Organic LETTERS

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[4 + 3] Cycloadditions with Bromo-Substituted Morita–Baylis–Hillman Adducts of Isatins and *N*-(*ortho*-Chloromethyl)aryl Amides

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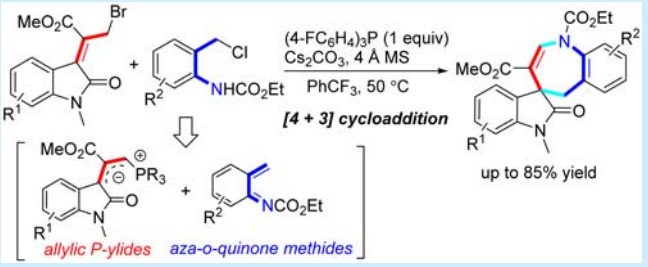
Supporting Information

ABSTRACT: Efficient construction of a challenging aza-spirocycloheptane oxindole scaffold is reported through an unprecedented [4 + 3] cycloaddition reaction with bromo-substituted Morita–Baylis–Hillman adducts of isatins and *N*-(*ortho*-chloromethyl)aryl amides. Both reactive intermediates, the allylic phosphonium ylides and aza-*o*-quinone methides, were *in situ* generated, chemoselectively facilitated by a Lewis base and Brønsted base, respectively.

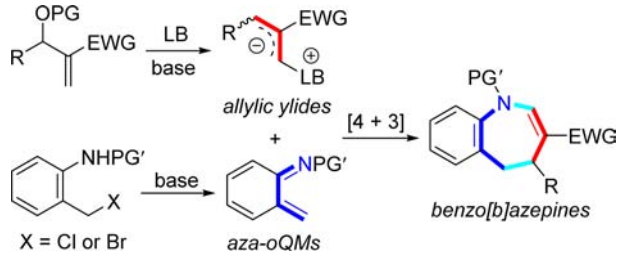


The [4 + 3] cycloaddition reaction has emerged as one of the most powerful strategies for the construction of seven-membered carbo- and heterocycles.[1] In recent years, impressive progress has been made and diverse 3C dienophiles have been utilized in [4 + 3] cycloaddition reactions besides classical allylic cations.[2] For example, the Chiu group reported silyl triflate-catalyzed [4 + 3] cycloadditions using epoxy enolsilanes as dienophiles.[3] Breslow intermediates generated from enals and an *N*-heterocyclic carbene (NHC) catalyst were successfully applied as the dienophiles by Ye and Glorius.[4] In addition, azomethine imines, azomethine yildes, nitrones, cyclopropanes, and metal vinylcarbenes were also shown to act as partners in [4 + 3] cycloadditions with different dienes, further enriching the structural diversity of the products.[5]

On the other hand, the Morita–Baylis–Hillman (MBH) derivatives could react with a Lewis base, generating zwitterionic allylic phosphonium, ammonium, or sulfonium ylides after deprotonation.[6] Such intermediates could serve as nucleophilic 3C synthons, and fruitful [3 + 2][7] and [3 + 3][8] cycloaddition reactions have subsequently been developed. In contrast, their application in more challenging [4 + 3] cycloadditions has received much less attention, probably because it is difficult to find suitable electrophilic diene components.[9]

Aza-*o*-quinone methides (aza-*o*QMs), first introduced by Corey and Steinhagen through the base-mediated elimination of *N*-(*ortho*-chloromethyl)aryl amides, have been applied as useful synthons in [4 + 2] cycloaddition reactions.[10] Later, Xiao and co-workers developed the formal [4 + 1] cycloadditions of sulfur ylides and aza-*o*QMs.[11] In Scheidt's work, dihydroquinolones and 2-aryl indoles were synthesized through [4 + 1] and [4 + 2] cycloaddition reactions, by combining aza-*o*QMs with acyl anion and enolate equivalents, respectively, via NHC catalysis.[12] In our continuing efforts to expand the synthetic transformations with MBH derivatives via Lewis base catalysis,[13] we wondered whether a novel [4 + 3] cycloaddition reaction could be accomplished between allylic ylides and aza-*o*QMs, as outlined in Scheme 1. However, this unprecedented protocol might be very challenging, as both reactants must be in situ generated from multifunctional starting materials, and subtle conditions would be necessary to control the formation of the intermediates and the following cycloaddition process.

Scheme 1. Proposed [4 + 3] Cycloadditions of in situ Generated Allylic Ylides and Aza-*o*-quinone Methides



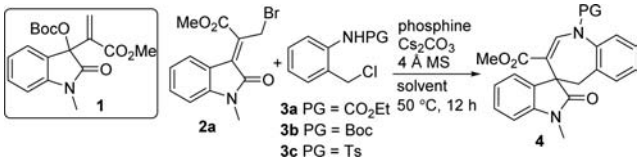
Consequently, MBH carbonate **1** derived from *N*-methyl isatin, which has been successfully applied in tertiary amine-catalyzed [3 + 2] cycloadditions,[13a,e] was initially selected in a reaction with ethyl [2-(*ortho*-chloromethyl)phenyl]-carbamate **3a**, in order to construct an aza-spirocycloheptane oxindole skeleton that might be useful in medicinal chemsitry.[14] Unfortunately, complex reactions were generally observed, when either DABCO or PPh_3 was employed as the Lewis base catalyst in combination with Cs_2CO_3 or other Brønsted bases. The desired [4 + 3] cycloadduct could not be detected in the

Received: August 5, 2015
Published: September 11, 2015

DOI: 10.1021/acs.orglett.5b02279
Org. Lett. 2015, 17, 4750–4753

mixture. After extensive screenings, a γ-regioselective [4 + 3] cycloaddition product **4a** was obtained in 62% yield at 50 °C after 12 h, by using the bromo-substituted MBH adduct[15] **2a** and precursor **3a** as the starting materials in the presence of stoichiometric Ph_3P and excess Cs_2CO_3. The addition of 4 Å molecule sieves was beneficial for the reaction (Table 1, entry 1). It should be noted that such a [4 + 3] cycloaddition still did not occur by using DABCO or DMAP as the promoter. Subsequently, an array of tertiary phosphine substances were explored (entries 2−9). While hexamethyl phosphoryamide (HMPT), nBu_3P, and tri(2-furyl) phosphine failed to produce the expected product (entries 2−4), the other phosphine compounds exhibited comparable activity, and better results were achieved with $(4\text{-}FC_6H_4)_3P$ (entry 9). In addition, solvent effects were further investigated (entries 10−13), and the yield was improved to 80% in $PhCF_3$ (entry 13). On the other hand, the *N*-protecting group of aza-*o*QM precursor was examined. An inferior yield was obtained by using *N*-Boc precursor **3b** (entry 14). Nevertheless, the *N*-Ts group was not suitable and the expected [4 + 3] cycloadduct was formed in a very low yield due to the dimerization of **3c** via *N*-alkylation reaction (entry 15). Moreover, the yields were slightly diminished at lower or higher temperature (entries 16 and 17). It was found that the reaction could smoothly proceed with 50 mol % of $(4\text{-}FC_6H_4)_3P$, albeit in a modest yield (entry 18). Finally, a diversity of chiral phosphines were explored in order to induce the chirality into the product; unfortunately, complex or side reactions were generally observed, and the desired cycloadduct **4a** could not be successfully isolated.[16] Therefore, the asymmetric [4 + 3] version still remains to be explored.

Table 1. Screening Conditions of [4 + 3] Cycloaddition[a]

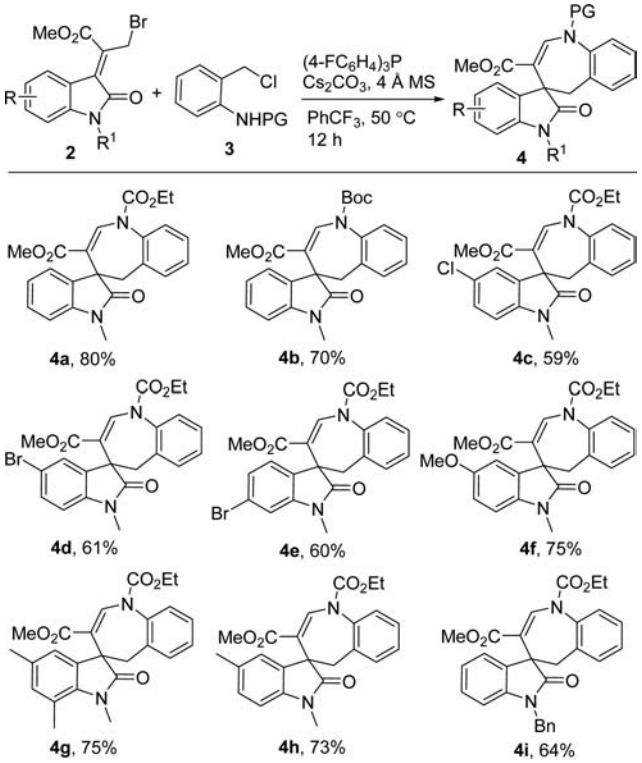


entry	phosphine	solvent	PG	yield/%[b]
1	Ph_3P	toluene	CO_2Et	**4a**, 62
2	HMPT	toluene	CO_2Et	–
3	nBu_3P	toluene	CO_2Et	–
4	$(2\text{-furyl})_3P$	toluene	CO_2Et	–
5	Cy_3P	toluene	CO_2Et	**4a**, 55
6	$MePh_2P$	toluene	CO_2Et	**4a**, 68
7	$(2\text{-}MeC_6H_4)_3P$	toluene	CO_2Et	**4a**, 38
8	$(4\text{-}MeC_6H_4)_3P$	toluene	CO_2Et	**4a**, 60
9	$(4\text{-}FC_6H_4)_3P$	toluene	CO_2Et	**4a**, 73
10	$(4\text{-}FC_6H_4)_3P$	DCE	CO_2Et	**4a**, 60
11	$(4\text{-}FC_6H_4)_3P$	$CHCl_3$	CO_2Et	**4a**, 56
12	$(4\text{-}FC_6H_4)_3P$	THF	CO_2Et	**4a**, 43
13	$(4\text{-}FC_6H_4)_3P$	$PhCF_3$	CO_2Et	**4a**, 80
14	$(4\text{-}FC_6H_4)_3P$	$PhCF_3$	Boc	**4b**, 70
15	$(4\text{-}FC_6H_4)_3P$	$PhCF_3$	Ts	–
16[c]	$(4\text{-}FC_6H_4)_3P$	$PhCF_3$	CO_2Et	**4a**, 74
17[d]	$(4\text{-}FC_6H_4)_3P$	$PhCF_3$	CO_2Et	**4a**, 79
18[e]	$(4\text{-}FC_6H_4)_3P$	$PhCF_3$	CO_2Et	**4a**, 54

[a]Unless noted otherwise, reactions were performed with **2a** (0.1 mmol), **3** (0.25 mmol), phosphine (0.1 mmol), Cs_2CO_3 (1.0 mmol), and 4 Å MS (80 mg) in solvent (2.0 mL) at 50 °C for 12 h. [b]Isolated yield. [c]At 40 °C. [d]At 60 °C. [e]0.05 mmol of $(4\text{-}FC_6H_4)_3P$ was used.

With the optimized reaction conditions in hand, substrate scope and limitations for [4 + 3] cycloadditions were examined in $PhCF_3$ in the presence of stoichiometric $(4\text{-}FC_6H_4)_3P$ and excess Cs_2CO_3. At first, different bromo-substituted MBH adducts **2** were investigated in reactions with ethyl [2-(chloromethyl)phenyl]-carbamate **3a**. As summarized in Scheme 2, the bromo-substituted MBH adducts **1** with diverse electron-donating or -withdrawing groups on the aryl ring could smoothly afford the aza-spirocycloheptane oxindole products **4c−4h** in moderate to good yields. In general, substrates with electron-donating groups exhibited higher reactivity than those with electron-withdrawing groups, probably because the latter substituents would lower the nucleophilicity of the allylic phosphonium ylides. In addition, a moderate yield for product **4i** was obtained by using the bromo-substituted MBH adduct with an *N*-benzyl group. It should be noted that the bromo-substituted MBH adducts from aryl aldehydes and methyl acrylate failed to participate in this type of [4 + 3] cycloaddition reaction under the same conditions.

Scheme 2. Scope of Bromo-substituted MBH Adducts 2[a,b]

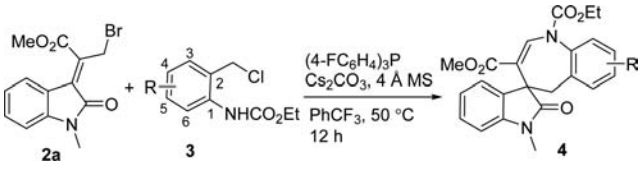


[a]Reactions were performed with **2** (0.1 mmol), **3a** (0.25 mmol), $(4\text{-}FC_6H_4)_3P$ (0.1 mmol), Cs_2CO_3 (1.0 mmol), and 4 Å MS (80 mg) in $PhCF_3$ (2.0 mL) at 50 °C for 12 h. [b]Isolated yield.

Subsequently, a series of ethyl [2-(chloromethyl)phenyl]-carbamates **3** bearing different substituents were explored in reactions with the bromo-substituted MBH adduct **2a**. As summarized in Table 2, good tolerance for diverse electron-donating or -withdrawing groups at different positions on the phenyl ring was observed. A spectrum of aza-spirocycloheptane oxindoles **4j−4t** were generally produced in modest yields (Table 2, entries 1−11). Moreover, as outlined in Scheme 3, an ethyl [3-(chloromethyl)naphthalen-2-yl]carbamate **3o** could also be successfully used. The corresponding [4 + 3] cycloaddition **4u** was obtained in a good yield, which showed

DOI: 10.1021/acs.orglett.5b02279
Org. Lett. 2015, 17, 4750−4753

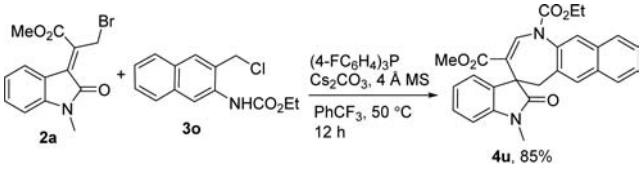
Table 2. Scope of 2-(Chloromethyl)phenyl-carbamates 3[a]



entry	R (3)	4	yield/%[b]
1	5-F (**3d**)	**4j**	66
2	3-Cl (**3e**)	**4k**	45
3	4-Cl (**3f**)	**4l**	62
4	5-Cl (**3g**)	**4m**	71
5	4-Br (**3h**)	**4n**	63
6	5-CF_3 (**3i**)	**4o**	60
7	3-Me (**3j**)	**4p**	64
8	4-Me (**3k**)	**4q**	68
9	6-Me (**3l**)	**4r**	56
10	4-MeO (**3m**)	**4s**	73
11	5,6-Me_2 (**3n**)	**4t**	53

[a]Reactions were performed with **2a** (0.1 mmol), **3** (0.25 mmol), (4-$FC_6H_4)_3P$ (0.1 mmol), Cs_2CO_3 (1.0 mmol) and 4 Å MS (80 mg) in $PhCF_3$ (2.0 mL) at 50 °C for 12 h. [b]Isolated yield.

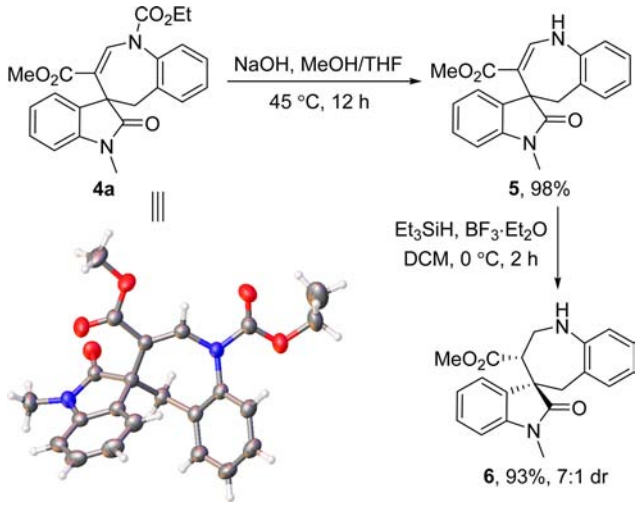
Scheme 3. Reaction of Ethyl [3-(Chloromethyl)naphthalen-2-yl]-carbamate 3o



that the precursor of aza-diene was not limited to *N*-(*ortho*-chloromethyl)phenyl amides.

As illustrated in Scheme 4, the structure of [4 + 3] cycloaddition product **4a** was unambiguously identified by X-ray analysis.[17] Additionally, the *N*-CO_2Et group of cycloadduct **4a** could be easily and chemoselectively removed with NaOH in a mixture of MeOH and THF, and product **5** was produced in an almost quantitative yield. Moreover, the enamine functionality of **5** could be further reduced with Et_3SiH and $BF_3{\cdot}OEt_2$, giving tetrahydrospiro[benzo[*b*]azepine-4,3′-indoline] **6** in a high yield and with good diastereoselectivity.

Scheme 4. Transformations of Product 4a



In summary, we have developed a challenging and efficient method for rapid construction of aza-spirocycloheptane oxindole frameworks through a new [4 + 3] cycloaddition reaction between *N*-(*ortho*-chloromethyl)aryl amides and bromo-substituted MBH adducts derived from isatins, employing tertiary phosphine and Cs_2CO_3 as the promoters. This process relies on the *in situ* generation of allylic phosphonium ylides facilitated by a Lewis base and Brønsted base, and aza-*o*-quinone methides via Brønsted base mediated elimination. Moreover, the cycloadduct could be further transformed to tetrahydrospiro[benzo[*b*]azepine-4,3′-indoline] architecture through simple deprotection and reduction under mild conditions. Currently, more attempts to develop an asymmetric [4 + 3] cycloaddition process are under investigation in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02279.

Complete experimental procedures and characterization of new products; NMR spectra (PDF)

Crystallographic data for cycloadduct **4a** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the NSFC (21122056, 21321061, and 21572135) and Program for Changjiang Scholars and Innovative Research Team in University (IRT13031).

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(16) For more details, see the Supporting Information.

(17) CCDC-1421940 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.orglett.5b02279
Org. Lett. 2015, 17, 4750−4753