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Practical and Efficient Iridium Catalysis for Benzannulation: An Entry To Isoindolines

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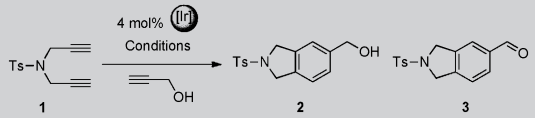
Benzannulation reactions are among the most efficient and direct methods to assemble highly substituted aromatic compounds.[1] Transition metals have proven their synthetic utility in the construction of complex and heavily substituted benzene-derived systems from relatively simple starting materials. The most useful cobalt, nickel, rhodium, and ruthenium catalysts offer the possibility to catalyze [2+2+2] cycloadditions leading to aromatic compounds.[2] However, only a few examples in the literature have demonstrated the use of iridium catalysis.[3] Takeuchi described an iridium-catalyzed (i.e., $[Ir(cod)Cl]_2$/dppe) [2+2+2] cycloaddition of diynes and alkynes to synthesize dihydro-indene and dihydro-isobenzofuran derivatives in benzene or dioxane.[3a] Surprisingly, the iridium-catalyzed [2+2+2] cycloaddition of nitrogen-based diynes and alkynes to access isoindoline scaffolds has been less studied. To the best of our knowledge, synthesis of the isoindoline scaffold via a [2+2+2] iridium-catalyzed cycloaddition has only been described by Shibata et al. in the context of the preparation of atropoenantioenriched complex polyaromatic biaryl structures,[3g–k] or on solid supported systems by Martinez et al.[3b] In the latter report, the role of Takeuchi's catalyst system was explored and the use of microwave irradiation proved essential for access to isoindoline derivatives.

Considering that isoindolines are highly interesting and useful building blocks for the synthesis of biologically active compounds,[4] and owing to the limitation of Takeuchi's catalyst system to access isoindolines, we decided to embark upon the investigation of an efficient iridium-catalyzed benzannulation approach to isoindoline systems. One key point of our study was to use a simple, easy to handle, and air-stable catalyst that would operate in an environmentally and industrially friendly solvent. The second issue was the possibility to introduce functional groups allowing further cross-coupling reactions. In our previous reports we demonstrated the versatility and the efficiency of triply halogen-bridged iridium(III) complexes in the asymmetric hydrogenation of cyclic imines,[5a] quinolines,[5b] quinolinium salts,[5c] and quinoxalines.[5d] We also reported that this class of catalysts is able to catalyze the stereoselective dimerization of enynes.[5e] We wish to report herein the synthesis of isoindoline scaffolds via a [2+2+2] cycloaddition of diynes and alkynes employing the stable and practical ionic triply iodo-bridged iridium-catalyzed $[\{Ir(H)[rac\text{-binap}]\}_2(\mu\text{-}I)_3]I$ with a focus on benign solvent system such as isopropyl alcohol[6] toward a greener [2+2+2] cycloaddition process.

We started our investigations by studying the cycloaddition of diyne **1** with propargyl alcohol in refluxing toluene (Table 1, entries 1 and 2). The reaction proceeded with good conversion. Nonetheless, the iridium-catalyzed cycloaddition provided a mixture of two different products, the desired alcohol **2** and its oxidized version, an aldehyde **3**, as the major product. Varying the reaction time did not show significant improvement in this ratio (entries 1 and 2). We next performed the reaction in a sealed tube. The temperature had to be kept close to the boiling point of toluene to provide a good conversion (entries 3–5). To our delight, when running the reaction for a longer period of time (entry 6), the desired compound **2** was obtained in good yield.

Next, we tried to reduce the reaction time by adding a co-solvent to the reaction mixture. Toluene/acetone gave promising results (Table 1, entry 7) toward the generation of alcohol **2**.

Table 1. Optimization table.[a]



1 2 3

Entry	Solvent	T [°C]	t [h]	Conv. [%]	Yield **2**:**3**[d] [%]
1	toluene	reflux	17	>90	32:49
2	toluene	reflux	12	>90	38:44
3	toluene	80[b]	17	60	n.d[c]
4	toluene	110[b]	17	>90	34:24
5	toluene	130[b]	17	>90	n.d[c]
6	toluene	130[b]	48	>98	71:8
7	toluene/acetone	130[b]	17	>90	56:27
8	toluene/isopropyl alcohol	130[b]	17	>90	71:15
9	acetone	RT[b]	17	<5	n.d[c]
10	isopropyl alcohol	RT[b]	17	<5	n.d[c]
11	acetone	80[b]	17	>98	78:5
12	isopropyl alcohol	80[b]	17	>98	80:5

[a] Reaction conditions: 0.2 mmol of diyne **1** and 3 equivalents of propargyl alcohol, 4 mol% $[\{Ir(H)[rac\text{-binap}]\}_2(\mu\text{-}I)_3]I$ in 1 mL of solvent. [b] Reaction run in sealed tube. [c] Yield not determined. [d] Isolated yield, determined by ^1H NMR.

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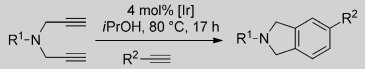
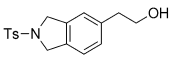
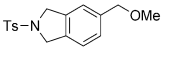
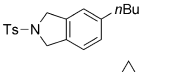
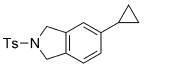
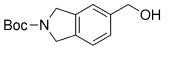
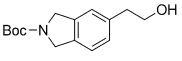
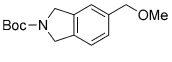
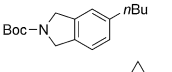
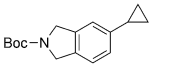
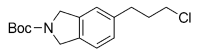
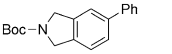
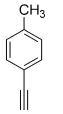
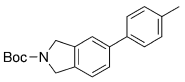
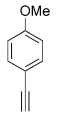
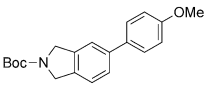
We then turned our attention to a system composed of toluene/isopropyl alcohol. Pleasingly, we were able to access the desired compound **2** in 71% yield (Table 1, entry 8). Considering the importance of acetone and isopropyl alcohol in the solvent mixture we decided to perform the reaction in either isopropyl alcohol or acetone as sole solvent. The reactions carried out at room temperature were not successful (entries 9 and 10). Delightfully, we observed full conversion by increasing the temperature to 80 °C, and excellent isolated yields of **2** were obtained (entries 11 and 12). We found that isopropyl alcohol was well suited for this transformation and used Normapur quality without any further purification (see the Experimental Section).

With this catalytic system in hand, we explored the scope of this iridium-catalyzed process, and our results are highlighted in Table 2. We carried out the cycloaddition of diyne **1** with terminal alkynes bearing a selection of substituents. A number of functional groups were tolerated, including alcohol (entry 1), ether (entry 2), alkyl (entry 3), and cycloalkyl (entry 4). Unfortunately, the reaction showed poor conversion with aromatic substituted alkynes. Therefore, due to the lack of reactivity of diyne **1**, we turned our attention to Boc-protected amine diyne partner **4**. The same trend was observed, alcohols (entries 5 and 6), ether (entry 7), alkyl (entry 10), and cyclopropyl (entry 11) were also tolerated, and diyne **4** proved to be more efficient than diyne **1** in most cases. Specifically, we found that Boc-protected diyne **4** also underwent smooth cycloaddition with chloropentyne to give the corresponding isoindoline **14** in reasonable yield (entry 10). Pleasingly, the cycloaddition of **4** performed under the same reaction conditions was also successful with aromatic substituted alkynes providing the desired isoindoline derivatives **15**–**17** in reasonable yield (entries 11–13). With these exciting observations in hand, we decided to extend this chemistry to include more heavily substituted diynes to target highly functionalized aromatic systems. When we applied the method on diyne **19** with propargyl alcohol, we were delighted to observe the desired compound **20** in 73% yield (Scheme 1).

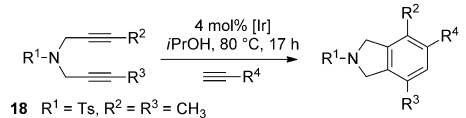
The cycloaddition of unsymmetrical diyne **19** with cyclopropylacetylene or propargyl alcohol gave a regioisomeric mixture of the corresponding isoindolines, always favoring the *ortho* isomer: **21** (72:28) and **22** (67:63) were obtained in respectable yields given the challenging nature of the diyne substrate (Scheme 1). In an effort to employ more synthetically versatile functionalities, we decided to incorporate a boronate moiety within the system. Indeed, aromatic boronic acid derivatives represent an important target as they are widely acknowledged as being amongst the most versatile intermediates in synthetic chemistry.[7] Alkynyl boronates have been used previously as partners in transition metal-catalyzed cycloaddition reactions, allowing direct access to functionalized aromatic boronic ester derivatives.[8] To our delight, diyne **18** and *n*-butyl alkynyl boronate **23** underwent [2+2+2] cycloaddition to furnish the corresponding isoindoline **25** in useful yield. With this promising result in hand, we decided to use terminal alkyne **24** in the cycloaddition. Interestingly, the reaction of diyne **18** with alkyne **24** proved to be more efficient, resulting in a signif-

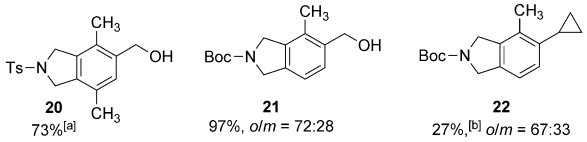
Table 2. Substrate scope.[a]



Entry	R^1	Alkyne	Product		Yield [%]
1	Ts			**5**	69
2	Ts			**6**	70
3	Ts			**7**	62[b]
4	Ts			**8**	61[b]
5	Boc			**9**	85
6	Boc			**10**	90
7	Boc			**11**	64
8	Boc			**12**	63[b]
9	Boc			**13**	66[b]
10	Boc			**14**	61[b]
11	Boc			**15**	47
12	Boc			**16**	59
13	Boc			**17**	52

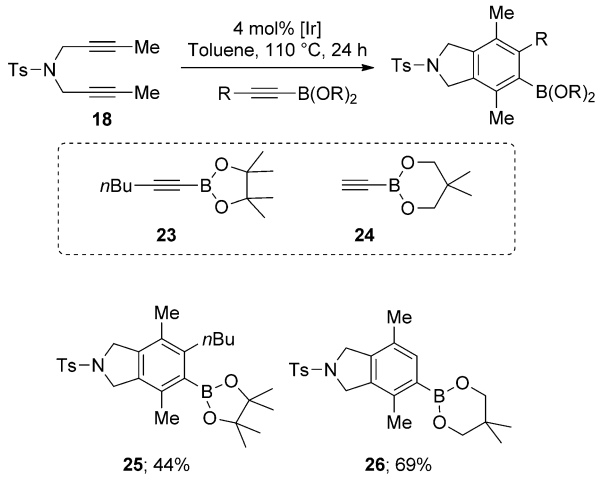
[a] Reaction conditions: 1 equivalent of diyne and 3 equivalents of alkyne in 1 mL of isopropyl alcohol. [b] 10 equivalents of alkyne.



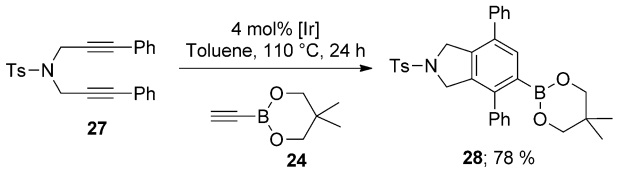


Scheme 1. Reaction conditions: 1 equivalent of diyne and 3 equivalents of alkyne in 1 mL of isopropyl alcohol. [a] 48 h at 130 °C. [b] 10 equivalents of alkyne.

icant yield improvement (**26**, 69%) (Scheme 2). Moreover, diphenyl-substituted diyne **27** was also tolerated and led to isoindoline **28** in high yield (78%; Scheme 3). The reaction performed under the standard *i*PrOH conditions unfortunately gave a complex mixture of products, probably due to partial transesterification of the boronate starting materials and products. The best results were obtained with toluene as this limited side reactions, furnishing a cleaner reaction profile.



Scheme 2. Reaction conditions: 1 equivalent of diyne and 1.1 equivalents of alkynyl boronate in 1 mL of toluene.



Scheme 3. Reaction conditions: 1 equivalent of diyne and 1.1 equivalents of alkynyl boronate in 1 mL of toluene.

These results demonstrate that the present iridium-catalyzed [2+2+2] cycloaddition allows easy and efficient preparation of precious, hindered aryl boronates from readily available starting materials.

In conclusion, we have demonstrated that isoindolines bearing a range of substitution patterns can be efficiently accessed via an iridium-catalyzed [2+2+2] cycloaddition of diynes and alkynes. This catalytic environmentally friendly and atom-economical reaction proceeds in isopropyl alcohol with symmetrical and unsymmetrical diynes, affording highly substituted, functionalized isoindoline derivatives and provides a comparatively non-toxic alternative to those previously described in benzene or dioxane using iridium complexes. The catalyst is convenient to handle and it is not sensitive to water or air, as the reaction gave similar results when carried out with or without an inert atmosphere, and does not require microwave assistance. With regard to the synthesis of boronate-substituted isoindolines, the versatility of this class of compound represents great potential for further synthetic elaboration. To the best of our knowledge, the Ir-catalyzed [2+2+2] cycloaddition with alkynyl boronates is unprecedented and leads to compounds of significant interest to the synthetic community. Finally, the present methodology provides a powerful means for the generation of heavily substituted aromatic products which can be used as key intermediates in drug syntheses.

Experimental Section

Experimental details are provided in the Supporting Information.

Acknowledgements

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Keywords: alkynes · cycloaddition · homogeneous catalysis · iridium · isoindolines

[1] a) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901 – 2915; b) M. Rubin, A. W. Sromek, V. Gevorgyan, *Synlett* **2003**, 2265 – 2291; c) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095 – 1108.

[2] a) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, 4741 – 4767; b) Y. Yamamoto, *Curr. Org. Chem.* **2005**, *9*, 503 – 519; c) V. Gandon, C. Aubert, M. Malacria, *Chem. Commun.* **2006**, 2209 – 2217; d) V. Gandon, C. Aubert, M. Malacria, *Curr. Org. Chem.* **2005**, *9*, 1699 – 1712; e) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307 – 2327; f) D. Leboeuf, V. Gandon, M. Malacria, *Transition Metal-Mediated [2+2+2] Cycloadditions, in Handbook of Cyclization Reactions, Vol. 1* (Ed.: S. Ma), Wiley-VCH, Weinheim, **2009**, pp. 367 – 406.

[3] a) S. Kezuka, S. Tanaka, T. Ohe, Y. Nakaya, R. Takeuchi, *J. Org. Chem.* **2006**, *71*, 543 – 552; b) M. Shanmugasundaram, A. L. Aguirre, M. Leyva, B. Quan, L. E. Martinez, *Tetrahedron Lett.* **2007**, *48*, 7698 – 7701; c) T. Matsuda, S. Kadowaki, T. Goya, M. Murakami, *Org. Lett.* **2007**, *9*, 133 – 136; d) G. Onodera, M. Matsuzawa, T. Aizawa, T. Kitahara, Y. Shimizu, S. Kezuka, R. Takeuchi, *Synlett* **2008**, *5*, 755 – 758; e) R. Takeuchi, Y. Nakaya, *Org. Lett.* **2003**, *5*, 3659 – 3662; f) R. Takeuchi, S. Tanaka, Y. Nakaya, *Tetrahedron lett.* **2001**, *42*, 2991 – 2994; For the enantioselective iridium-catalyzed preparation of polyaromatics, see: g) T. Shibata, S. Yoshida, Y. Arai, M. Otsuka, K. Endo, *Tetrahedron* **2008**, *64*, 821 – 830; h) T. Shibata, Y. Arai, K. Takami, K. Tsuchikama, T. Fujimoto, S. Takebayashi, K. Takagi, *Adv. Synth. Catal* **2006**, *348*, 2475 – 2483; i) T. Shibata, K. Tsuchikama, M. Otsuka, *Tetrahedron: Asymmetry* **2006**, *17*, 614 – 619; j) T. Shibata, K. Tsuchikama, *Chem. Commun.* **2005**, 6017 – 6019; k) T. Shibata, T. Fujimoto, K. Yokota, K. Takagi, *J. Am. Chem. Soc.* **2004**, *126*, 8382 – 8383.

[4] a) S. Van Goethem, P. Van der Veken, V. Dubois, A. Soroka, A-M. Lambeir, X. Chen, A. Haemers, S. Scharpé, I. De Meester, K. Augustyns, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4159 – 4162; b) A. J. Woodhead, H. Angove, M. Carr, G. Chessari, M. Congreve, J. E. Coyle, J. Cosme, B. Graham, P. J. Day, R. Downham, L. Fazal, R. Feltell, E. Figueroa, M. Frederickson, J. Lewis, R. McMenamin, C. W. Murray, M. A. O'Brien, L. Parra, S. Patel, T. Phillips, D. C. Rees, S. Rich, D.-M. Smith, G. Trewartha, M. Vinkovic, B. Williams, A. J.-A. Woolford, *J. Med. Chem.* **2010**, *53*, 5956 – 5969; c) S. Ruchirawatt, P. Sahakitpichan, *Tetrahedron Lett.* **2000**, *41*, 8007 – 8010; d) M. Horiuchi, T. Maoka, N. Iwase, K. Ohnishi, *J. Nat. Prod.* **2002**, *65*, 1204 – 1205; e) V. Rys, A. Couture, E. Deniau, P. Grandclaudon, *Eur. J. Org. Chem.* **2003**, 1231 – 1237; f) X. Zhang, W. Ye, S. Zhao, C.-T. Che, *Phytochemistry* **2004**, *65*, 929 – 932; g) T. Berg, S. B. Cohen, J. Deshamals, C. Sonderegger, D. J. Maslyar, J.

Goldbers, D. L. Boger, P. K. Vogt, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 3830 – 3835; h) D. L. Boger, J. Desharnais, K. Capps, *Angew. Chem.* **2003**, *115*, 4270 – 4309; *Angew. Chem. Int. Ed.* **2003**, *42*, 4138 – 4176.

[5] a) T. Yamagata, H. Tadaoka, M. Nagata, T. Hirao, Y. Kataoka, V. Ratovelomanana-Vidal, J.-P. Genêt, K. Mashima, *Organometallics* **2006**, *25*, 2505 – 2513; b) C. Deport, M. Buchotte, K. Abecassis, H. Tadaoka, T. Ayad, T. Ohshima, J.-P. Genêt, K. Mashima, V. Ratovelomanana-Vidal, *Synlett* **2007**, *17*, 2743 – 2747; c) D. Cartigny, T. Nagano, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima, V. Ratovelomanana-Vidal, *Adv. Synth. Catal.* **2010**, *352*, 1886 – 1891; d) H. Tadaoka, D. Cartigny, T. Nagano, T. Gosavi, T. Ayad, J.-P. Genêt, T. Ohshima, V. Ratovelomanana-Vidal, K. Mashima, *Chem. Eur. J.* **2009**, *15*, 9990 – 9994; e) M. Ez-Zoubir, F. Le Boucher d'Herouville, J. Brown, V. Ratovelomanana-Vidal, V. Michelet, *Chem. Commun.* **2010**, *46*, 6332 – 6334.

[6] a) For the use of isopropyl alcohol in pharmaceutical applications, see: A. J. Papa, in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. 30*, Wiley-VCH, Weinheim, **2005**, pp. 243 – 254; b) C. Capello, U. Fischer, K. Hungerbühler, *Green Chem.* **2007**, *9*, 927 – 934.

[7] *Boronic Acids—Preparation, Applications in Organic Synthesis and Medicine* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**.

[8] a) G. Hilt, K. Smolko, *Angew. Chem.* **2003**, *115*, 2901 – 2903; *Angew. Chem. Int. Ed.* **2003**, *42*, 2795 – 2797; b) Y. Yamamoto, J.-I. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712 – 3713; c) V. Gandon, D. Leboeuf, S. Amslinger, K. P. C. Volhardt, M. Malacria, *Angew. Chem.* **2005**, *117*, 7276 – 7280; *Angew. Chem. Int. Ed.* **2005**, *44*, 7114 – 7118; d) A.-L. Auvinet, G. Hilt, J. P. A. Harrity, *J. Org. Chem.* **2010**, *75*, 3893 – 3896; e) A.-L. Auvinet, J. P. A. Harrity, *Angew. Chem.* **2011**, *123*, 2821 – 2824; *Angew. Chem. Int. Ed.* **2011**, *50*, 2769 – 2772.

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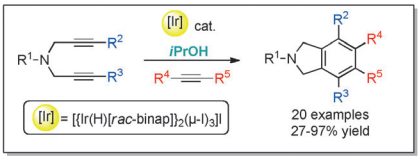
Iridium(III) catalysis provides a convenient and general method for the synthesis of isoindolines via [2+2+2] cycloaddition reactions of diynes and alkynes. The reaction proceeds smoothly in environmentally benign and non-distilled isopropyl alcohol, providing highly functionalized aromatic compounds in moderate to excellent yields.



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Practical and Efficient Iridium Catalysis for Benzannulation: An Entry To Isoindolines

