Cobalt-mediated regio- and stereoselective assembly of dienamides by hydroaminative alkyne coupling of α,ω-diynes†

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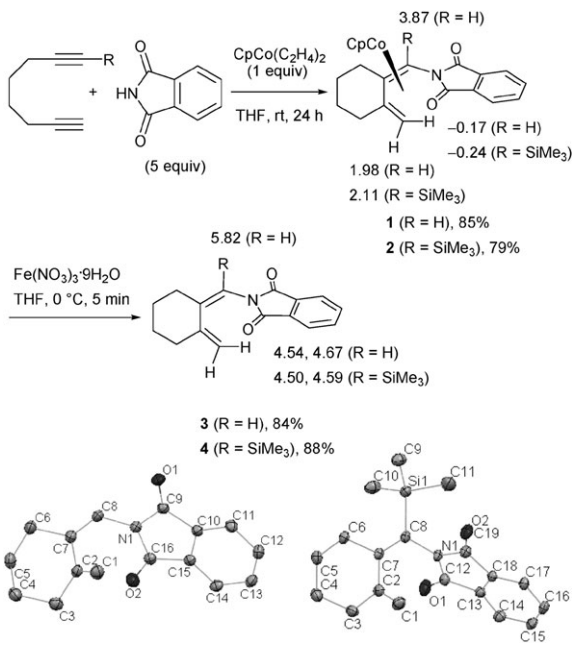
In the presence of $CpCo(C_2H_4)_2$, α,ω-diynes undergo hydroaminative coupling with amides to furnish new dienamides with control of regio- and stereochemistry.

Dienamides are important Diels–Alder partners that have been used for the preparation of polycyclic systems, including natural products.[1] Transition metal-mediated or -catalyzed methods for the formation of these compounds are relatively scarce. Thus, linear (*E*)-*N*-(1,3-butadienyl)amides have been made by Ru-catalyzed co-oligomerization of *N*-vinylamides with alkynes[2] or Ti-mediated coupling of ynamides with alkynes.[3] In addition, *N*-(1,3-buta-2-dienyl)amides have been synthesized *via* Ru-catalyzed enynamide metathesis[4] or Pd-catalyzed cross-coupling of *N*-vinylamides with vinyl triflates.[5] Wakatsuki and Yamazaki observed that (η^5-cyclopentadienyl)(triphenylphosphine)-2,3,4,5-tetraphenylcobaltacyclopentadiene added thioacetanilide and two thiourea derivatives to give the corresponding uncomplexed *N*-butadienamides, although stereochemistry was not established rigorously.[6] Recently, we reported that 2- and 4-pyridone react with 1,7-octadiyne and $CpCo(C_2H_4)_2$ by alkyne coupling with simultaneous N–H activation to yield 1-pyridonyl(η^4-1,3-butadiene)cyclopentadienyl-cobalt complexes.[7] These results for Co suggested potential generality, prompting the title studies.

To avoid competitive cobalt-catalyzed [2 + 2 + 2] oligomerization of the diyne,[8] or [2 + 2 + 2] cooligomerization of the diyne with ethene,[9] we carried out simultaneous slow additions of the alkyne (1 equiv.) and $CpCo(C_2H_4)_2$ (1 equiv.)[10] to a solution (or slurry) of the amine at room temperature using a syringe pump. Simple amines (dimethylamine, cyclopentylamine) proved inert to these conditions. Turning to a more acidic substrate, attempted coupling of phthalimide (5 equiv.) with 1,7-octadiyne (1 equiv.) in dry degassed DMF or DMSO as solvents gave only complex mixtures, while acetone compromised the diyne to give the corresponding fused 2*H*-pyran.[11] Gratifyingly, however, in MeOH or (better) THF, complex **1** emerged, with the added feature of complete *Z* stereoselectivity (Scheme 1). To probe the potential regiochemistry of this transformation, 1-trimetylsilyl-1,7-octadiyne was exposed to identical conditions, again providing only one product, **2**, in which the imido group has transferred exclusively to the substituted diene terminus. The structures of **1** and **2** were readily assigned on the basis of the characteristic shieldings of CpCo-complexed diene hydrogens,[7,12] and by X-ray structural analyses of **2**[13] and of ligands **3** and **4**. The latter were obtained by oxidative demetallation of **1** and **2**, respectively, using iron(III) nitrate.[14]†

The scope of this reaction with other amides was tested next. Since the synthetic interest lay with the organic products, a simple one pot procedure was executed, in which the initial mixture was treated with solid $Fe(NO_3)_3{\cdot}9H_2O$ (1 equiv.) at 0 °C. The results are summarized in Table 1. With simple amides, acetamide performed relatively poorly (entry 1), but dienamides derived from 2-pyrrolidinone (entry 2) and oxindole (entry 3) were isolated in 55% and 65% yield, respectively. Similarly, with imides, diacetamide gave **8** in only moderate yield (entry 4), but phthalimide (using the one pot procedure) converted to **3** in 81% isolated yield (entry 5).



Scheme 1 Synthesis of complexes **1–4** [^{1}H NMR ($CDCl_3$) δ (ppm)] and ORTEP views of **3** and **4** (30% probability ellipsoids).

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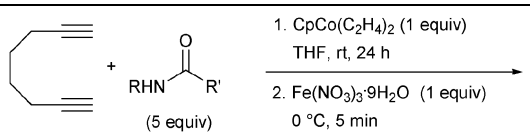
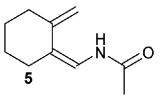
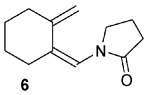
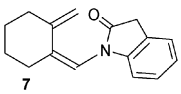
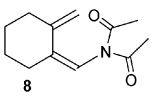
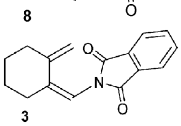
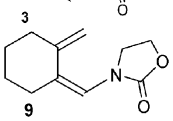
† Electronic supplementary information (ESI) available: Experimental details, spectral data of new compounds, computations. CCDC reference numbers 664316 (**3**), 664315 (**4**), 664317 (**10a**), 664319 (**14a**), 664318 (**21a**) and 664320 (**23a**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b716841a

Table 1 *N*-(*Z*)-(2-Methylenecyclohexylidene)methanamines from 1,7-octadiyne and amides

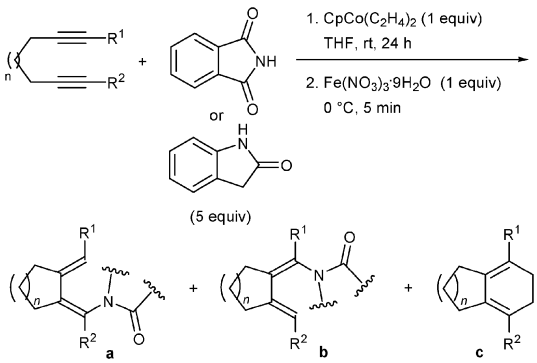


Entry	Substrate	Product	Yield (%)
1	Acetamide	 **5**	24
2	2-Pyrrolidinone	 **6**	55
3	Oxindole	 **7**	65
4	Diacetamide	 **8**	32
5	Phthalimide	 **3**	81
6	2-Oxazolidinone	 **9**	69

Finally, the carbamate 2-oxazolidinone transformed to **9** in 69% yield (entry 6).[15] All of these compounds were obtained as single diastereomers and their stereochemical assignment was based on the X-ray structural analyses of **2–4**, above, as well as **10a**, **12a** and **14a** (*vide infra*). Further corroboration derived from the presence of ^{1}H NMR NOE enhancements of the proton signals of the amidyl bearing terminal diene position with the neighboring cyclohexyl CH_2, and the absence of any such effects on the signals of the other alkenyl hydrogens.

Using phthalimide and oxindole as the amide partners, the effect of varying the structure of the diyne on this process was examined (Table 2). Interestingly, the parent 1,6-hepta- and 1,8-nonadiynes underwent [2 + 2 + 2] oligomerization exclusively. On the other hand, while monosilylation of the latter did not improve on this outcome (entry 13), 1-trimethylsilyl-1,6-heptadiyne allowed the formation of dienamide **10a** as a single isomer in 72% yield (entry 1). Its structure was ascertained by X-ray analysis (see ESI†). Similarly, 1,7-bis-(trimethylsilyl)-1,6-heptadiyne resulted in **11a** in 64% yield (entry 2). Further experiments focused on the 1,7-octadiyne framework (entries 3–12). Thus, **4** emerged from the one pot procedure in yields comparable to the stepwise sequence (entry 3). Switching from mono-$SiMe_3$ to Ph maintained regioselectivity (entry 4), and 1,8-diphenylocta-1,7-diyne converted to **13a** (entry 5), albeit in lower yield. To compare the relative directing power of these substituents, entry 6 was executed. A mixture containing mainly **14a** ensued, from which crystals suitable for X-ray diffraction precipitated, revealing the attachment of the heterocycle to the silylated carbon (see ESI†). The method proved compatible with alcohols

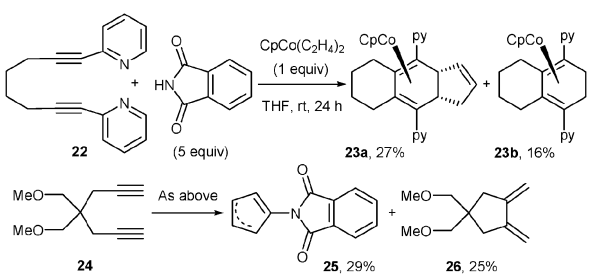
Table 2 Hydroaminative coupling of substituted α,ω-diynes



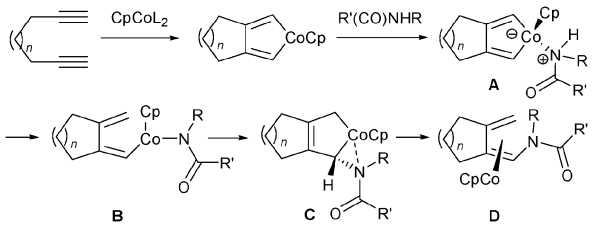
Entry	Substrate	Yield (**a** : **b** : **c**, %)[a]
	Phthalimide	
1	n = 1, R^1 = H, R^2 = $SiMe_3$	**10a** : **10b** : **10c** = 72 : 0 : 0
2	n = 1, R^1 = R^2 = $SiMe_3$	**11a,b** : **11c** = 64 : 0
3	n = 2, R^1 = H, R^2 = $SiMe_3$	**4a** : **4b** : **4c** = 66 : 0 : 0
4	n = 2, R^1 = H, R^2 = Ph	**12a** : **12b** : **12c** = 70 : 0 : 0
5	n = 2, R^1 = R^2 = Ph	**13a,b** : **13c** = 48 : 0
6	n = 2, R^1 = Ph, R^2 = $SiMe_3$	**14a** : **14b** : **14c** = 62 : 18 : 0[b]
7	n = 2, R^1 = H, R^2 = CMe_2OH	**15a** : **15b** : **15c** = 70 : 0 : 0
8	n = 2, R^1 = R^2 = CMe_2OH	**16a,b** : **16c** = 58 : 0
9	n = 2, R^1 = H, R^2 = CO_2Me	Complex mixture
10	n = 2, R^1 = R^2 = CO_2Me	**17a,b** : **17c** = 0 : 70
11	n = 2, R^1 = H, R^2 = BPin[c]	**18a** : **18b** : **18c** = 22 : 13 : 0
12	n = 2, R^1 = R^2 = BPin	**19a,b** : **19c** = 0 : 60
13	n = 3, R^1 = H, R^2 = $SiMe_3$	[2 + 2 + 2] Oligomers
	Oxindole	
14	n = 2, R^1 = H, R^2 = $SiMe_3$	**20a** : **20b** : **20c** = 14 : 65 : 0
15	n = 2, R^1 = H, R^2 = Ph	**21a** : **21b** : **21c** = 78[d] : 0 : 0

[a] Stereo- and regiochemical assignments are based on X-ray structural analyses, NOE experiments and comparison of NMR chemical shifts. [b] Not separated. [c] Pin = 2,3-dimethylbutane-2,3-dioxy. [d] Z : E = 70 : 30.

(entries 7 and 8), but not with esters (entries 9 and 10). With dimethyl deca-2,8-diynedioate (entry 10), the isolation of **17c** indicates competitive ethene interception of the intermediate cobaltacyclopentadiene (*vide infra*). Switching from carbonic to boronic esters appears promising at least for monoboronates (entry 11), furnishing the novel borylated dienamides **18a** and **18b**, although so far inefficiently and without much selectivity. Diboronates failed, transforming to **19c** only (entry 12). An indication of the energetic closeness of the regiochemical alternatives of hydroamination is provided by entry 14. Here, oxindole, unlike phthalimide (entry 3), couples efficiently with 1-trimethylsilyl-1,7-octadiyne to deliver the amide



Scheme 2 Cp transfer reactions to **22** and **24**, respectively. Yields are based on $CpCo(C_2H_4)$.



Scheme 3 Mechanism of hydroaminative coupling.

group predominantly to the non-silylated side, as in **20b**. However, regiochemistry is restored when using 1-phenylocta-1,7-diyne (entry 15). This is the only case in which the expected product (*Z*)-**21a** (structurally ascertained by X-ray diffraction, see ESI†) has suffered (presumably acid-catalyzed)[7] partial isomerization into the *E* isomer.

Finally, very surprising involvement of the normally inert Cp ligand[8] was observed on attempted conversion of **22** and **24**, respectively, with phthalimide. In the case of **22**, a cyclopentadienyl ligand was trapped by [2 + 2 + 2] cocyclization to give complex **23a**,[16] the structure of which was confirmed by X-ray analysis (ESI,† Scheme 2). Complex **23b** arising from ethene insertion was also isolated from the product mixture. On the other hand, a redox reaction appears to prevail with diyne **24**, the *N*-cyclopentadienylated **25** (mixture of double bond isomers) formally derived by oxidative coupling of its components, being complemented by the reductively coupled **26**.

It seems likely that the mechanism of this reaction follows that previously described using DFT computations for the N–H activation of pyridones.[17] We have expanded on these calculations with cyclopentylamine, 2-pyrrolidinone and succinimide (see ESI† for details). To summarize (Scheme 3), a cobaltacyclopentadiene is first formed by oxidative coupling of the two triple bonds. It reacts with the amide to give the corresponding *N*-coordinated 18-electron complex **A**. Proton transfer from nitrogen to carbon occurs to give a dienylcobalt species **B**, a step that has a prohibitively high barrier for alkanamines. This intermediate rearranges subsequently into an *N*-coordinated cobaltacyclopentene **C**. The latter reductively valence tautomerizes selectively in the opposite direction of the amido group to give **D**, which accounts for the stereoselectivity. The regiochemistry (with the exception of that in **20b**) appears to be controlled by initial proton transfer to the least substituted (or hindered) position in the cobaltacyclopentadiene.

In summary, we have discovered a simple route to dienamides that combines the coupling of α,ω-diynes with hydroamination. This methodology allows the rapid chemo-, regio- and stereoselective construction of amidated 1,2-dimethylenecycloalkanes. While limited to diynes and non-catalytic,[18] it gives rise to novel structures and establishes the feasibility of the strategy. We are now evaluating the products as Diels–Alder partners for the construction of complex molecules.

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18 Monoalkynes, such as diphenyl-, phenyl- and trimethylsilylacetylene led to [2 + 2 + 2] cycloadducts only. There is no catalytic turnover of Co, even at elevated temperatures. Several other metal systems based on Rh, Ir and Ru were ineffective.