

Phosphine-Catalyzed Highly Enantioselective [3 + 3] Cycloaddition of Morita–Baylis–Hillman Carbonates with C,N-Cyclic Azomethine Imines

Lei Zhang, Honglei Liu, Guanyu Qiao, Zhanfeng Hou, Yang Liu, Yumei Xiao, and Hongchao Guo*

Department of Applied Chemistry, China Agricultural University, Beijing 100193, P. R. China

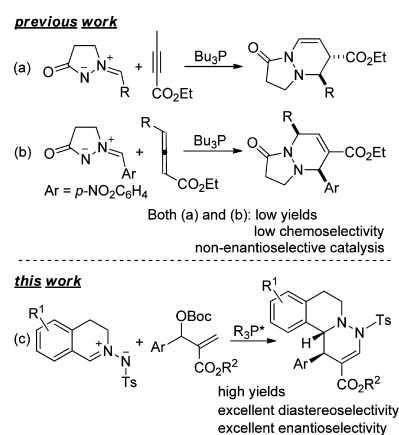
S Supporting Information

ABSTRACT: The first phosphine-catalyzed highly enantioselective [3 + 3] cycloaddition of Morita–Baylis–Hillman carbonates with C,N-cyclic azomethine imines is described. Using a spirocyclic chiral phosphine as the catalyst, a novel class of pharmaceutically interesting 4,6,7,11b-tetrahydro-1*H*-pyridazino[6,1-*a*]iso-quinoline derivatives were obtained in high yields with good to excellent diastereoselectivities and extremely excellent enantioselectivities (98–>99% ee).

Nucleophilic phosphine-catalyzed annulation reaction is one of the most powerful tools for the synthesis of a wide range of synthetically useful or biologically important carbocyclic and heterocyclic compounds¹ and total synthesis of natural products.² In the past decade, chiral phosphine-catalyzed asymmetric annulation reactions have attracted much attention, and a variety of asymmetric reactions including [2 + 2],³ [3 + 2],⁴ [4 + 1],⁵ [4 + 2],⁶ and other annulations⁷ have been developed.^{1g–k} Among various annulation reactions, phosphine-catalyzed [3 + 3] annulations provide a very useful alternative tool to the [4 + 2] annulation reactions for the synthesis of biologically significant six-membered carbocycles and heterocycles. However, this type of reactions has received little attention and met with limited success.⁸ Particularly, to the best of our knowledge, phosphine-catalyzed enantioselective [3 + 3] cycloaddition has never been achieved.

Nucleophilic phosphine-catalyzed annulations generally proceed via phosphonium (di)enolate zwitterions, which were formed through nucleophilic attack of the phosphine catalysts at activated alkenes, allenes, alkynes, or Morita–Baylis–Hillman (MBH) carbonates.¹ When this reaction intermediate acts as three-membered synthon to react with a three-membered electrophilic coupling partner, the [3 + 3] annulation might occur. In our previous work (Scheme 1), employing a 1,3-dipole as the electrophilic coupling partner, we developed the phosphine-catalyzed [3 + 3] cycloaddition of N,N'-cyclic azomethine imines and allenates or 2-butyrate to produce tetrahydropyrazolopyridazinone derivatives.^{8d,e} In these two reactions, phosphonium (di)enolate zwitterions act as a three- and two-carbon synthon, and the competing [3 + 3] and [3 + 2] cycloadditions concurrently proceed, leading to very low chemoselectivity and poor yields for [3 + 3] cycloadducts. In order to overcome this problem, the formation of a reaction intermediate that only functions as a three-carbon synthon will be quite important for achieving highly selective [3 + 3]

Scheme 1. Phosphine-Catalyzed [3 + 3] Cycloadditions of Azomethine Imines



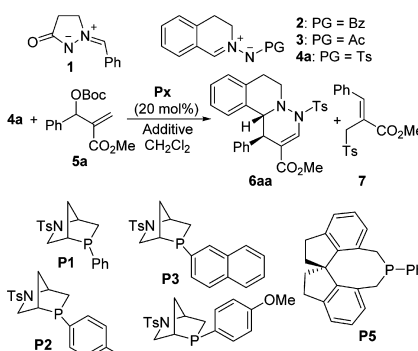
cycloaddition. Generally, phosphonium enolate zwitterions from MBH carbonates often work as a three-membered synthon; therefore, MBH carbonates could be an ideal reaction partner for [3 + 3] annulation. As a kind of readily accessible substrate, MBH carbonates have extensively been used in organocatalysis for the formation of C–C or C–heteroatom bonds.⁹ In particular, in nucleophilic phosphine catalysis, with phosphonium enolate zwitterions formed from MBH carbonates as a three-carbon synthon, a variety of phosphine-catalyzed annulation reactions, such as [3 + 2],¹⁰ [3 + 3],^{8b} [3 + 4],¹¹ and [3 + 6]¹² annulations, have been developed.¹³ On the basis of these reactions, we pondered that under phosphine catalysis conditions, when MBH carbonates meet with azomethine imines, phosphine-catalyzed [3 + 3] annulation will be achieved (Scheme 1). Herein, we report the first phosphine-catalyzed enantioselective [3 + 3] cycloaddition of MBH carbonates with C,N-cyclic azomethine imines to give a novel class of dinitrogen-fused heterocycles combining the biologically important tetrahydroisoquinoline core and pyridazine core.¹⁴

Azomethine imines are a kind of readily accessible and stable 1,3-dipole and have been extensively applied in metal-catalyzed and organocatalytic 1,3-dipolar cycloadditions.¹⁵ In our initial attempt, we first examined the reaction of N,N'-cyclic azomethine imine (**1**) with MBH carbonate (**5a**) in the presence of various achiral phosphines, but no desired product was

Received: February 2, 2015

observed. We then turned our attention to C,N-cyclic azomethine imines **2–4**; **2** has been used in phosphine-catalyzed [3 + 2] and [4 + 3] cycloadditions with allenates.^{4u,15l} Unfortunately, no matter which achiral phosphine was employed as the catalyst, when the reaction of azomethine imine **2** or **3** with MBH carbonate **5a** was carried out in dichloromethane at rt, the thermal [3 + 2] cycloaddition of azomethine imine **2** with alkene always controlled the reaction process,¹⁶ and the desired phosphine-catalyzed [3 + 3] cycloadduct was obtained in <20% yield. To our delight, using 20 mol % of Me₂PPh as the catalyst, the reaction of azomethine imine **4a** with MBH carbonate **5a** proceeded smoothly in dichloromethane at rt for 13 h to give the [3 + 3] cycloadduct **6aa** in 84% yield with >20:1 dr. Next, employing several commercially available cyclic chiral phosphines (**P1–P5**), we explored the asymmetric reaction between azomethine imine **4a** and MBH carbonate **5a** (Table 1).

Table 1. Screening of the Reaction Conditions for Asymmetric Catalysis^a



entry	Px	additive	T/°C	t/h	yield (%) ^b	ee (%) ^c
1	P1	—	rt	22	36	6
2	P2	—	rt	22	48	0
3	P3	—	rt	22	33	0
4	P4	—	rt	22	0	—
5	P5	—	rt	8	49	>99
6	P5	4 Å MS	rt	8	56	>99
7	P5	4 Å MS	0	21	62	>99
8	P5	4 Å MS	−10	36	79	>99
9	P5	4 Å MS, K ₂ CO ₃	−10	36	81	>99
10 ^d	P5	4 Å MS, K ₂ CO ₃	−10	24	87	>99

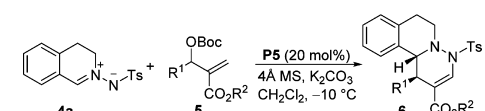
^aUnless otherwise stated, all reactions were carried out with **4a** (0.1 mmol), **5a** (0.12 mmol), 4 Å MS (100 mg), K₂CO₃ (0.15 mmol), and catalyst (0.02 mmol) in CH₂Cl₂ (2 mL). ^bIsolated yield. ^cDetermined by chiral HPLC analysis. dr is >20:1, determined by ¹H NMR analysis of the crude product. ^d0.2 mmol of **5a** was used.

The phosphines (**P1–P4**) displayed weak catalytic capability for this [3 + 3] cycloaddition. In the presence of this kind of phosphines, a racemic or nearly racemic desired product was obtained in poor yields (entries 1–4), and an unexpected Ts addition product (**7**) was also observed.¹⁶ Since chiral phosphine **P5** has showed good capability in asymmetric organocatalysis,^{6e,7f,10e,i} especially because its alkyl analogue could catalyze the asymmetric [3 + 2] cycloaddition of azomethine imine with allenates,^{8d} **P5** was tried. Delightfully, the product **6aa** was obtained in 49% yield and >99% ee, (entry 5). Since an extremely excellent ee had been obtained, we then focused on improving the yield through screening various reaction conditions. Using 4 Å MS as the additive, the yield was slightly increased to 56% (entry 6). Lowering the reaction temperature could effectively

improve the yield, as a result of suppressing the formation of byproduct **7** (entries 7–8). The use of K₂CO₃ resulted in a slight increase in yield (entry 9).¹⁷ Finally, increasing the loading of MBH carbonate **5a** to 2 equiv led to a satisfactory 87% yield (entry 10). On the basis of the above-mentioned results, the optimized conditions are as follows: reaction of **4a** with 2 equiv of **5a** in CH₂Cl₂ at −10 °C in the presence of 20 mol % of **P5**, 1.5 equiv of K₂CO₃, and 4 Å MS.

Under the optimized reaction conditions, we explored the substrate scope of MBH carbonates in this asymmetric [3 + 3] cycloaddition (Table 2). A variety of MBH carbonates bearing

Table 2. Scope of MBH Carbonates in Asymmetric Catalysis^a



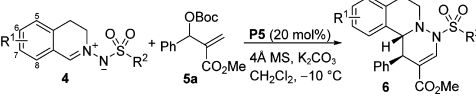
entry	R ¹ /R ²	t/h	6	yield (%) ^b	ee (%) ^c
1	Ph/Me (5a)	24	6aa	87	>99
2	2-FC ₆ H ₄ /Me (5b)	24	6ab	68	>99
3	3-FC ₆ H ₄ /Me (5c)	26	6ac	87	>99
4	4-FC ₆ H ₄ /Me (5d)	24	6ad	80	>99
5	2-ClC ₆ H ₄ /Me (5e)	24	6ae	71	>99 ^d
6	3-ClC ₆ H ₄ /Me (5f)	26	6af	85	>99
7	4-ClC ₆ H ₄ /Me (5g)	24	6ag	80	>99
8	3-BrC ₆ H ₄ /Me (5h)	24	6ah	85	>99
9	4-BrC ₆ H ₄ /Me (5i)	25	6ai	90	>99
10	3-NO ₂ C ₆ H ₄ /Me (5j)	26	6aj	86	>99
11	4-NO ₂ C ₆ H ₄ /Me (5k)	26	6ak	77	>99
12	3-CF ₃ C ₆ H ₄ /Me (5l)	25	6al	84	>99
13	3-CNC ₆ H ₄ /Me (5m)	26	6am	93	>99
14	3,4-2ClC ₆ H ₃ /Me (5n)	26	6an	93	98
15	3,5-2ClC ₆ H ₃ /Me (5o)	25	6ao	95	>99
16	3,4,5-3FC ₆ H ₂ /Me (5p)	21	6ap	63	>99
17	3-MeC ₆ H ₄ /Me (5q)	26	6aq	88	>99
18	4-MeC ₆ H ₄ /Me (5r)	26	6ar	80	>99
19	3-OMeC ₆ H ₄ /Me (5s)	26	6as	72	>99
20	4-OMeC ₆ H ₄ /Me (5t)	26	6at	70	>99
21	4- <i>i</i> -PrC ₆ H ₄ /Me (5u)	26	6au	75	>99
22	2-naphthyl/Me (5v)	26	6av	89	>99
23	2-thienyl/Me (5w)	30	6aw	61	>99
24	Et/Me (5x)	24	6ax	0	—
25	Ph/Et (5y)	24	6ay	81	>99
26	Ph/Bn (5z)	24	6az	72	>99

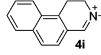
^aUnless otherwise stated, all reactions were carried out with **4a** (0.1 mmol), **5** (0.2 mmol), 4 Å MS (100 mg), K₂CO₃ (0.15 mmol), and catalyst (0.02 mmol) in CH₂Cl₂ (2 mL) at −10 °C. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. Unless otherwise stated, dr is >20:1, determined by ¹H NMR analysis of the crude product. ^ddr = 6:1.

different aromatic groups, regardless of the steric and electronic properties of the substituents on the aromatic ring, underwent the reaction to give the corresponding products in 63–95% yield with extremely excellent enantioselectivities (98–>99% ee) (entries 1–21). Except for the product **6ae** from 2-ClC₆H₄-substituted MBH carbonate (**5e**) (entry 5), other products were obtained in excellent diastereoselectivities (>20:1 dr). Notably, 2-naphthyl- and 2-thienyl-substituted MBH carbonates (**5v** and **5w**) also worked efficiently in this reaction, affording the corresponding products with satisfactory yields and excellent ee values (entries 22–23). Moreover, varying the ester moiety of

MBH carbonates could be tolerated, and excellent enantioselectivities were maintained (entries 25–26). Unfortunately, the alkyl-substituted MBH carbonates are not compatible substrates, and the desired [3 + 3] cycloadducts could not be obtained under the current system (entry 24). The absolute configurations of the [3 + 3] cycloadducts were assigned by X-ray crystallographic analysis of **6ao** and **6ea** (see Table 3).¹⁸

Table 3. Scope of C,N-Cyclic Imines (4**) in Asymmetric Catalysis^a**



entry	4 (R ¹ /R ²)	t/h	6	yield (%) ^b	ee (%) ^c
1	5-Me/4-MeC ₆ H ₄ (4b)	26	6ba	84	>99
2	7-Me/4-MeC ₆ H ₄ (4c)	26	6ca	75	>99
3	7-OMe/4-MeC ₆ H ₄ (4d)	21	6da	76	>99
4	7-Cl/4-MeC ₆ H ₄ (4e)	26	6ea	72	>99
5	5-Br/4-MeC ₆ H ₄ (4f)	21	6fa	72	>99
6	6-Br/4-MeC ₆ H ₄ (4g)	28	6ga	66	>99
7	7-Br/4-MeC ₆ H ₄ (4h)	25	6ha	71	>99
8	 (4i)	21	6ia	86	98
9	H/Ph (4j)	26	6ja	70	>99
10	H/4- <i>n</i> -PrC ₆ H ₄ (4k)	26	6ka	67	>99
11	H/4- <i>t</i> -BuC ₆ H ₄ (4l)	26	6la	74	>99

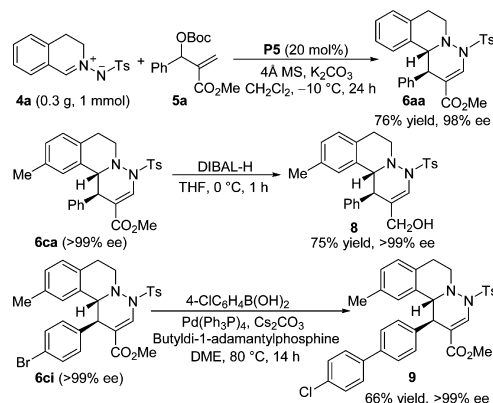
^aUnless otherwise stated, all reactions were carried out with **4** (0.1 mmol), **5a** (0.2 mmol), 4 Å MS (100 mg), K₂CO₃ (0.15 mmol), and catalyst (0.02 mmol) in CH₂Cl₂ (2 mL) at −10 °C. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. dr is >20:1, determined by ¹H NMR analysis of the crude product.

We then examined the substrate scope of azomethine imines (Table 3). An array of azomethine imines, irrespective of methyl, methoxy, and halogen substituents on the aromatic ring, reacted well with **5a** to produce the corresponding products in reasonable yields with excellent diastereoselectivities and extremely excellent enantioselectivities (entries 1–7). Condensed-ring azomethine imine (**4i**) was also compatible with current reaction conditions, affording the tetracyclic product **6ia** in 86% yield and 98% ee (entry 8). The steric bulk of the substituent at the 4-position of the phenyl ring of arylsulfonyl protecting group had no significant influence on stereoselectivity, and the corresponding cycloadducts were obtained in high yields with uniformly excellent diastereo- and enantioselectivities (entries 9–11).

It is worth noting that the present catalytic system is quite robust, allowing the reaction to be performed on the 1 mmol scale without significant loss of diastereoselectivity, enantioselectivity, and yield. (Scheme 2). The cycloadducts could be further transformed to other synthetically or biologically useful heterocyclic compounds (Scheme 2). Treatment of the product **6ca** with DIBAL-H in THF at 0 °C for 1 h led to the reduction of the ester group, giving the alcohol **8** in 75% yield and >99% ee. In the presence of Pd(Ph₃P)₄, the cycloadduct **6ci** bearing a bromine atom at the aromatic moiety underwent a coupling reaction to afford chiral biphenyl heterocyclic compound **9** in 66% yield and >99% ee.

In summary, the first phosphine-catalyzed enantioselective [3 + 3] annulation of C,N-cyclic azomethine imines with MBH carbonates has been achieved, providing 1,2-dinitrogen-containing heterocycles in high yields with good to excellent diastereoselectivities and extremely excellent enantioselectivities.

Scheme 2. Synthetic Transformations of the Cycloadducts



A variety of MBH carbonates could undergo the reaction with azomethine imines under mild reaction conditions. Moreover, the reaction could be scaled up without significant loss of diastereo- and enantioselectivity and yield. These merits make the reaction a very valuable method for the synthesis of biologically important chiral 1,6,7,11b-tetrahydro-4H-pyridazino[6,1-a]isoquinoline derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data, and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*hchguo@cau.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the NSFC (21172253 and 21372256).

■ REFERENCES

- (1) For selected reviews on phosphine-promoted annulations, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (d) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069. (e) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (f) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. (g) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (h) Wang, S.-X.; Han, X. Y.; Zhong, F. R.; Wang, Y. Q.; Lu, Y. X. *Synlett* **2011**, 2766. (i) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, 48, 1724. (j) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927. (k) Xiao, Y. M.; Sun, Z. H.; Guo, H. C.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089.
- (2) (a) Wang, J. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (b) Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737. (c) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289. (d) Koech, P. K.; Krische, M. J. *Tetrahedron* **2006**, *62*, 10594. (e) Webber, P.; Krische, M. J. *J. Org. Chem.* **2008**, *73*, 9379. (f) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849. (g) Sampath, M.; Lee, P.-Y. B.; Loh, T. P. *Chem. Sci.* **2011**, *2*, 1988. (h) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510. (i) Villa, R. A.; Xu, Q. H.; Kwon, O. *Org. Lett.* **2012**, *14*, 4634. (j) Barcan, G. A.; Patel, A.; Houk, K. N.; Kwon, O. *Org. Lett.* **2012**, *14*, 5388.
- (3) (a) Ibrahim, A. A.; Wei, P. H.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2010**, *75*, 7901. (b) Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, *14*, 1784.

- (4) (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (b) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (c) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (d) Voituriez, A.; Panossian, A.; Fleury-Bregeot, N.; Retaillieu, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (e) Fang, Y. Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660. (f) Voituriez, A.; Panossian, A.; Fleury-Bregeot, N.; Retaillieu, P.; Marinetti, A. *Adv. Synth. Catal.* **2009**, *351*, 1968. (g) Sampath, M.; Loh, T. P. *Chem. Commun.* **2009**, *45*, 1568. (h) Voituriez, A.; Pinto, N.; Neel, M.; Retaillieu, P.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 12541. (i) Pinto, N.; Neel, M.; Panossian, A.; Retaillieu, P.; Frison, G.; Voituriez, A.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 1033. (j) Sampath, M.; Loh, T. P. *Chem. Sci.* **2010**, *1*, 739. (k) Xiao, H.; Chai, Z.; Zheng, C. W.; Yang, Y. Q.; Liu, W.; Zhang, J. K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467. (l) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293. (m) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726. (n) Pinto, N.; Retaillieu, P.; Voituriez, A.; Marinetti, A. *Chem. Commun.* **2011**, *47*, 1015. (o) Duvvuru, D.; Pinto, N.; Gomez, C.; Betzer, J.-F.; Retaillieu, P.; Voituriez, A.; Marinetti, A. *Adv. Synth. Catal.* **2012**, *354*, 408. (p) Zhao, Q.; Han, X.; Wei, Y.; Shi, M.; Lu, Y. *Chem. Commun.* **2012**, *48*, 970. (q) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767. (r) Steurer, M.; Jensen, K. L.; Worgull, D.; Jørgensen, K. A. *Chem.—Eur. J.* **2012**, *18*, 76. (s) Marco-Martinez, J.; Marcos, V.; Reboredo, S.; Filippone, S.; Martin, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5115. (t) Zhang, X.-N.; Shi, M. *ACS Catal.* **2013**, *3*, 507. (u) Wang, D.; Lei, Y.; Wei, Y.; Shi, M. *Chem.—Eur. J.* **2014**, *20*, 15325. (v) Henry, C. E.; Xu, Q. H.; Fan, Y. C.; Martin, T. J.; Belding, L.; Dudding, T.; Kwon, O. *J. Am. Chem. Soc.* **2014**, *136*, 11890. (5) (a) Zhang, X. N.; Deng, H. P.; Huang, L.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 8664. (b) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183. (c) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643. (d) Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, DOI: 10.1021/jacs.5b01944. (6) (a) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (b) Xiao, H.; Chai, Z.; Wang, H. F.; Wang, X. W.; Cao, D. D.; Liu, W.; Lu, Y. P.; Yang, Y. Q.; Zhao, G. *Chem.—Eur. J.* **2011**, *17*, 10562. (c) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231. (d) Xiao, H.; Chai, Z.; Cao, D.; Wang, H.; Chen, J.; Zhao, G. *Org. Biomol. Chem.* **2012**, *10*, 3195. (e) Takizawa, S.; Arteaga, F. A.; Yoshida, Y.; Suzuki, M.; Sasai, H. *Asian J. Org. Chem.* **2014**, *3*, 412. (7) (a) Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2225. (b) Ye, L. W.; Wang, S. B.; Wang, Q. G.; Sun, X. L.; Tang, Y.; Zhou, Y. G. *Chem. Commun.* **2009**, *45*, 3092. (c) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9725. (d) Shi, Z.; Yu, P.; Loh, T. P.; Zhong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7825. (e) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 943. (f) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2525. (8) (a) Guo, H.; Xu, Q.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318. (b) Zheng, S.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 4532. (c) Hu, J.; Dong, W.; Wu, X.-Y.; Tong, X. *Org. Lett.* **2012**, *14*, 5530. (d) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (e) Liu, J.; Liu, H.; Na, R.; Wang, G.; Li, Z.; Yu, H.; Wang, M.; Zhong, J.; Guo, H. *Chem. Lett.* **2012**, *41*, 218. (9) (a) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101. (b) Rios, R. *Catal. Sci. Technol.* **2012**, *2*, 267. (10) (a) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (b) Feng, J.; Lu, X.; Kong, A.; Han, X. *Tetrahedron* **2007**, *63*, 6035. (c) Zheng, S.; Lu, X. *Org. Lett.* **2008**, *10*, 4481. (d) Selvakumar, K.; Vaithyanathan, V.; Shanmugam, P. *Chem. Commun.* **2010**, *46*, 2826. (e) Wang, Q.-G.; Zhu, S.-F.; Ye, L.-W.; Zhou, C.-Y.; Sun, X.-L.; Tang, Y.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, *352*, 1914. (f) Deng, H. P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348. (g) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (h) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (i) Wang, D.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 2764. (j) Zhong, F.; Chen, G.; Han, X.; Yao, W.; Lu, Y. *Org. Lett.* **2012**, *14*, 3764. (k) Deng, H.-P.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2012**, *354*, 783. (l) Hu, F.; Wei, Y.; Shi, M. *Tetrahedron* **2012**, *68*, 7911. (m) Zhang, L.; Yu, H.; Yang, Z.; Liu, H.; Li, Z.; Guo, J.; Xiao, Y.; Guo, H. *Org. Biomol. Chem.* **2013**, *11*, 8235. (11) (a) Zheng, S.; Lu, X. *Org. Lett.* **2009**, *11*, 3978. (b) Zhou, R.; Wang, J.; Duan, C.; He, Z. *Org. Lett.* **2012**, *14*, 6134. (12) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987. (13) For other annulation reactions, see: (a) Xie, P.; Huang, Y.; Chen, R. *Org. Lett.* **2010**, *12*, 3768. (b) Chen, Z.; Zhan, J. *Chem.—Asian J.* **2010**, *5*, 1542. (c) Tian, J.; Zhou, R.; Sun, H.; Song, H.; He, Z. *J. Org. Chem.* **2011**, *76*, 2374. (d) Xie, P.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2012**, *18*, 7362. (e) Xie, P.; Li, E.; Zheng, J.; Li, X.; Huang, Y.; Chen, R. *Adv. Synth. Catal.* **2013**, *355*, 161. (14) For bioactivities of isoquinoline and pyridazine derivatives, see: (a) Sato, J.; Fukuda, K.; Ito, K.; Suzuki, K.; Nawamaki, T.; Watanabe, S. *JP 03063278* [*Chem. Abstr.* **1991**, *115*, 273451]. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (c) Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545. (d) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (e) Bentley, K. W. *Nat. Prod. Rep.* **2005**, *22*, 249. (f) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444. (g) Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676. (h) Pulka, K. *Curr. Opin. Drug Discovery Devel.* **2010**, *13*, 669. (i) Vincenzi, B.; Napolitano, A.; Frezza, A. M.; Schiavon, G.; Santini, D.; Tonini, G. *Pharmacogenomics* **2010**, *11*, 865. (j) Carter, N. J.; Keam, S. J. *Drugs* **2010**, *70*, 355. (15) For a review, see: (a) Qiu, G.; Kuang, Y.; Wu, J. *Adv. Synth. Catal.* **2014**, *356*, 3483. For selected examples, see: (b) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (c) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (d) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (e) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (f) Shintani, R.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12356. (g) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (h) Shapiro, N. D.; Shi, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 11654. (i) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076. (j) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3489. (k) Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049. (l) Jing, C.; Na, R.; Wang, B.; Liu, H.; Zhang, L.; Liu, J.; Wang, M.; Zhong, J.; Kwon, O.; Guo, H. *Adv. Synth. Catal.* **2012**, *354*, 1023. (m) Li, J. T.; Lian, X. J.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2013**, *19*, 5134. (n) Qian, Y.; Zavalij, P. J.; Hu, W. H.; Doyle, M. P. *Org. Lett.* **2013**, *15*, 1564. (o) Xu, X. F.; Xu, X. C.; Zavalij, P. Y.; Doyle, M. P. *Chem. Commun.* **2013**, *49*, 2762. (p) Zhou, Y.-Y.; Li, J.; Ling, L.; Liao, S.-H.; Sun, X.-L.; Li, Y.-X.; Wang, L.-J.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1452. (q) Tong, M.-C.; Chen, X.; Tao, H.-Y.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12377. (r) Xu, X.; Zavalij, P. Y.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12664. (s) Guo, H.; Liu, H.; Zhu, F.-L.; Na, R.; Jiang, H.; Wu, Y.; Zhang, L.; Li, Z.; Yu, H.; Wang, B.; Xiao, Y.; Hu, X.-P.; Wang, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12641. (t) Li, Z.; Yu, H.; Liu, H.; Zhang, L.; Jiang, H.; Wang, B.; Guo, H. *Chem.—Eur. J.* **2014**, *20*, 1731. (u) Li, W.; Jia, Q.; Du, Z.; Zhang, K.; Wang, J. *Chem.—Eur. J.* **2014**, *20*, 4559. (16) For the structure of the thermal cycloaddition product, see the Supporting Information. For a discussion on the formation of side product 7, see: (a) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2003**, *44*, 4673. (b) Chandrasekhar, S.; Saritha, B.; Jagadeeshwer, V.; Narsihmulu, C.; Vijay, D.; Sarma, G. D.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 2981. (c) Li, H.-H.; Dong, D.-J.; Jin, Y.-H.; Tian, S.-K. *J. Org. Chem.* **2009**, *74*, 9501. (d) Karnakar, K.; Shankar, J.; Murthy, S. N.; Nageswar, Y. V. D. *Helv. Chim. Acta* **2011**, *94*, 875. (e) Li, X. Q.; Xu, S. S.; Tang, Y. C. *Org. Biomol. Chem.* **2013**, *11*, 1739. (17) The base may help form phosphonium enolate zwitterions from MBH carbonates. (18) Crystallographic data for **6a** and **6ea** have been deposited with the Cambridge Crystallographic Data Centre as deposition numbers CCDC 1041720 and 1041719, respectively.