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Regioselective Cycloaddition of 3-Azetidinones and 3-Oxetanones with Alkynes through Nickel-Catalysed Carbon–Carbon Bond Activation

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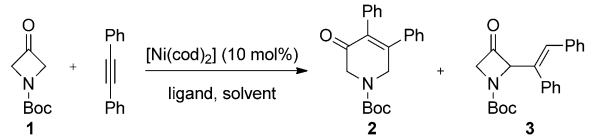
The transition-metal-catalysed activation of single carbon-carbon (C–C) bonds has been studied with several classes of strained carbocycles but not with small heterocycles.[1] In this context, we have recently reported the first example of a transition metal-catalyzed C–C bond activation of azetidine derivatives in the rhodium-catalyzed intramolecular hydroacylation of aldehyde-tethered 3-alkylideneazetidines.[2,3] We hypothesised that the strain energy of azetidines and oxetanes could promote other processes involving transition-metal-catalysed C–C bond activation.[4] Herein, we report that 3-azetidinones and 3-oxetanones can undergo a regioselective cycloaddition in the presence of alkynes and a nickel catalyst. These results suggest a vast realm of potential transformations of azetidine and oxetane derivatives in transition-metal-catalysed heterocyclic chemistry.

Murakami and co-workers have shown that cyclobutanones undergo alkyne insertion when treated with 10 mol% $[Ni(cod)_2]$ (COD = cyclooctadiene) and 20 mol% $P(c\text{Hex})_3$ in toluene at 110 °C.[5] However, exposing commercially available *N*-Boc-3-azetidinone **1** (Boc = *tert*-butoxycarbamoyl) and bis-phenylacetylene to these reaction conditions led to the formation of the expected product **2** in only modest yield alongside substituted azetidinone **3** (Table 1, entry 1), which was presumably obtained through carbon–hydrogen activation next to the nitrogen atom and alkyne insertion.[6] Interestingly, the selectivity in favour of **2** was improved by replacing $P(c\text{Hex})_3$ with the smaller and less basic PPh_3 group (Table 1, entry 2), whereas this ligand was completely inefficient in reactions with cyclobutanones.[5b] Critical to the selective formation of **2** was an increase of the loading of phosphine to 30 mol% (Table 1, entry 4 vs. 5) and a decrease of the temperature to 90 °C (Table 1, entry 5 vs. 6). It is noteworthy that only a slight excess of alkyne (1.1 equiv) is necessary without the requirement of slow addition. Moreover, control experiments in which only PPh_3 or only $[Ni(cod)_2]$ were used did not produce **2**, supporting the conclusion that a nickel–phosphine complex is responsible for the transformation. Phenylacetylene did not give the expected product, presumably due to oligomerisation.

Table 1. Optimisation of the reaction conditions.



Entry	L [(mol%)]	Solvent	*T* [°C]	**2/3**[a]	Yield [%][b]
1[c]	$P(c\text{Hex})_3$ (20)	toluene	110	1:1	30
2[c]	PPh_3 (20)	toluene	110	1.4:1	55
3[c]	PPh_3 (20)	dioxane	100	5:1	79
4[d]	PPh_3 (20)	dioxane	100	5:1	77
5[d]	PPh_3 (30)	dioxane	100	10:1	81
6[d]	PPh_3 (30)	dioxane	90	>20:1[e]	90

[a] Ratio determined by ^{1}H NMR spectroscopy of the crude material. [b] Yields of isolated **2**. [c] 1.5 equiv of alkyne was used. [d] 1.1 equiv of alkyne was used. [e] Compound **3** could not be detected by using ^{1}H NMR spectroscopy of the crude material.

We then examined the scope and regioselectivity of the insertion of unsymmetrical alkynes (Table 2). In most cases, the regioselectivity[7] was good and regioisomers **5** and **6** could be separated easily by flash chromatography, giving excellent yields of the major isolated regioisomer. Alkynes bearing an alkyl and an aryl substituents gave 1,2-dihydropyridin-3(6H)-ones **5a**–**5e** as the major regioisomer, which display the alkyl group (R^1) in α position to the carbonyl (Table 2, entries 1–5). This regioselectivity was not influenced by an electron-rich or electron-poor substituent on the benzene ring of alkynes **4a**–**4c** (Table 2, entries 1–3). A slight erosion of regioselectivity was observed when the size of the alkyl group was increased in alkynes **4d** and **4e** (Table 2, entries 4 and 5). The weak steric differentiation between the substituents of the triple carbon–carbon bond of alkynes **4f** and **4g** led to a modest regioselectivity (Table 2, entries 6 and 7), which was restored completely when a larger alkyl group was present, as in **4h**, giving **5h** in 87% yield (Table 2, entry 8). The reactivity observed with *tert*-butyl-substituted internal alkyne **4h** is remarkable, because examples of metal-catalysed C–C bond formation involving such alkynes have been reported only on rare occasions, all involving aldehydes instead of bulkier ketones.[8] Interestingly, the regioselectivity obtained with 1,3-enyne **4i** was far better than that observed with **4g** (Table 2, entry 9 vs. 7), although the steric differentiation between substituents does

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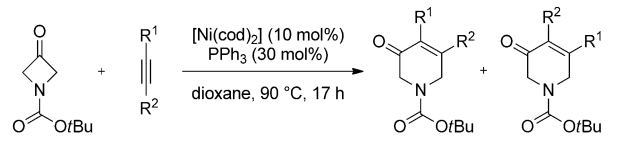
Table 2. Regioselective nickel-catalysed cycloaddition of *N*-Boc-3-azetidinone **1** with unsymmetrical alkynes **4**.



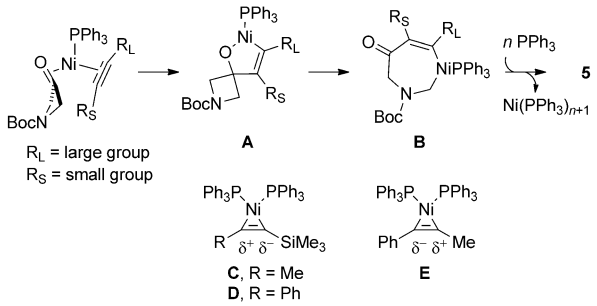
1 **4** (1.1 equiv) **5** **6**

Entry	R^1	R^2	**4**	**5/6**[a]	Yield [%][b]
1	Me	Ph	**4a**	87:13	92
2	*n*Bu	*p*-$MeOC_6H_4$	**4b**	89:11	89
3	*n*Bu	*p*-$MeCOC_6H_4$	**4c**	89:11	99
4	*c*Hex	*p*-$MeOC_6H_4$	**4d**	86:14	88[c]
5	*i*Bu	*p*-$MeOC_6H_4$	**4e**	84:16	91[c]
6	*p*-$CF_3C_6H_4$	*p*-$MeOC_6H_4$	**4f**	55:45[d]	82
7	Me	*i*Pr	**4g**	60:40[d]	90
8	Me	*t*Bu	**4h**	100:0[e]	87[f]
9	Et	C(Me)=CH_2	**4i**	88:12	88
10	C(Me)=CH_2	*p*-PhC_6H_4	**4j**	60:40[d]	86
11	$SiMe_3$	Ph	**4k**	97:3[g]	91[f]
12	$SiMe_3$	*n*Oct	**4l**	80:20[d]	80[h]

[a] Unless otherwise noted, this ratio was determined from the isolated yields of separated products **5** and **6**. [b] Combined isolated yields of **5** and **6**. [c] Alkyne and azetidinone were premixed. [d] Ratio determined by ^{1}H NMR spectroscopy on an inseparable mixture of **5** and **6**. [e] Compound **6h** could not be detected by ^{1}H NMR spectroscopy of the crude material. [f] Isolated yield of **5**. [g] Ratio determined by ^{1}H NMR spectroscopy of the crude. [h] 1.5 equiv of alkyne was used.

not vary greatly when one compares those two substrates. This result is in good accordance with reports by Jamison and co-workers, which propose that the alkene moiety of 1,3-enynes directs their intermolecular nickel-catalyzed reductive coupling with aldehydes and ketones by coordination of the alkene to the metal.[8d,9] This is also in agreement with recent theoretical investigations.[10] Evaluating the directing effects of an alkene and a benzene ring with 1,3-enyne **4j**, we observed a decrease of the regioselectivity normally induced by aromatic substituents (Table 2, entry 10 vs. 1–5), confirming the influence of the alkenyl substituent. Finally, reactions of trimethylsilyl-substituted alkynes **4k** and **4l** gave predominantly regioisomers **5k** and **5l**, respectively, which display the silyl group in the α position to the carbonyl.

In line with experimental results,[8d,9,11] recent theoretical investigations suggest that the regioselectivity of nickel-catalyzed reductive coupling of simple alkynes and aldehydes is dictated by steric effects.[10] A similar model with *N*-Boc-3-azetidinone **1** would favour the formation of metallacycle **A** by minimisation of steric interactions (Scheme 1) and would be consistent with the results presented in entries 1–8 of Table 2. Hence, intermediate **A** would undergo C–C bond activation toward **B** and reductive elimination would afford the major product **5**. The diminished steric differentiation between substituents R^1 and R^2 in alkynes **4f** and **4g** would explain the poor regioselectivity observed with these substrates. The intermediates invoked in this postulated mechanistic sequence are consistent with the isolation of η^2,η^2-1,5-enone-nickel complexes[12] and dimeric nickeladihydrofuran



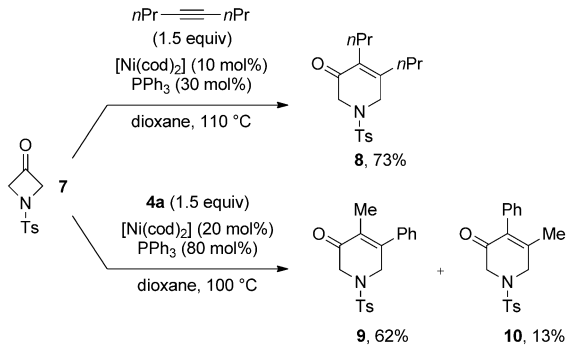
Scheme 1. Proposed rationale for the observed regioselectivity.

complexes.[13] Moreover, only one phosphine ligand would be present on the metal during the regioselectivity-determining event[10] whereas the excess of phosphine required under our optimised reaction conditions would promote the final reductive elimination.

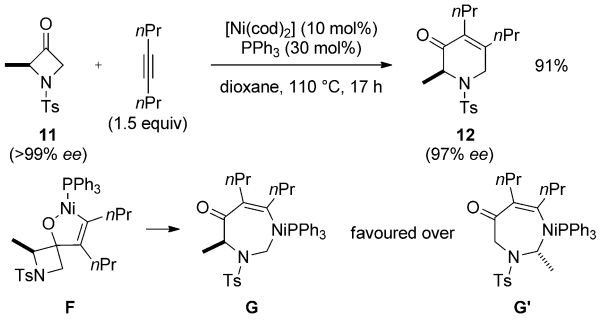
Although the regioselectivity observed with silylated alkynes **4k** and **4l** is in agreement with the results obtained in other intermolecular nickel-catalyzed reactions of silylated alkynes with electrophiles,[11b,d,g,14] it cannot be explained by the same steric considerations. The axial strain values of methyl, isopropyl, trimethylsilyl, and phenyl groups (1.74, 2.21, 2.5 and 2.8 kcal mol^{-1}, respectively)[15] suggest that the steric differentiation between substituents R^1 and R^2 is larger in **4g** than in **4k**. Nevertheless, the regioselectivity observed with **4k** was excellent, whereas it was poor with **4g**. Similarly, steric effects appear inconsequential in the case of **4l**, the major product displaying the larger silyl substituent next to the carbonyl group, in contradiction to the trend observed with **4a–4e**. Hence, stereoelectronic effects appear predominant in determining the regioselectivity of alkynes **4k** and **4l**. In this context, it is interesting to consider the reversed and significantly accentuated polarisation of the silylated alkyne ligands in known complexes **C** and **D** as compared with **E**, which has been established by ^{13}C NMR spectroscopy.[16] Whereas steric effects would predominate in the mechanistic pathway involving less polarized alkynes, the regioselectivity of the reactions of **4k** and **4l** would be dictated by the polarity of the alkynes when coordinated to nickel in a nucleophilic attack onto **1**.[17,18]

It was also possible to observe reaction with *N*-Ts-3-azetidinone **7** (Ts=*para*-tolylsulfonyl), although a greater excess of alkynes, slightly higher reaction temperature, and a higher catalyst loading (in the case of **4a**) were required to reach full conversion (Scheme 2). Hence, pyridinone **8** was isolated in 74% yield. The higher reaction temperature might explain the slightly lower selectivity obtained for regioisomers **9** and **10** in the cycloaddition of **4a** with **7** as compared with the result obtained with *N*-Boc-3-azetidinone **1** (Table 2, entry 1).

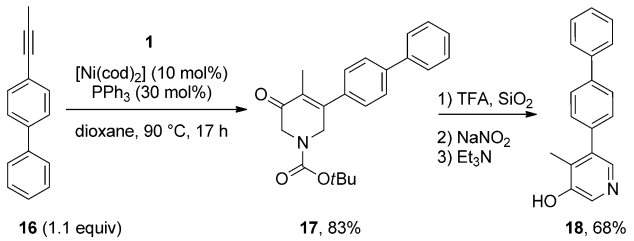
We then examined the regioselectivity of the ring-opening of α-substituted azetidinone **11**, which gave exclusively **12** in 91% yield (Scheme 3), indicating that only the less substituted bond of **11** is cleaved in the putative rearrangement of **F** to **G** (Scheme 4). Presumably, the minimisation of steric



Scheme 2. Nickel-catalysed cycloaddition of *N*-Ts-azetidinone **7**.



Scheme 3. Regioselective ring-opening of *N*-Ts-azetidinone **11**.

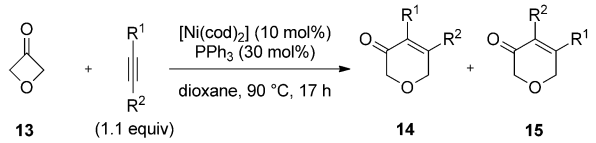


Scheme 4. Rapid synthesis of 4,5-disubstituted 3-hydroxypyridines.

hindrance favours the formation of **G** over **G′**. Importantly, the enantiomeric purity was not significantly eroded during the cycloaddition. An *N*-Ts-3-azetidinone with a benzyl substituent in α-position did not undergo the nickel-catalyzed cycloaddition.

Gratifyingly, we also observed the clean cycloaddition of commercially available 3-oxetanone **13** with alkynes under our optimized reaction conditions (Table 3). Hence, pyranone **14** was isolated in 82% yield (Table 3, entry 1). Excellent yields were also obtained with unsymmetrical alkynes **4c** and **4k** (Table 3, entries 2 and 3), albeit the **14c/15c** ratio obtained with **4c** (Table 3, entry 2) was lower than the **5c/6c** ratio obtained when the same alkyne underwent reaction with azetidinone **1** (Table 2, entry 3). This decrease of selectivity might be imputed to the diminished steric hindrance imposed by the oxygen atom of the oxetane ring of **13** as compared with the large carbamoyl group on the nitrogen atom of **1**.

Table 3. Nickel-catalysed cycloaddition of 3-oxetanone **13** with alkynes.



Entry	R^1	R^2	Alkyne	**14/15**[a]	Yield [%][b]
1	Ph	Ph	–[c]	–	82
2	*n*Bu	*p*-$MeCOC_6H_4$	**4c**	79:21	92
3	$SiMe_3$	Ph	**4k**	96:4	99

[a] The ratio was determined from the isolated yields of separated products **14** and **15**. [b] Combined isolated yields of **14** and **15**. [c] Bis-phenylacetylene.

The pyridinones obtained by nickel-catalysed cycloaddition of unsymmetrical alkynes with 3-azetidinones are useful intermediates for the preparation of 4,5-disubstituted 3-hydroxypyridines. Hence, carbamoyl-protected pyridinone **17** was obtained in 83% yield from **1** and **16** using our optimised conditions.[19] Then, an acidic treatment in the presence of silica followed by oxidation gave **18** isolated in 68% yield (Scheme 4). Our approach toward 4,5-disubstituted 3-hydroxypyridines with two different substituents in positions 4 and 5 necessitates only the preparation of an unsymmetrical alkyne and offers a good alternative to previous strategies that rely on the synthesis of more elaborated unsymmetrical precursors.[20]

In conclusion, we have demonstrated that transition-metal-catalysed C–C bond activation of small rings, traditionally studied with all-carbon rings,[1] can be generalized to 3-azetidinones and 3-oxetanones, owing presumably to the strain energies of these heterocyclic compounds. This approach represents a shift of strategy as compared with previous synthetic designs used for ring-opening[21] or ring-enlargement[22–24] of azetidines, which all involved cleavage of a carbon–nitrogen bond, as opposed to one of the C–C bond of the small heterocyclic ring.

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Keywords: 3-azetidinone · 3-oxetanone · C–C activation · nickel · ring-expansion

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