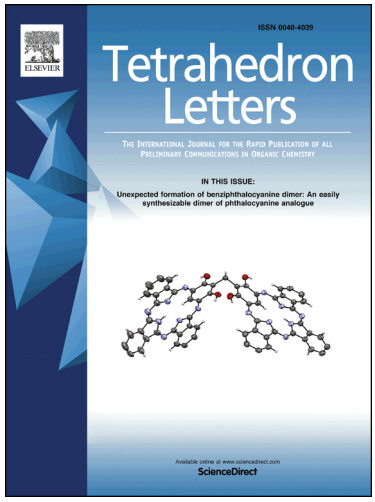

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Thermally induced reaction of diazoamides with isatins: a complementary approach to the 3,3'-bioxindole derivatives

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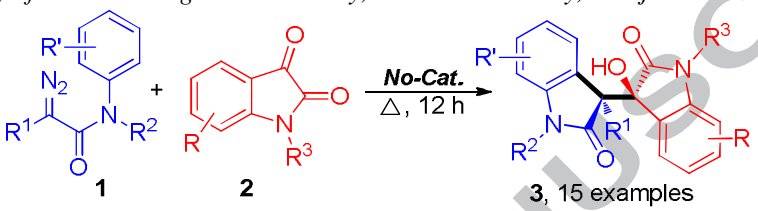

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Thermally induced reaction of diazoamides with isatins: a complementary approach to the 3,3'-bioxindole derivatives

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ABSTRACT

An efficient and thermally induced reaction of diazoamide with isatin under mild reaction conditions is described, which provides a complementary approach to the 3,3'-bioxindole in high yields with excellent diastereoselectivity. In comparison to the metal-catalyzed versions, this is the only example under catalyst-free conditions *via* a non-carbene reaction pathway.

1. Introduction

Bioxindole is a useful synthon in synthetic organic chemistry,[1] and this moiety is prevalently existing as an important structural unit in complex natural products and pharmaceutical agents (Fig. 1).[2] Thus, the development of efficient approaches for the construction of bioxindole skeletons is of continuing interest in organic synthesis. Generally, they are prepared via formal homodimerization[3] or heterodimerization[4] of isatin derivatives. For example, in 2008, Overman disclosed an effective method for the synthesis of 3-hydroxy-3,3'-bioxindoles via a two-step process, including enolization and following Lewis-acid-promoted Mukaiyama aldol addition (Scheme 1a).[5] Recently, Hu's group reported a straightforward access to the bioxindole derivatives by trapping the zwitterionic intermediate (Scheme 1b, **B**) with isatin[6a] or other electrophiles.[6b-e] Later, the ylide trapping reaction[7] with isatins was expanded by Shi[8] and Muthusamy[9] independently, which also directly produced the bioxindole derivatives selectively. These efficient approaches have emerged as promising and economically attractive alternative for the construction of bioxindole frameworks; however, the reactions require the expensive dirhodium catalyst. In particular, in the preparation of pharmaceuticals or their candidates, the development of novel strategy involving the use of inexpensive, non-toxic, or no transition-metal catalyst under environmentally benign conditions is highly desirable.

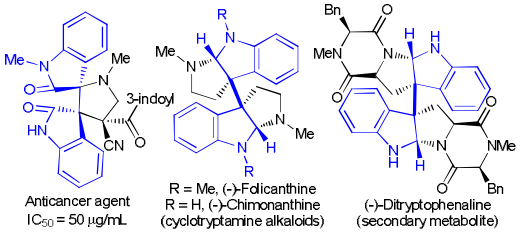
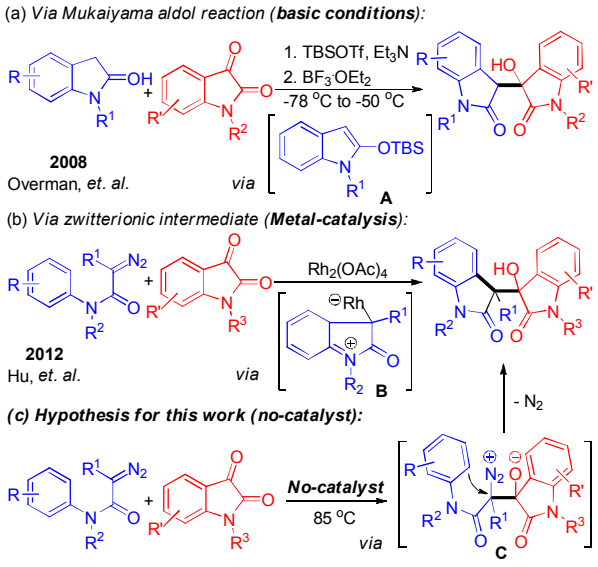


Figure 1. Representative bio-active compounds containing bioxindole unit.

In contrast to the traditional reactions involving metal carbene,[10] the metal-carbene-free transformation of diazo compounds has emerged as a complementary paradigm recently,[11] and these reactions have shown unique merits in experimental simplicity and under mild reaction conditions. For example, the carbon of the diazo group could act as a synthetic equivalent of a 1,1-dipole for the *gem*-difunctionalization, which will react with the electrophile to form a diazonium ion intermediate, and then can be intercepted by a nucleophile.[12-17] In this context, electrophilic reagents, including proton, [11c,12] organoboron reagents,[13] carbonyl compounds,[14] imines[15] and α,β-unsaturated carbonyl compounds[16] have been investigated. Recently, Zhu,[17a] Huang,[17b] Hu[17c] and our group[17d,17e] have independently disclosed that the halogenic cation could be used as the electrophile in this transformation. Inspired by these works and as a continuation of our own interest in this area, herein, we report a thermally induced reaction of isatin with diazoamide, which provides a novel approach for the direct construction of



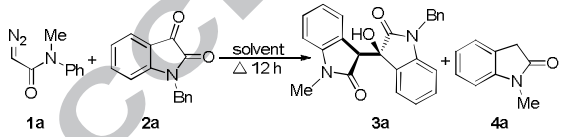
Scheme 1. General accesses to the 3,3'-bioxindole skeletons.

bioxindole derivatives under catalyst-free conditions. In comparison to the reported significant achievement in catalytic non-carbene transformations of diazo compounds with carbonyl compounds, including epoxidation disclosed by Gong,[14a] and formal insertion reactions reported by Ryu[14b-14d] and Feng[14e-14g] independently, we envisaged an non-carbene pathway via the diazonium ion intermediate **C** followed by intramolecular Friedel–Crafts alkylation for the synthesis of bioxindoles (Scheme 1c).

2. Results and Discussion

Initially, we investigated the reaction of *N*-methyl-*N*-phenyl diazoamide (**1a**) and *N*-benzyl isatin (**2a**) under thermal conditions. Solvents were screened at 70 °C, and trifluorotoluene ($PhCF_3$) was found superior to the other solvents and gave the desired product in 55 % isolated yield (Table 1, entry 1-4). In the reaction with acetonitrile, the byproduct **4a** was isolated in 60% yield, which was generated from the the Pschorr reaction of diazo compound **1a**. Subsequently, the temperature was explored and the best result was obtained in 75% yield at 90 °C with >95:5 *dr*

Table 1. Optimization of the reaction conditions[a].



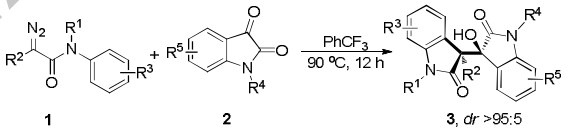
Entry	Solvent	T (°C)	*dr*	Yield of **3a** (%)[b]
1	MeCN	70	**3a**, >95:5	20 (60)[c]
2	THF	70	**3a**, >95:5	51
3	Toluene	70	**3a**, >95:5	52
4	$PhCF_3$	70	**3a**, >95:5	55
5	$PhCF_3$	80	**3a**, >95:5	65
6	$PhCF_3$	90	**3a**, >95:5	75
7	$PhCF_3$	100	**3a**, >95:5	76[d]

[a] The reaction was carried out with **1a** (0.3 mmol) and **2a** (0.15 mmol) in solvent (2.0 mL) for 12 h. The diazoamide **1a** was added as a solution in 1.0 mL of the same solvent via syringe pump in 50 min.
[b] Isolated yields.
[c] Yield of **4a**.
[d] Excess of the diazo compound **1a** was decomposed.

(entry 5-7), which was determined by the proton NMR of the crude reaction mixture (see Figure S4 and S5), and the *syn* configuration of the obtained product **3** was determined according to the reported reference.[6a] Although comparable yield was achieved at higher temperature (entry 7, 100 °C, 76% yield), the diazo compound started to decompose at this point, and it turened out not be easy for the purification. In addition, fully conversion of **1a** to **4a** could be observed in the absence of **2a** under these conditions (see Figure S3).

With the optimized reaction conditions in hand, we next investigate the generality of this thermally induced reaction by exploring the reaction between various diazoamides and isatins (Table 2). The substrates scope was quite general and the substitutions on the nitrogen or on the aromatic ring had little impact on the reaction to give the corresponding products in >72% yields (Table 2, entry 1-9), although temperature adjustment was applied in some cases to achieve high yields (see note c, d and f). Interestingly, water could be used as the solvent in the case with α-methyl diazoamide **1j**, and higher isolated yield was observed for product **3j** compared to the result under standard conditions (entry 10, 83% vs 50%).[18] In addition, these conditions could be expanded to the reaction of **1a** with *N*-unprotected isatin **2b** to produce **3k** in 60% yield (entry 11). The scope of the reaction with respect to isatin **2** was further evaluated. In general, the *N*-methyl isatin **2c** and isatins with electron-donating or electron-withdrawing substituents on the aromatic ring all resulted in good yields with high diastereoselectivities (entries 12-15, **3l**-**3o**).

Table 2. Substrate Scope[a].



Entry	$R^1/R^2/R^3$ (**1**)	R^4/R^5 (**2**)	**3**	Yield (%)[b]
1	Me/H/H (**1a**)	Bn/H (**2a**)	**3a**	75
2	4-BrBn /H/H (**1b**)	Bn/H (**2a**)	**3b**	72
3[c]	4-NO_2Bn/H/H (**1c**)	Bn/H (**2a**)	**3c**	75
4[c]	Et /H/H (**1d**)	Bn/H (**2a**)	**3d**	73
5	Me/H/4-Br (**1e**)	Bn/H (**2a**)	**3e**	72
6	Me/H/4-OMe (**1f**)	Bn/H (**2a**)	**3f**	78
7	Me/H/3-OMe (**1g**)	Bn/H (**2a**)	**3g**	75
8	Me/H/2-OMe (**1h**)	Bn/H (**2a**)	**3h**	76
9[d]	Me/H/4-CF_3 (**1i**)	Bn/H (**2a**)	**3i**	75
10	Me/Me/H (**1j**)	Bn/H (**2a**)	**3j**	50 (83)[e]
11	Me/H/H (**1a**)	H/H (**2b**)	**3k**	60[f]
12	Me/H/H (**1a**)	Me/H (**2c**)	**3l**	82
13	Me/H/H (**1a**)	Bn/5-F (**2d**)	**3m**	78
14	Me/H/H (**1a**)	Bn/5-Me (**2e**)	**3n**	77
15	Me/H/H (**1a**)	Bn/7-CF_3 (**2f**)	**3o**	82

[a] The reaction was carried out with **1** (0.3 mmol) and **2** (0.15 mmol) in $PhCF_3$ (2.0 mL) at 90 °C for 12 h. The diazoamide **1** was added as a solution in 1.0 mL of $PhCF_3$ *via* syringe pump in 50 min.
[b] Isolated yields.
[c] Reaction was carried out at 105 °C.
[d] Reaction was carried out in PhCl (2.0 mL) at 130 °C.
[e] Reaction was carried out in H_2O (2.0 mL) at 90 °C, and all the materials were added in one-time.
[f] Reaction was carried out at 70 °C.

In order to gain insight into the reaction mechanism, control experiments were carried out. When **4a** was used as the starting material, instead of **1a**, under standard conditions, the bioxindole

product **3a** was also obtained in 65% yield (eq 1). This result indicates that an alternative pathway involving indolone as the intermediate, which forms from corresponding diazoamide **1**, is also possibly coexisting in this reaction. Further comparison is carried out between this control reaction of **4a** and the template reaction with **1a** by detecting the conversions at different reaction times. As shown in Figure 2, the template reaction (blue line) gives higher conversions when compared to the results with indolone **4a** (red line) at the same reaction times. Based on these results and previous observations,[17] reaction mechanism through the diazonium ion intermediate **C** followed by an intramolecular Friedel–Crafts alkylation is proposed (Scheme 1c). However, the pathway that through indolone followed by reacting with isatin *via* aldol type addition also contribute to the formation of desired product **3** (see Table S1 and Figure S2). And further studies are needed to unambiguously establish the reaction transformation.

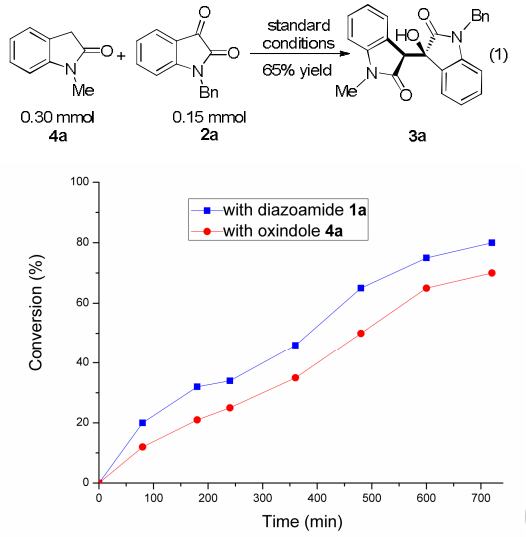


Figure 2 Conversion comparison based on the limited reagent **2a**.

3. Conclusions

In summary, we have developed an efficient and catalyst-free reaction of diazoamide with isatin, which provides a complementary approach to the 3-hydroxy-3,3'-bioxindole in high yields with excellent diastereoselectivity under mild reaction conditions. Mechanistic study indicates that the transformation proceeds through the diazonium ion intermediate followed by an intramolecular Friedel−Crafts alkylation; and that the aldol addition of isatin with oxindole, which is *in situ* formed via thermally-induced Pschorr reaction of diazoamide, is also possible to contribute to the formation of bioxindoles. Further investigations on the reaction mechanism and further applications in the *gem*-difunctionalization of diazo compounds through intercepting the diazonium ion intermediate are currently under way in our laboratory.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://

References and notes

1. (a) Link JT, Overman LE. *J Am Chem Soc.* 1996;118:8166;
(b) Hoyt SB, Overman LE. *Org Lett.* 2000;2:3241;
(c) Pérez-Balado C, Lera de AR. *Org Lett.* 2008;10:3701;
(d) Movassaghi M, Schmidt MA, Ashenhurst JA. *Angew Chem Int Ed.* 2008;47:1485;
(e) Kim J, Movassaghi M. *J Am Chem Soc.* 2010;132:14376;
(f) Ghosh S, Bhunia S, Kakde BN, De S, Bisai A. *Chem Commun.* 2014;50:2434;
(g) Ghosh S, Chaudhuri S, Bisai A. *Chem Eur J.* 2015;21:17479.
2. (a) Reddy CN, Nayak VL, Mani GS, Kapure JS, Adiyala PR, Maurya RA, Kamal A. *Bioorg Med Chem Lett.* 2015;25:4580;
(b) Greiner D, Bonaldi T, Eskeland R, Roemer E, Imhof A. *Nat Chem Biol.* 2005;1:143;
(c) Zhang YX, Chen Y, Guo XN, Zhang XW, Zhao WM, Zhong L, Zhou J, Xi Y, Lin LP, Ding J. *Anti-Cancer Drugs.* 2005;16:515;
(d) Blunt JW, Copp BR, Munro HHG, Northcote PT, Prinsep MR. *Nat Prod Rep.* 2006;23:26;
(e) Kam TS, Choo YM. In The Alkaloids: Chemistry and Biology; Cordell GA. ed. Academic Press, San Diego; 2006;63:181;
(f) Ruis-Sanchis P, Savina SA, Alberecio F, Álvarez M. *Chem Eur J.* 2011;17:1388.
3. (a) Jia WL, He J, Yang JJ, Gao XW, Liu Q, Wu LZ. *J Org Chem.* 2016;81:7172;
(b) Wang L, Zhang Y, Hu HY, Fun HK, Xu JH. *J Org Chem.* 2005;70:3850;
(c) Ghosh S, Chaudhuri S, Bisai A. *Org Lett.* 2015;17:1373;
(d) Overman LE, Peterson EA. *Angew Chem Int Ed.* 2003;42:2525;
(e) Xia PJ, Sun YH, Xiao JA, Zhou ZF, Wen SS, Xiong Y, Ou GC, Chen XQ, Yang H, *J Org Chem.* 2015;80:11573;
(f) Suman K, Srinu L, Thennarasu S. *Org Lett.* 2014;16:3732.
4. (a) Han YY, Chen WB, Han WY, Wu ZJ, Zhang XM. *Org Lett.* 2012;14:490;
(b) Zhao HW, Chen XQ, Yang Z, Tian T, Li B, Meng W, Song XQ, Pang HL. *RSC Adv.* 2015;5:103116;
(c) Xiao JA, Zhang HG, Liang S, Ren JW, Yang H, Chen XQ, *J Org Chem.* 2013;78:11577;
(d) Chen DF, Zhang Cl, Hu Y, Han ZY, Gong LZ. *Org Chem Front.* 2015;2:956;
(e) Liu YL, Wang X, Zhao YL, Zhu F, Zeng XP, Chen L, Wang CH, Zhao XL, Zhou J. *Angew Chem Int Ed.* 2013;52:13735;
(f) Chen DF, Zhao F, Hu Y, Gong LZ. *Angew Chem Int Ed.* 2014;53:10763.
5. Ellis JM, Overman LE, Tanner HR, Wang J. *J Org Chem.* 2008;73:9151.
6. (a) Li M, Zan L, Prajapati D, Hu W. *Org Biomol Chem.* 2012;10:8808;
(b) Jing C, Xing D, Hu W. *Org Lett.* 2015;17:4336;
(c) Jing C, Xing D, Wang C, Hu W. *Tetrahedron.* 2015;71:3597;
(d) Xing D, Jing C, Li X, Qiu H, Hu W. *Org Lett.* 2013;15:3578;
(e) Qiu H, Li M, Jiang LQ, Lv FP, Zan L, Zhai CW, Doyle MP, Hu W. *Nat Chem.* 2012;4:733.
7. Pioneering works in this area: (a) Wang YH, Zhu YX, Chen ZY, Mi AQ, Hu WH, Doyle MP. *Org Lett.* 2003;5:3923;
(b) Wang Y, Chen Z, Mi A, Hu W. *Chem Commun.* 2004;21:2486.
For reviews: (c) Lv F, Liu S, Hu W. *Asian J Org Chem.* 2013;2:824;
(d) Guo X, Hu W. *Acc Chem Res.* 2013;46:2427;
(e) Xing D, Hu W. *Tetrahedron Lett.* 2014;55:777.
8. Mei LY, Tang XY, Shi M. *Org Biomol Chem.* 2014;12:1149.
9. Muthusamy S, Ramkumar R. *Tetrahedron.* 2014;70:5594.
10. For reviews, see: (a) Xu X, Doyle MP. *Acc Chem Res.* 2014;47:1396;
(b) Doyle MP, Forbes DC. *Chem Rev.* 1998;98:911;
(c) Zhao X, Zhang Y, Wang J. *Chem Commun.* 2012;48:10162;
(d) Doyle MP, Duffy R, Ratnikov M, Zhou L. *Chem Rev.* 2010;110:704;
(e) Liu L, Zhang J, *Chem Soc Rev.* 2016;45:506;
(f) Davies HML, Hedley SJ. *Chem Soc Rev.* 2007;361;1109;
(g) Padwa A, *Chem Soc Rev.* 2009;38:3072;
(h) Davies HML, Morton D. *Chem Soc Rev.* 2011;40:1857;
(i) Davies HML, Denton JR, *Chem Soc Rev.* 2009;38:3061;
(j) Xiao Q, Zhang Y, Wang J. *Acc Chem Res.* 2013;46:236;
(k) Zhu S, Zhou QL. *Acc Chem Res.* 2012;45:1365;

(l) Hu F, Xia Y, Ma C, Zhang Y, Wang J, *Chem Commun.* 2015;51:7986.

11. For reviews, see: (a) Ye T, McKervey MA. *Chem Rev.* 1994;94:1091;
(b) Candeias NR, Paterna R, Gois PMP. *Chem Rev.* 2016;116:2937;
(c) Johnston JN, Muchalski H, Troyer TL. *Angew Chem Int Ed.* 2010;49:2290.
12. (a) Miller DJ, Moody CJ, Morffitt CN. *Aust J Chem.* 1999;52:97;
(b) Smith LI, *Chem Rev.* 1938;23:193;
(c) Smith AB, Dieter RK. *Tetrahedron*. 1981;37:2407;
(d) Ryang HS, Foote CS. *Tetrahedron Lett.* 1982;23:2551;
(e) Jones J, Kresge AJ. *J Org Chem.* 1993;58:2658;
(f) Fattori D, Henry S, Vogel P. *Tetrahedron*. 1993;49:1649;
(g) Hashimoto T, Maruoka K. *Bull Chem Soc Jpn.* 2013;86:1217;
(h) Luo X, Chen G, He L, Huang X. *J Org Chem.* 2016;81:2943.
13. (a) Barluenga J, Tomás-Gamasa M, Aznar F, Valdés C. *Nat Chem.* 2009;1:494;
(b) Luan Y, Schaus SE. *Org Lett*. 2011;13:2510;
(c) Luan Y, Yu J, Zhang X, Schaus SE, Wang G. *J Org Chem.* 2014;79:4694;
(d) Allwood DM, Blakemore DC, Brown AD, Ley SV. *J Org Chem.* 2014;79:328;
(e) Peng C, Zhang W, Yan G, Wang J. *Org Lett.* 2009;11:1667;
(f) Li H, Wang L, Zhang Y, Wang J. *Angew Chem Int Ed.* 2012;51:2943;
(g) Li H, Shangguan X, Zhang Z, Huang S, Zhang Y, Wang J. *Org Lett.* 2014;16:448.
14. (a) Liu WJ, Lv BD, Gong LZ. *Angew Chem Int Ed.* 2009;48:6503;
(b) Kang BC, Nam DG, Hwang GS, Ryu DH. *Org Lett.* 2015;17:4810;
(c) Gao L, Kang BC, Hwang GS, Ryu DH. *Angew Chem Int Ed.* 2012;51:8322;
(d) Gao L, Kang BC, Ryu DH. *J Am Chem Soc.* 2013;135:14556;
(e) Li W, Tan F, Hao X, Wang G, Tang Y, Liu X, Lin L, Feng X. *Angew Chem Int Ed.* 2015;54:1608;
(f) Li W, Wang J, Hu X, Shen K, Wang W, Chu Y, Lin L, Liu X, Feng X. *J Am Chem Soc.* 2010;132:8532;
(g) Li W, Liu X, Tan F, Hao X, Zheng J, Lin L, Feng X. *Angew Chem Int Ed.* 2013;52:10883.
15. (a) Hashimoto T, Nakatsu H, Yamamoto K, Maruoka K. *J Am Chem Soc.* 2011;133:9730;
(b) Williams AL, Johnston JN. *J Am Chem Soc.* 2004;126:1612;
(c) Hu G, Gupta AK, Huang RH, Mukherjee M, Wulff WD. *J Am Chem Soc.* 2010;132:14669;
(d) Huang L, Wulff WD. *J Am Chem Soc.* 2011;133:8892;
(e) Akiyama T, Suzuki T, Mori K. *Org Lett*. 2009;11:2445.
16. (a) Lee SI, Kang BC, Hwang GS, Ryu DH. *J Am Chem Soc.* 2013;135:7126;
(b) Lee SI, Kang BC, Hwang GS, Ryu DH. *Org Lett.* 2013;15:1428;
(c) Gao L, Hwang GS, Ryu DH. *J Am Chem Soc.* 2011;133:20708.
17. (a) Mao H, Tang Z, Hu H, Cheng Y, Zheng WH, Zhu C. *Chem Commun.* 2014;50:9773;
(b) Chen G, Song J, Yu Y, Luo X, Li C, Huang X. *Chem Sci.* 2016;7:1786;
(c) Ma C, Xing D, Hu W. *Org Lett.* 2016;18:3134;
(d) Dong K, Yan B, Chang S, Chi Y, Qiu L, Xu X. *J Org Chem.* 2016;81:6887;
(e) Wang X, Dong K, Yan B, Zhang C, Qiu L, Xu X. *RSC Adv.* 2016;6:70221.
18. (a) Paladhi S, Bhati M, Panda D, Dash J. *J Org Chem.* 2014;79:1473;
(b) Thakura PB, Meshram HM. *RSC Adv.* 2014;4:5343;
(c) Duan Z, Zhang Z, Qian P, Han J, Pan Y. *RSC Adv.* 2013;3:10127;
(d) Ramireddy N, Zhao JCG. *Tetrahedron Lett.* 2014;55:706.

Highlights

- Thermally induced reaction of diazoamides with isatins.
- Mild approach to the 3,3'-bioxindole derivatives.
- Good to high yields with excellent diastereoselectivity.
- *gem*-Difunctionalization of diazo compounds via a non-carbene process under catalyst-free conditions.