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Investigation of Alkyne Regioselectivity in the Ni-catalyzed Benzannulation of Cyclobutenones

Timo Stalling, Wesley R. R. Harker, Anne-Laure Auvinet, Erik J. Cornel, and Joseph P. A. Harrity*[a]

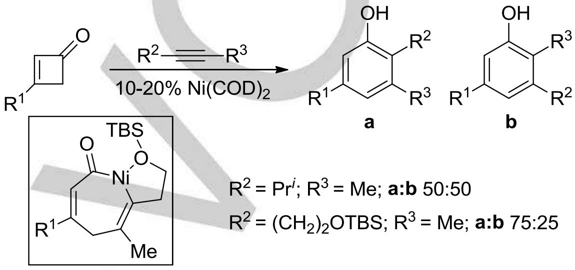
Abstract: A Ni-catalyzed benzannulation reaction of cyclobutenones and alkynes provides a rapid synthesis of heavily substituted phenols. The regioselectivity of this reaction can be modulated by variation of substituents on the alkyne. While the incorporation of Lewis basic donors provides modest selectivities, the use of aryl substituents can provide high levels of regiocontrol. Finally, alkynylboronates derived from alkyl-substituted acetylenes provide both high yields and regioselectivities. This study suggests that alkynes bearing one sp^2- and one sp^3-based substituent can undergo benzannulation with high levels of regiocontrol whereby the sp^3-based group is incorporated ortho-to the phenolic OH.

Introduction

Transition metal catalyzed annulation reactions offer an effective strategy for the synthesis of aromatic and heteroaromatic compounds.[1] This approach complements the stepwise introduction of substituents by electrophilic aromatic substitution and directed ortho-metalation reactions, and represents a more convergent way of generating polysubstituted products. Among the many exemplifications of metal catalyzed annulations, the transition metal catalyzed activation of four-membered ring compounds is an interesting subset that has attracted significant attention. Specifically, cyclobutanones, 3-oxetanones and 3-azetidonones are efficiently transformed into the corresponding carbo- and heterocycles when reacted with alkynes.[2] In addition, Rh-catalysis has been shown to offer routes to a range of carbocycles from both inter- and intramolecular cyclization reactions of alkenes.[3]

With respect to the synthesis of aromatic products, Liebeskind reported that the Ni-catalyzed reaction of cyclobutenones and alkynes generated densely substituted phenols via an intermediate vinylketene complex.[4, 5] The reaction was found to proceed at room temperature but unsymmetrical alkynes were found to be incorporated with only modest levels of regiocontrol. In an effort to explore the potential of this reaction to generate products with higher regioselectivities, we decided to undertake a study of the scope of the reaction with a particular focus on the nature of the alkyne, and we report our findings herein.

Scheme 1 outlines some general trends relating to alkyne regioselectivity in the Ni-catalyzed benzannulation of cyclobutenones developed by the Liebeskind group.[4] The reaction appears to be relatively insensitive to the steric volume of alkyl substituents but the inclusion of a homopropargylic ether can lead to enhanced regiocontrol. Liebeskind suggested that this selectivity could be rationalized by invoking a Lewis acid-base interaction between the ether moiety and Ni(II) center during the cyclometalation step.



Scheme 1. Liebeskind's investigations in the Ni-catalyzed benzannulation of cyclobutenones.[4]

Results and Discussion

As the reactivity of arylacetylenes had not been disclosed in the original report, we began our studies by investigating benzannulation reactions of alkynes bearing a combination of phenyl and alkyl groups, with examples of latter bearing Lewis basic heteroatoms (Table 1). The reactions were conducted in the presence of 30 mol% Ni-catalyst in each case to minimize the effect of catalyst quality on reaction conversion. Under these conditions, we found that the reaction of 1-phenylhex-1-yne **3** proceeded in low conversion affording the corresponding products in low yield but with high levels of regioselectivity. Analysis of these products confirmed that the major regioisomer had incorporated the Bu^n group in the *ortho*-position (entries 1,2). We were able to enhance selectivity further by the incorporation of a homopropargylic methyl ether, but again the product yield was disappointingly low (entry 3). In order to explore the chelation effect proposed by Liebeskind, we prepared the *pseudo*-symmetrical alkyne **4** and found that this provided the phenol in higher yield, but with only a marginal preference for incorporation of the propargyl ether at C-2 (entries 4,5). Finally, the effect of adding a methylene spacer group between the alkyne and Ph-group on reaction efficiency and selectivity was explored. In the event the products were generated in relatively good yield but with modest selectivity (entries 6,7).

These preliminary studies highlighted a significant problem with low reaction conversions, even at high catalyst loading. Attempts to enhance catalyst lifetime by addition of phosphine ligands resulted in further diminished reaction conversion, however, the inclusion of norbornadiene had the effect of promoting benzannulation. Indeed, improved yields could be obtained in the case of 1-phenylhex-1-yne **3** when the reaction was conducted in toluene in the presence of this ligand and 10 mol% Ni-catalyst (Table 2).

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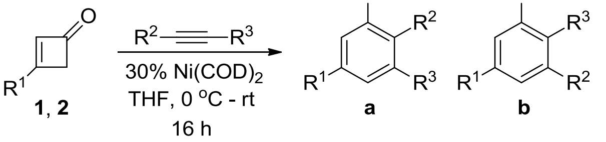
Table 1. Preliminary investigations.

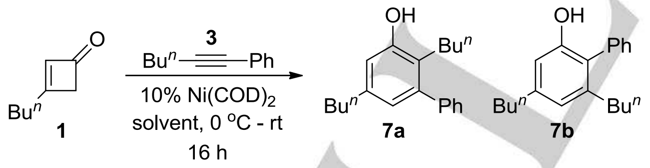


Entry[a]	R^1	R^2	R^3	Yield (**a**:**b**)[b], [c]
1	Bu^n; **1**	*n*-Bu	Ph; **3**	33% (93:7); **7**
2	Ph; **2**	*n*-Bu	Ph; **3**	38% (94:6); **8**
3	Bu^n; **1**	$(CH_2)_2OMe$	Ph ;**4**	30% (>98:2); **9**
4	Bu^n; **1**	$(CH_2)_2OMe$	Bu^n; **5**	42% (60:40); **10**
5	Ph; **2**	$(CH_2)_2OMe$	Bu^n; **5**	61% (52:48); **11**
6	Bu^n; **1**	Bn	Bu^n; **6**	60% (65:35)[d]; **12**
7	Ph; **2**	Bn	Bu^n; **6**	52% (64:36)[e]; **13**

[a] The reaction was performed with cyclobutenone **1**, **2** (1 eq, 0.40 mmol) and alkyne (1.1 eq, 0.44 mmol) in the presence of $Ni(COD)_2$ (30%, 0.12 mmol) under an argon atmosphere. [b] Isolated yield after column chromatography. [c] The ratio of isomers was determined by ^{1}H NMR spectroscopy of crude material. [d] The ratio was determined by LC-MS. [e] The ratio was determined by GC-MS.

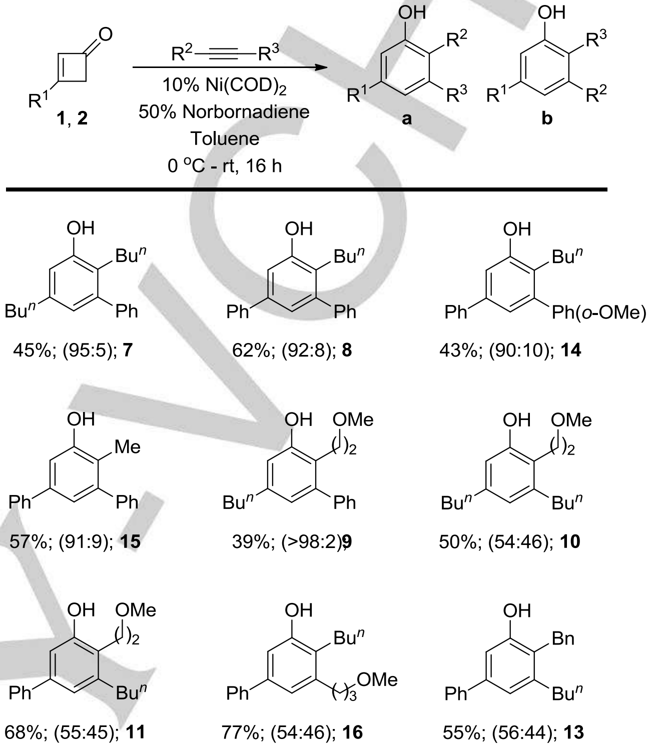
We next set out to employ these optimized conditions in the reaction of a selection of unsymmetrical alkynes, our results are shown in Scheme 2. In the event, the corresponding products were generated in comparable or better yields to those obtained at higher catalyst loading in the absence of promoter. However, the addition of norbornadiene did not serve to affect the regioselectivity of the reaction and broadly similar regiochemical outcomes were observed.

Table 2. Benzannulation optimization.



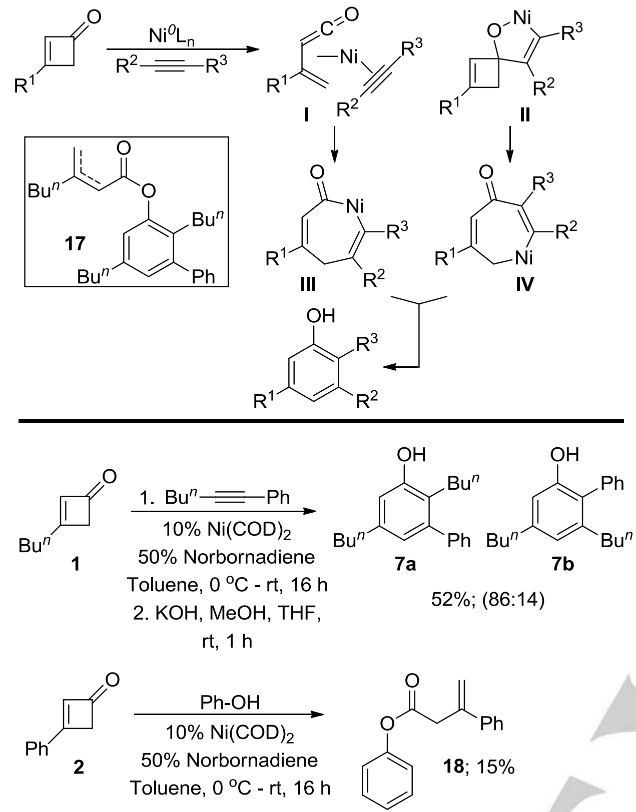
Entry[a]	Solvent	Promoter	Yield (**a**:**b**)[b], [c]
1	THF	--	29% (85:15)
2	Toluene	--	30% (93:7)
3	THF	Norbornadiene (0.5 eq)	35% (89:11)
4	Toluene	Norbornadiene (0.5 eq)	45% (95:5)

[a] The reaction was performed with cyclobutenone **1**, **2** (1 eq, 0.40 mmol) and alkyne (1.1 eq, 0.44 mmol) in the presence of $Ni(COD)_2$ (10%, 0.04 mmol) under an argon atmosphere. [b] Isolated yield after column chromatography. [c] The ratio of isomers was determined by ^{1}H NMR spectroscopy of crude material.



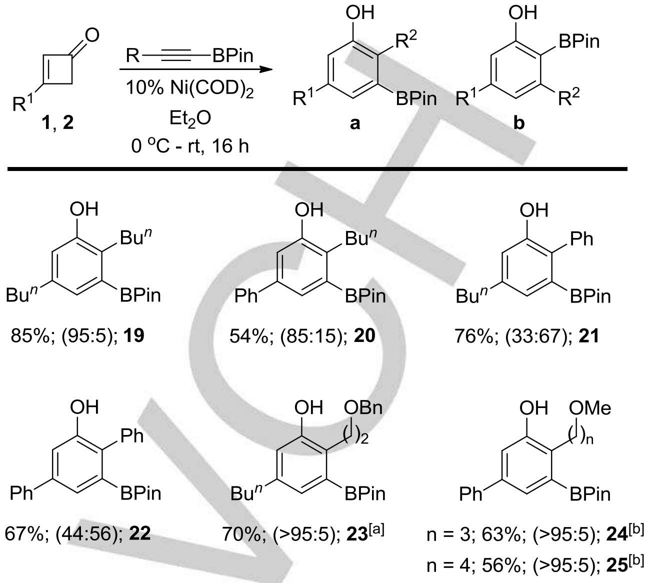
Scheme 2. Ni-catalyzed benzannulation using unsymmetrical alkynes. The reaction was performed with cyclobutenone **1**, **2** (1 eq, 0.40 mmol) and alkyne (1.1 eq, 0.44 mmol) in the presence of $Ni(COD)_2$ (10%, 0.04 mmol) and norbornadiene (0.5 eq, 0.20 mmol) under an argon atmosphere.

With regard to the mechanism of the benzannulation, Liebeskind proposed that the Ni-catalyst first inserts into the cyclobutenone to provide a metal ketene complex **I**, before undergoing a cyclization and reductive elimination sequence.[4] A related mechanism has recently been suggested by Lin in the cycloaddition of alkynes and 3-azetidinones.[6] However, an alternative proposal that can conceivably be put forward is based on Murakami's Ni-catalyzed alkyne insertion into cyclobutanones,[2a] and Kurosawa's work on the mechanism of Ni-catalyzed addition of carbonyl compounds to alkenes and alkynes. In this case, a cyclopentannulation provides spirocycle **II** that progresses to product via **IV** (Scheme 3).[7] In this context, and during our initial investigations into the reaction of **1** and **3** we observed a small amount of by-product **17**, which was isolated as a mixture of alkene isomers making clear characterization of this compound rather challenging. However, saponification of the crude material from the benzannulation reaction successfully hydrolyzed these esters and provided a slightly enhanced yield of phenols **7a,b** (*cf* Scheme 2). Moreover, subjecting phenol to the benzannulation in the presence of **2** allowed **18** to be isolated cleanly, albeit in modest yield. Taken together, these results are consistent with the formation of ketene intermediates suggesting that the Liebeskind mechanism provides the more accurate description of the reaction pathway.



Scheme 3. Mechanism of the benzannulation reaction.

Recent studies in our labs have exploited alkynylboronates as substrates for the rapid construction of highly functionalized aromatic boronic acid derivatives.[8, 9] These alkynes often provide much higher levels of regiocontrol in cycloadditions as compared to similar reactions of unsymmetrical hydrocarbon substituted alkynes. Accordingly, we decided to undertake a study of Ni-catalyzed benannulations of alkynylboronates and cyclobutenones and our results are presented in Scheme 4.[10] As shown, the alkynylboronate derived from 1-hexyne underwent a highly regioselective cycloaddition to provide the corresponding products in excellent yield. In contrast, the boronic esters derived from phenylacetylene were much less selective and favoured formation of the other regioisomer. We next turned our attention to the reaction of alkynylboronates bearing Lewis basic substituents. These reactions were found to undergo efficient benzannulation to provide a single regioisomer with the boronate at C-3.

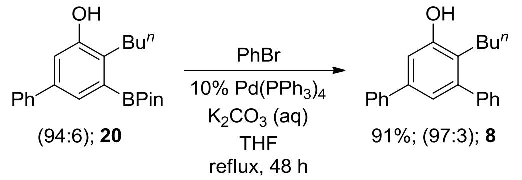


Scheme 4. Ni-catalyzed benzannulation using alkynylboronates. The reaction was performed with cyclobutenone **1**, **2** (1 eq, 0.40 mmol) and alkyne (2 eq, 0.80 mmol) in the presence of Ni(COD)$_2$ (10%, 0.04 mmol) under an argon atmosphere. [b] Reaction conducted in the presence of 20 mol% Ni(COD)$_2$. [c] 1.1 eq alkyne was used. Pin = pinacol.

Overall therefore, these studies suggested that the regioselectivity of the Ni-catalyzed benzannulation of the cyclobutenones proceeds in favour of incorporating alkyl groups *ortho* to the newly formed phenol whereas aryl groups are incorporated at C-3. A BPin-substituent also appears to prefer incorporation at C-3, hence arylacetylene derived alkynylboronates undergo benzannulation with low regiocontrol. In contrast, alkynylboronates bearing alkyl substituents are very selective. The inclusion of ether substituents only appears to have a marginal effect on selectivity but does not offer a means for controlling the predominant regiochemical pathway. Studies towards formulating an explanation for these intriguing regiochemical insertion patterns are underway and will be reported in due course.

Although the present study has been restricted to the employment of 3-substituted cyclobutenones, cycloadditions of 3,4-disubstituted cyclobutenones with unsymmetrical dialkylacetylenes[4], and alkynylboronates[10], have been reported and follow the same regiochemical trends as in the 3-substituted systems. In contrast, our studies on the cycloaddition of 2,3-disubstituted cyclobutenones suggest these substrates are inert to Ni-catalyzed benzannulation.[11]

Finally, as well as representing a regiochemical controlling unit, the boronate offers the opportunity for late stage incorporation of aryl groups. This appears to be particularly important in the Ni-catalyzed benzannulation as arylacetylenes are generally less reactive than their alkyl-counterparts. In order to verify the potential of these substrates for the incorporation of aryl groups, we carried out a Pd-catalyzed cross-coupling of borylated phenol **20** with bromobenzene and obtained phenol **8** in high yield (Scheme 5).



Scheme 5. Pd-catalyzed cross-coupling. The reaction was performed with phenol **20** (1 eq, 0.23 mmol), bromobenzene (1.1 eq, 0.25 mmol) and K_2CO_3 (4 eq, 0.92 mmol) in the presence of $Pd(PPh_3)_4$) (10%, 0.023 mmol) under an argon atmosphere. Pin = pinacol.

Conclusions

In conclusion, the Ni-catalyzed benzannulation of cyclobutenones and unsymmetrical alkyl-substituted alkynes generally proceeds with low levels of regioselectivity, in-line with the observations made in Liebeskind's original report. Alkynes bearing aryl groups offer greater regiocontrol, but at the expense of alkyne reactivity. We have found that the inclusion of norbornadiene as a promoter can provide improved yields of products in these cases. However, alkynylboronates appear to be particularly well suited to the Ni-catalyzed reaction with cyclobutenones, providing superior yields and regioselectivities in many cases. The isolation of aryl esters as by-products in some cases is suggestive of the formation of ketene intermediates in this process and may help to guide further work towards elucidating the reaction mechanism. Nonetheless, this study suggests that alkynes bearing one sp^2- and one sp^3-based substituent can undergo benzannulation with high levels of regiocontrol whereby the sp^3-based group is incorporated ortho- to the phenolic OH.

Experimental Section

General procedure for the Ni-catalyzed benzannulation, exemplified by the synthesis of 8.

A flame-dried Schlenk tube was charged with 3-phenylcyclobut-2-enone (**2**) (57.7 mg, 0.40 mmol), 1-phenyl-1-hexyne **3** (69.6 mg, 0.44 mmol) and norbornadiene (18.4 mg, 0.02 mmol) in anhydrous and degassed toluene (1 mL) under an argon atmosphere. The mixture was cooled to 0 °C before $Ni(COD)_2$ (5.5 mg, 0.02 mmol, 5 mol%) was added. The mixture was stirred at 0 °C for 1.5 h and another portion of $Ni(COD)_2$ (5.5 mg, 0.02 mmol, 5 mol%) was added. The solution was allowed to reach room temperature and stirred for 16 h. All volatiles were removed *in vacuo* to obtain the crude product (ratio 92:8). Purification by flash chromatography over silica gel eluting with *n*-hexane/EtOAc (95:5) provided phenol **8** as a colorless oil (74.4 mg, 62%). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.4 Hz, CH_3), 1.22–1.31 (2H, m, CH_2), 1.47–1.53 (2H, m, CH_2), 2.57–2.61 (2H, m, CH_2), 4.94 (1H, s, OH), 7.05 (1H, d, J = 1.8 Hz, Ar-H), 7.09 (1H, d, J = 1.8 Hz, Ar-H), 7.31–7.45 (8H, m, Ar-H), 7.58–7.60 (2H, m, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9, 23.0, 26.7, 32.2, 113.0, 121.7, 126.2, 127.1, 127.1, 127.4, 128.1, 128.9, 129.3, 139.5, 140.6, 142.0, 144.2, 154.3. FTIR (film): 3413 (m), 3083 (w), 3058 (w), 3028 (w), 2956 (s), 2925 (s), 2856 (s), 1599 (w), 1566 (m), 1463 (m), 1442 (w), 1402 (m), 1263 (m), 1187 (m), 1130 (m), 757 (s), 697 (s) cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{23}O^+$: 303.1749 [*M*+H]$^+$; found: 303.1747.

Acknowledgements

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Keywords: catalysis • cycloadditions • nickel • phenols • regioselectivity

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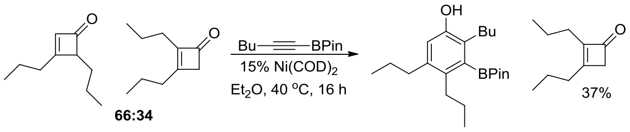
[11] For example, the benzannulation of a mixture of 2,3-di-*n*-Pr cyclobutenone and the corresponding 3,4-isomer shows that only the latter substrate reacts:



97:3 (alkyne insertion selectivity)
63% Conversion
51% isolated yield

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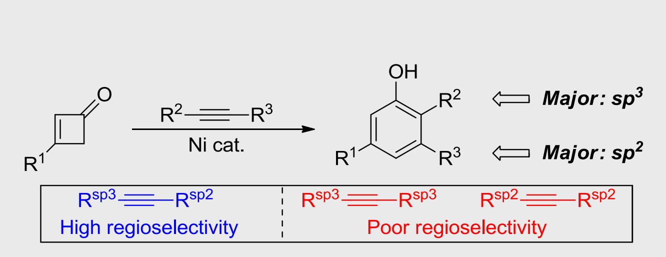
FULL PAPER



The Ni-catalyzed benzannulation of cyclobutenones and a series of alkynes highlight a preference for the incorporation of alkyl substituents at C-2 of the phenol products. In contrast, aryl, and pinacol borane esters show a preference for incorporation at C-3. Accordingly, alkynes bearing a combination of sp^2- and sp^3-based substituents undergo benzannulation with high levels of regiocontrol.

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