a**) and nitrosobenzene (**2a**) were coupled in the presence of 2 mol% of quinine-derived squaramide **A**. In other words, the addition promoted by the bifunctional catalyst was highly selective for N-addition, and any O-addition products were not observed. Meanwhile, the bifunctional catalyst exhibited good activity in this Michael addition. Therefore, we attempted to prepare various spirocyclic oxindoles through a one-pot process using only one catalyst.

Considering that both nitrosoarenes and methyleneindolinones are electrophilic, we initially investigated the one-pot

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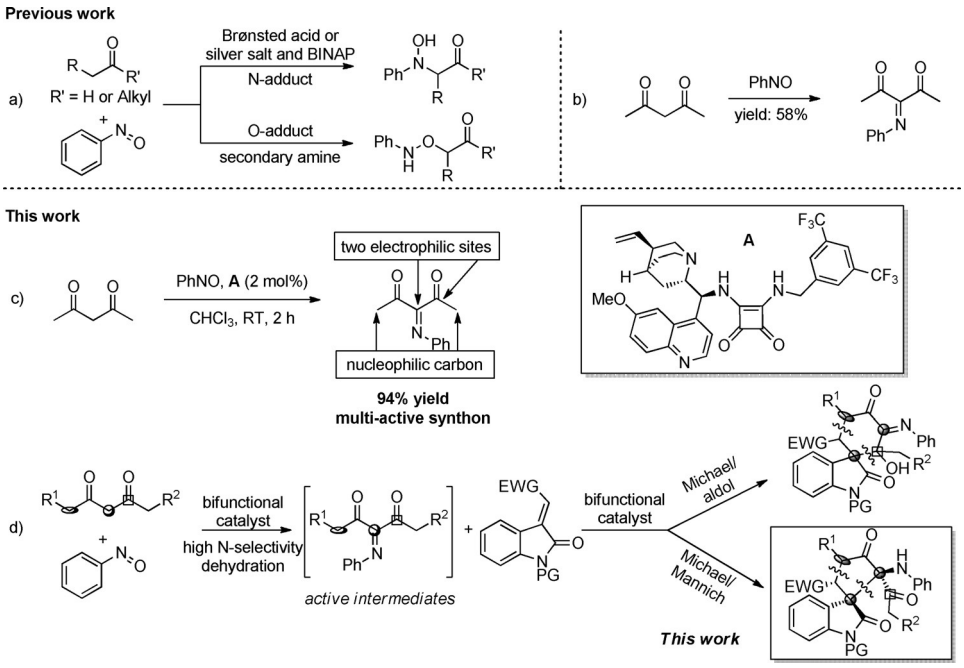
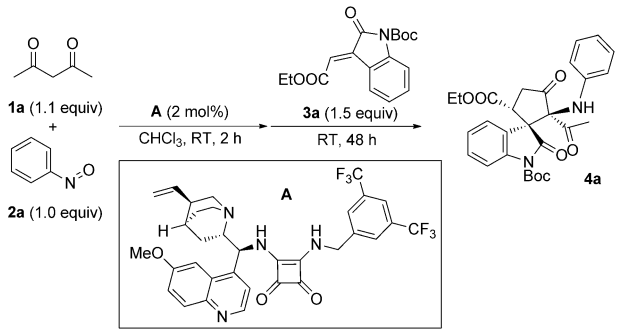



***Scheme 1.*** Highly selective N-addition and Michael–Mannich/aldol sequences towards spirocyclic oxindoles. EWG = electron-withdrawing group, PG = protecting group.

process through the stepwise addition of one electrophile for each stage of the process. First, acetylacetone (**1a**) and nitrosobenzene (**2a**) were allowed to react in the presence of 2 mol% of quinine-derived squaramide **A** in $CHCl_3$ at room temperature for two hours. After the nitrosobenzene had been consumed, methyleneindolinone **3a** was added directly, and the reaction mixture was stirred for another 48 hours. To our delight, the desired five-membered spirocyclic oxindole **4a** was formed in 80% yield with >20:1 diastereoselectivity and 96% *ee* (Table 1, entry 1). Thereafter, the catalyst loading and different solvents were examined, showing that 2 mol% of **A** and $CHCl_3$ were optimal. The addition of 4 Å molecular sieves[18a] was beneficial for the dehydration of the adducts and the enantioselectivity of the following cyclization (entry 2).

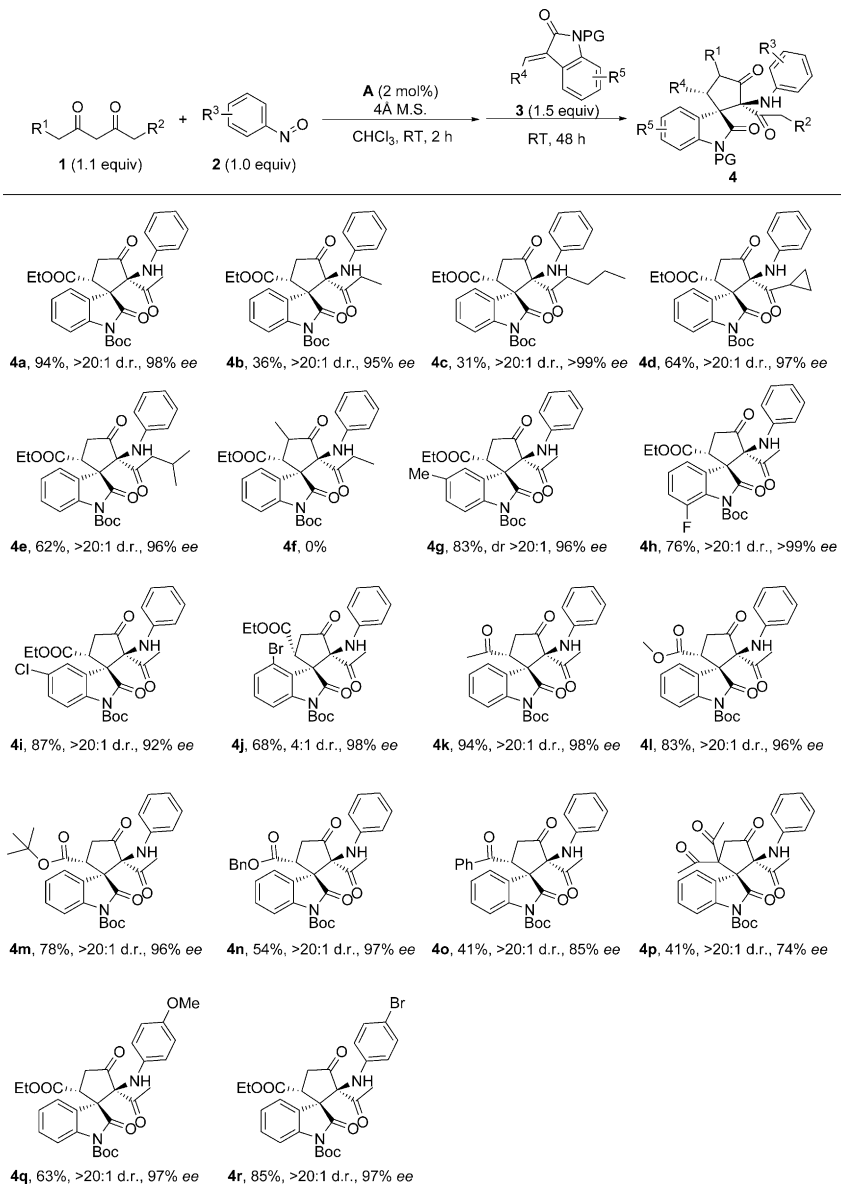
With the optimized conditions in hand, the substrate scope was studied. As shown in Scheme 2, β-dicarbonyl compounds bearing different carbon chains were tested under the optimized conditions. Several derivatives were obtained in moderate to excellent yields (**4a**–**4e**, 31–94%) with excellent diastereoselectivities (>20:1 d.r. in all cases) and enantioselectivities (95–99% *ee*). Notably, the reaction of 3,5-heptanedione with nitrosobenzene proceeded well, but the following Michael addition did not take place to furnish the desired product **4f**. Moreover, both electron-withdrawing and electron-donating groups on the aryl ring of the methyleneindolinone were well-tolerated, and the corresponding products were obtained in moderate to good yields (**4g**–**4i**, 76–87%) and excellent diastereoselectivities (>20:1 d.r.) and enantioselectivities (up to >99% *ee*). With substitution at the 4-position of methyleneindolinone, the desired products were formed in excellent enantioselectivity (98% *ee*), albeit in lower yield (**4j**, 68%) and diastereoselectivity (4:1 d.r.). Furthermore, we evaluated methyleneindolinones with various electron-withdrawing groups ($R^4$) at the methylene position under the standard reaction conditions. These reactions delivered the desired products in moderate to excellent yields (**4k**–**4n**) with excellent stereoselectivities (>20:1 d.r., 96–98% *ee*). The introduction of benzoyl (**4o**) or diacetyl groups (**4p**)[19] was detrimental for both the reactivity and selectivity. The absolute configuration of product **4e** was assigned by X-ray diffraction.[19] Finally, the influence of the electronic character of the nitrosoarene was examined. Both methoxy- and bromo-substituted nitrosobenzene afforded the desired products (**4q** and **4r**) in good yields (63 and 85%) and stereoselectivities (>20:1 d.r., 97% *ee*).

***Table 1:*** Optimization of the Michael–Mannich reaction for the synthesis of five-membered spirocyclic oxindoles.



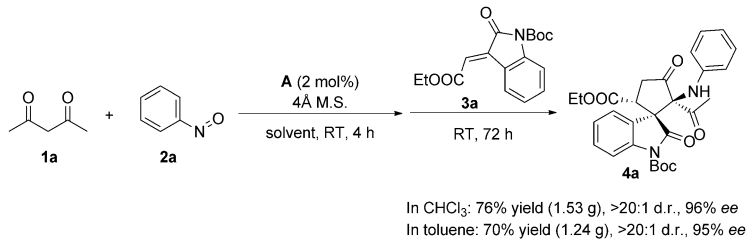

| Entry[a] | Catalyst [mol%] | Solvent | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|
| 1 | 2 | $CHCl_3$ | 80 | 96 |
| 2[d] | 2 | $CHCl_3$ | 94 | 98 |
| 3 | 1 | $CHCl_3$ | 33 | 95 |
| 4 | 4 | $CHCl_3$ | 80 | 96 |
| 5 | 2 | $CCl_4$ | 77 | 97 |
| 6 | 2 | $CH_2Cl_2$ | 85 | 95 |
| 7 | 2 | THF | 82 | 96 |
| 8 | 2 | toluene | 76 | 95 |

[a] Unless otherwise noted, all reactions were performed with **1a** (0.22 mmol, 1.1 equiv), **2a** (0.2 mmol, 1.0 equiv), **3a** (0.3 mmol, 1.5 equiv), and catalyst **A** (0.004 mmol, 2 mol%) in 0.2 mL of the indicated solvent. The diastereomeric ratios were determined by $^1$H NMR spectroscopy of the crude reaction mixtures (>20:1 d.r. in all cases). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 4 Å molecular sieves (M.S.; 50 mg) were added. Boc = *tert*-butyloxycarbonyl.




***Scheme 2.*** Scope of the one-pot reaction.

To illustrate the preparative utility of this asymmetric one-pot reaction, a gram-scale reaction was conducted under the standard conditions (Scheme 3). The five-membered spirocyclic oxindole **4a** was obtained in good yield (76%) with excellent diastereoselectivity (>20:1 d.r.) and slightly decreased enantioselectivity (96% *ee*). The reaction was also run in toluene, which would be more convenient in potential industrial applications, where it also proceeded smoothly, giving the desired product **4a** in 70% yield with excellent diastereoselectivity (>20:1 d.r.) and enantioselectivity (95% *ee*).




***Scheme 3.*** Gram-scale one-pot reaction.

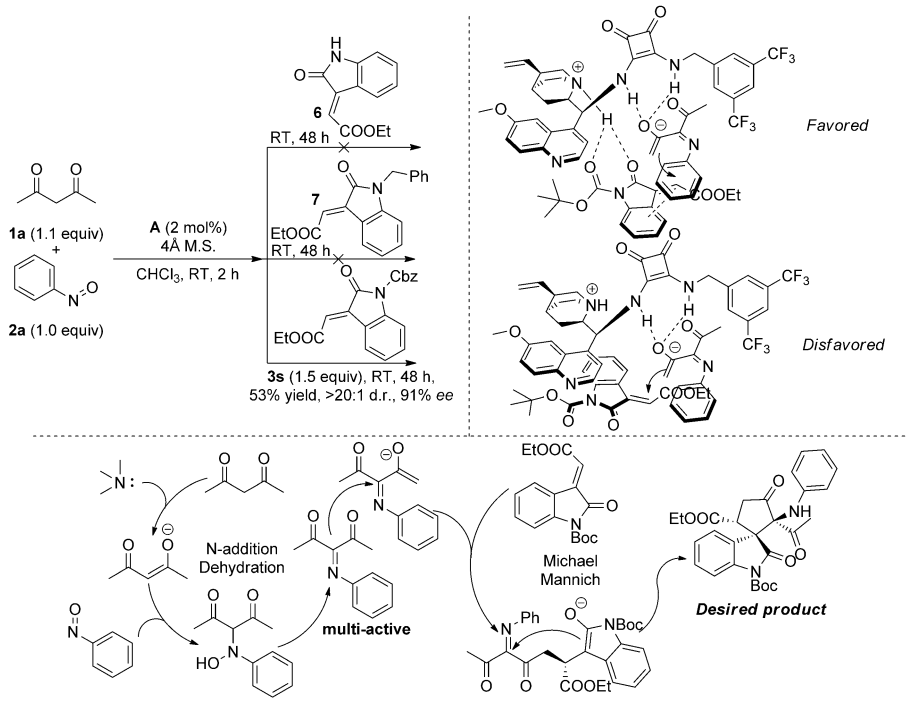
To investigate the stereochemical outcome of this one-pot reaction, specific control experiments were designed and performed (Scheme 4). First, unprotected or benzyl-protected methyleneindolinones did not afford the desired products. Second, benzyloxycarbonyl-protected methyleneindolinone furnished the desired product with decreased enantioselectivity (91% *ee*). These results demonstrate that the Boc group, which is a hydrogen-bond acceptor and electron-deficient, is essential for activating the methyleneindolinones. Also, the steric hindrance of the Boc moiety is beneficial to the enantioselectivity of the reaction. A proposed mechanism is depicted in Scheme 4. Enolization of acetylacetone promoted by the tertiary amine group of the bifunctional catalyst is followed by N-selective addition to nitrosobenzene under basic conditions. The resulting ketimine is then transformed into the corresponding enoate, and the methyleneindolinone is activated by the same catalyst.[20] Subsequent intermolecular Michael addition and the final irreversible cyclization proceed smoothly to afford the enantioenriched product.

In conclusion, a highly efficient method for the preparation of α-imino-β-dicarbonyl compounds under mild conditions has been developed. The resulting ketimines with multiple active sites provide simple and efficient access to five-membered spirocyclic oxindoles bearing three contiguous stereocenters and two adjacent quaternary centers from readily available substrates in excellent yields (up to 94%) and stereoselectivities (up to >20:1 d.r., >99% *ee*). The one-pot reaction was easily scaled up and performed in the presence of only 2 mol% of a bifunctional quinine-derived squaramide catalyst. Further explorations of new transformations based on multi-active synthons are ongoing in our laboratory and will be reported in due course.

## Experimental Section

General procedure: A solution of the quinine-derived squaramide (2.5 mg, 0.004 mmol, 2 mol%), **1a** (23 μL, 0.22 mmol, 1.1 equiv), 4 Å molecular sieves (50 mg), and **2a** (21.4 mg, 0.20 mmol, 1.0 equiv) in $CHCl_3$ (0.2 mL) was vigorously stirred at room temperature (25°C) for 2 h. Then, **3a** (96 mg, 0.3 mmol, 1.5 equiv) was added to the




***Scheme 4.*** Control experiments and proposed mechanism for the one-pot reaction.

yellow solution. The mixture was stirred at room temperature for 48 h. Upon complete consumption of the intermediate, the mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane = 7:1:1) to afford the desired product.

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**Keywords:** asymmetric synthesis · ketimines · Mannich reactions · Michael additions · nitrogen heterocycles · organocatalysis

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[1] a) E. V. Mercado-Marin, P. Garcia-Reynaga, S. Romminger, E. F. Pimenta, D. K. Romney, M. W. Lodewyk, D. E. Williams, R. J. Andersen, S. J. Miller, D. J. Tantillo, R. G. Berlinck, R. Sarpong, *Nature* **2014**, *509*, 318–324; b) Z. Bian, C. C. Marvin, M. Pettersson, S. F. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 14184–14192; c) I. M. Bell, C. A. Stump, S. N. Gallicchio, D. D. Staas, C. B. Zartman, E. L. Moore, N. Sain, M. Urban, J. G. Bruno, A. Calamari, A. L. Kemmerer, S. D. Mosser, C. Fandozzi, R. B. White, M. M. Zrada, H. G. Selnick, S. L. Graham, J. P. Vacca, S. A. Kane, C. A. Salvatore, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3941–3945; d) Z. Bian, C. C. Marvin, S. F. Martin, *J. Am. Chem. Soc.* **2013**, *135*, 10886–10889; e) K. Kong, J. A. Enquist, Jr., M. E. McCallum, G. M. Smith, T. Matsumaru, E. Menhaji-Klotz, J. L. Wood, *J. Am. Chem. Soc.* **2013**, *135*, 10890–10893; f) B. M. Trost, D. A. Bringley, T. Zhang, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 16720–16735.

[2] For the synthesis of spirocyclic oxindoles and asymmetric organocatalytic cyclization reactions, see: a) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407; b) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832; c) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165–5181; d) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023–1052; e) Y. Liu, H. Wang, J. Wan, *Asian J. Org. Chem.* **2013**, *2*, 374–386.

[3] For recently reported metal-catalyzed reactions, see: a) N. R. Ball-Jones, J. J. Badillo, N. T. Tran, A. K. Franz, *Angew. Chem. Int. Ed.* **2014**, *53*, 9462–9465; *Angew. Chem.* **2014**, *126*, 9616–9619; b) J. F. Brazeau, S. Zhang, I. Colomer, B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 2742–2749.

[4] B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397.

[5] For tertiary phosphine catalyzed [3+2] annulations, see: a) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2011**, *50*, 7837–7841; *Angew. Chem.* **2011**, *123*, 7983–7987; b) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672–4675; c) N. Pinto, M. Neel, A. Panossian, P. Retailleau, G. Frison, A. Voituriez, A. Marinetti, *Chem. Eur. J.* **2010**, *16*, 1033–1045.

[6] J. Peng, X. Huang, L. Jiang, H. L. Cui, Y. C. Chen, *Org. Lett.* **2011**, *13*, 4584–4587.

[7] For hydrogen bond donor catalyzed reactions, see: a) J. Zhou, Q. L. Wang, L. Peng, F. Tian, X. Y. Xu, L. X. Wang, *Chem. Commun.* **2014**, *50*, 14601–14604; b) W. Sun, L. Hong, G. Zhu, Z. Wang, X. Wei, J. Ni, R. Wang, *Org. Lett.* **2014**, *16*, 544–547; c) W. Sun, G. Zhu, C. Wu, L. Hong, R. Wang, *Chem. Eur. J.* **2012**, *18*, 6737–6741; d) X. Li, Y. M. Li, F. Z. Peng, S. T. Wu, Z. Q. Li, Z. W. Sun, H. B. Zhang, Z. H. Shao, *Org. Lett.* **2011**, *13*, 6160–6163; e) A. Noole, K. Ilmarinen, I. Jarving, M. Lopp, T. Kanger, *J. Org. Chem.* **2013**, *78*, 8117–8122.

[8] X. Tian, P. Melchiorre, *Angew. Chem. Int. Ed.* **2013**, *52*, 5360–5363; *Angew. Chem.* **2013**, *125*, 5468–5471.

[9] For secondary amine catalyzed reactions, see: a) S. L. Zhang, H. X. Xie, J. Zhu, H. Li, X. S. Zhang, J. Li, W. Wang, *Nat. Commun.* **2011**, *2*, 211; b) L. Z. Ding, T. S. Zhong, H. Wu, Y. M. Wang, *Eur. J. Org. Chem.* **2014**, 5139–5143.

[10] K. Jiang, B. Tiwari, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2382–2385.

[11] B. Xiang, K. M. Belyk, R. A. Reamer, N. Yasuda, *Angew. Chem. Int. Ed.* **2014**, *53*, 8375–8378; *Angew. Chem.* **2014**, *126*, 8515–8518.

[12] For synergistic catalytic reactions, see: a) S. Afewerki, G. N. Ma, I. Ibrahem, L. F. Liu, J. L. Sun, A. Cordova, *ACS Catal.* **2015**, *5*, 1266–1272; b) L. Deiana, Y. Jiang, C. Palo-Nieto, S. Afewerki, C. A. Incerti-Pradillos, O. Verho, C. W. Tai, E. V. Johnston, A. Cordova, *Angew. Chem. Int. Ed.* **2014**, *53*, 3447–3451; *Angew. Chem.* **2014**, *126*, 3515–3519; c) W. Sun, G. Zhu, C. Wu, L. Hong, R. Wang, *Chem. Eur. J.* **2012**, *18*, 13959–13963.

  

[13] J. R. Frost, S. M. Huber, S. Breitenlechner, C. Bannwarth, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 691 – 695; *Angew. Chem.* **2015**, *127*, 701 – 705.

[14] Q.-S. Sun, X.-Y. Chen, H. Zhu, H. Lin, X.-W. Sun, G.-Q. Lin, *Org. Chem. Front.* **2015**, *2*, 110 – 113.

[15] a) H. Lin, X. W. Sun, G. Q. Lin, *Org. Lett.* **2014**, *16*, 752 – 755; b) H. Lin, Y. Tan, X. W. Sun, G. Q. Lin, *Org. Lett.* **2012**, *14*, 3818 – 3821.

[16] For α-aminoxylation reactions with nitrosobenzene, see: a) N. Momiyama, H. Yamamoto, *Angew. Chem. Int. Ed.* **2002**, *41*, 2986 – 2988; *Angew. Chem.* **2002**, *114*, 3459; b) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038 – 6039; c) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem. Int. Ed.* **2004**, *43*, 1109 – 1112; *Angew. Chem.* **2004**, *116*, 1129 – 1132; d) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673 – 3684; e) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem. Int. Ed.* **2004**, *43*, 1112 – 1115; *Angew. Chem.* **2004**, *116*, 1132 – 1135; f) P. Merino, T. Tejero, *Angew. Chem. Int. Ed.* **2004**, *43*, 2995 – 2997; *Angew. Chem.* **2004**, *116*, 3055 – 3058; g) D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1577 – 1580; h) K. Huang, Z. Z. Huang, X. L. Li, *J. Org. Chem.* **2006**, *71*, 8320 – 8323; i) S. Kumarn, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2006**, 3211 – 3213; j) M. Matsuzawa, H. Kakeya, J. Yamaguchi, M. Shoji, R. Onose, H. Osada, Y. Hayashi, *Chem. Asian J.* **2006**, *1*, 845 – 851; k) J. Yamaguchi, M. Toyoshima, M. Shoji, H. Kakeya, H. Osada, Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 789 – 793; *Angew. Chem.* **2006**, *118*, 803 – 807; l) D. Font, A. Bastero, S. Sayalero, C. Jimeno, M. A. Pericas, *Org. Lett.* **2007**, *9*, 1943 – 1946; m) M. Kawasaki, P. Li, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, *47*, 3795 – 3797; *Angew. Chem.* **2008**, *120*, 3855 – 3857; n) M. Lu, Y. Lu, D. Zhu, X. Zeng, X. Li, G. Zhong, *Angew. Chem. Int. Ed.* **2010**, *49*, 8588 – 8592; *Angew. Chem.* **2010**, *122*, 8770 – 8774; o) R. Rios, P. Schyman, H. Sundén, G. L. Zhao, F. Ullah, L. J. Chen, A. Laaksonen, A. Córdova, *Chem. Eur. J.* **2010**, *16*, 13935 – 13940.

[17] For α-oxyamination reactions with nitrosobenzene, see: a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360 – 5361; b) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080 – 1081.

[18] For the addition of nitrosobenzene and β-dicarbonyl compounds, see: a) H. Nohira, K. Sato, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1963**, *36*, 870 – 872; b) J. Mirek, J. Moskal, A. Moskal, *Tetrahedron* **1975**, *31*, 2145 – 2149; c) J. Moskal, A. Moskal, *Tetrahedron* **1982**, *38*, 1787 – 1792; d) A. S. Hammam, A. S. Yanni, Z. H. Khalil, A. A. Abdel-Hafez, *J. Chem. Technol. Biotechnol.* **1982**, *32*, 485 – 488; e) H. Mustroph, L. Hennig, H. Wilde, *Z. Chem.* **1989**, *29*, 66 – 67; f) L. Spencer, M. Kim, W. B. Euler, W. Rosen, *J. Am. Chem. Soc.* **1997**, *119*, 8129 – 8130; g) W. Adam, N. Bottke, O. Krebs, I. Lykakis, M. Orfanopoulos, M. Stratakis, *J. Am. Chem. Soc.* **2002**, *124*, 14403 – 14409; h) J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 12276 – 12278.

[19] CCDC 1409824 (**4p**) and 1407100 (**4e**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[20] For the mechanism of Michael additions promoted by squaramides, see: B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631 – 5639.

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