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Regiochemistry of Copper(I)-Mediated Cyclization Reactions of Halo-dienamides

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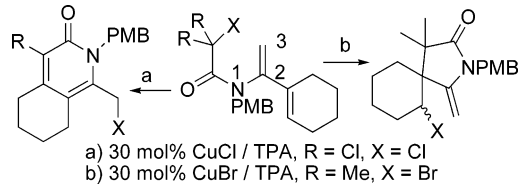
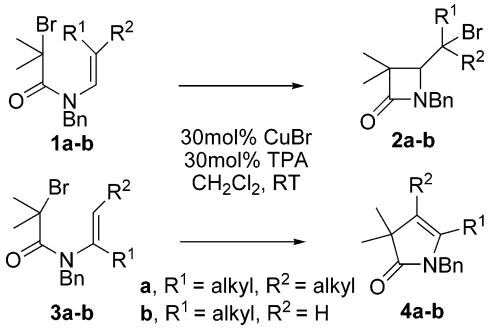


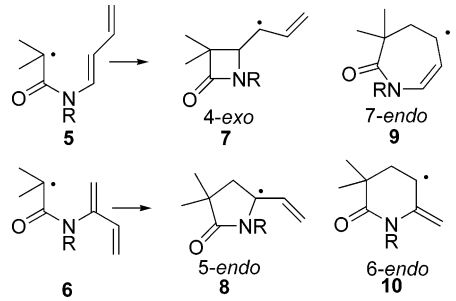
Reaction of 2-substituted dienamides with catalytic amounts of copper halide/tripyridylamine (TPA) furnishes either 5-*exo* or 6-*endo* products with the outcome dependent upon the radical initiating unit. Reaction of 3-substituted dienamides produces β-lactams via a 4-*exo* cyclization with termination of the reaction occurring via either halogen atom transfer, trapping with oxygen, elimination, or radical−radical coupling depending upon the diene.

Copper(I)-mediated halogen atom transfer radical and radical−polar crossover cyclizations have attracted considerable interest in recent years.[1] Initially, reactions were restricted to the cyclization of trichloro derivatives using CuCl and bipyridine[2] or TMEDA[3] as ligands. Recently, more active catalysts derived from Me_6-tren[4] or tripyridylamine (TPA)[5] have been developed which facilitate the cyclization of monobromo derivatives (e.g., **1** and **3**). While the majority of work has focused on 5-*exo* cyclizations, we have reported that CuBr/TPA mediates the cyclization of 3,3-disubstituted enamides **1a** via a 4-*exo* atom transfer reaction mode to give **2a**[6] and CuBr/Me_6-tren facilitates the cyclization of 2,3-disubstituted enamides **3a** via a 5-*endo* radical polar crossover process to give **4a** (Scheme 1).[4b] During the course of these studies, we noted that it was not possible to mediate the reaction of corresponding 3- and 2-monosubstituted derivatives (**1b** and **2b**, $R^2 = H$) using these and forcing (refluxing toluene) conditions.This prompted us to explore radical cyclizations onto dienamides. We postulated that cyclization of suitably substituted dienamides might facilitate these reactions by stabilizing thermodynamically the cyclized radicals as allyl species **7** and **8**. While the regiochemical outcome of radical cyclizations onto monoenamides has been well-documented,[7] to our knowledge, no information as to the regiochemistry of addition to dienamides of type **5** or **6** has appeared in the literature. While we predicted that cyclization of radical **5** would lead to the 4-*exo* product **7**, we could not rule out cyclization via alternative 5-*endo*, 6-*exo*, or 7-*endo* reaction pathways. Similarly for the cyclization of radicals of type **6**, alternative 4-*exo*, 5-*exo*, or 6-*endo* pathways could not be dismissed. While 7-*endo* cyclization of **5** and 6-*endo* cyclization of **6** also led to allylic radicals **9** and **10**, these modes of cyclization are rare and we did not expect to observe them (Scheme 2).

SCHEME 1



SCHEME 2. Possible Modes of Cyclization of Dienamides



Reaction of 3-Substituted Dieneamides: Our initial investigations focused upon the copper-mediated atom transfer cyclization reactions of dienamides **11a**−**d** (Scheme 3). We expected that these compounds would cyclize in a 4-*exo* mode based upon precedent from our studies with the corresponding 3,3-disubstituted compounds. Initial imine formation (by con-

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(3) (a) Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *41*, 14031. (b) De Buyck, L.; Cagnoli, R.; Ghelfi, F.; Merighi, G.; Mucci, A.; Pagnoni, U. M.; Parsons, A. F. *Synthesis* **2004**, *10*, 1680.
(4) (a) Clark, A. J.; De Campo, F.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastécouères, D.; Thomas, G. H.; Verlac J.-B.; Wongtap H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671. (b) Clark, A. J.; Dell, C. P.; Ellard, J. M.; Hunt, N. A.; McDonagh, J. P. *Tetrahedron Lett.* **1999**, *40*, 8619. (c) Clark, A. J.; Filik, R. P.; Thomas, G. H. *Tetrahedron Lett.* **1999**, *40*, 4885.
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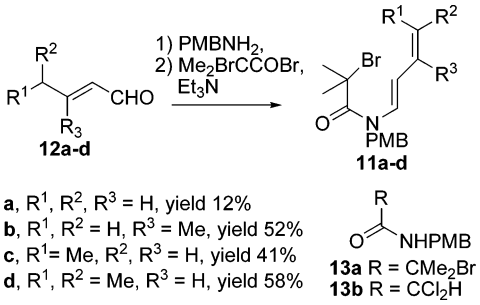
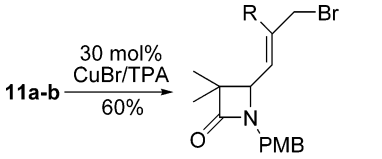
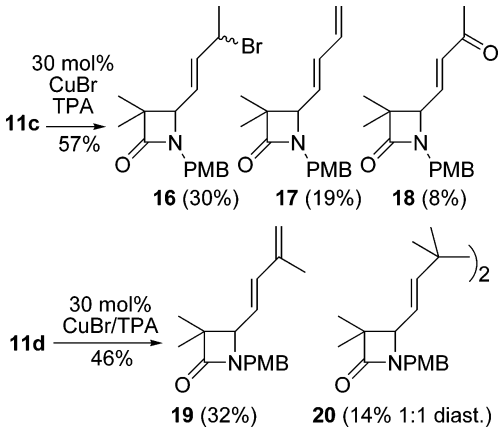
SCHEME 3. Preparation of 11a−d



SCHEME 4. Cyclization Reactions of 11a,b



SCHEME 5. Cyclization Reactions of 11c,d

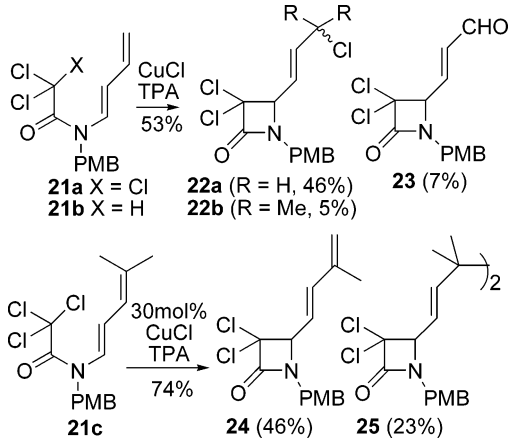


densation of aldehydes **12a**−**d** with *p*-methoxybenzylamine) followed by Et_3N-mediated acylation with 2-bromo-2-methylpropionyl bromide produced the desired cyclization precursors **11a**−**d**. The low yield (12%) for the synthesis of the dienamide **11a** was due to its relative instability when compared to that of the other compounds (**13a**, 20% was isolated during the purification of **11a**).

Treatment of a 0.12 M solution of **11a**−**d** in toluene with 30 mol % of CuBr/TPA furnished the corresponding *β*-lactams **14**−**20** (Schemes 4 and 5). The compounds **11a**,**b** underwent fairly rapid reactions (2 h) to give the primary allyl bromides **14** and **15** in 60 and 57% yields, respectively. Trapping of the intermediate cyclized allyl radicals only occurred at the 1° position in both cases.

Compounds **11c**,**d** (which contained substitution at the terminal carbon of the diene system) underwent much slower reactions (19 h) and gave rise to mixtures of products **16**−**20**. Reaction of **11c** (2:1 *E*:*Z*) led to three *β*-lactam products arising from atom transfer **16** (as a 1:1 mixture of diastereomers), elimination **17**, and oxidation **18**. Heating a pure sample of the secondary bromide **16** at reflux in toluene produced a 3.5:1 ratio of **16**:**17** after 6 h, providing tentative evidence that the eliminated product **17** arises via thermal elimination from the bromide **16**. Reaction of **11d** produced the corresponding diene

SCHEME 6. Cyclization of Trichloro Analogues



19 (presumably from elimination of the undetected 3° bromide) and the dimer **20** (as a 1:1 mixture of diastereomers).

Interestingly, reaction of the analogues **21a**−**c** (Scheme 6) was significantly slower than that of their **11a**−**d** counterparts (18 h for **21a** compared to 2 h for **11a**). For the reaction of **21a**, a significant amount of the oxidized aldehyde **23** was detected (**22a**:**23** = 7:1). This ratio could be reversed if the reaction was carried out under oxygen (**22a**:**23** = 1:2); however, the yield dropped to 26%.[8] Reaction of derivative **21b** (a 5:1 mixture of rotamers at room temperature) gave a complex mixture of decomposition products on treatment with 30 mol % of CuCl/TPA in refluxing toluene for 20 h. The known amide **13b** was the only identifiable compound isolated from the crude mixture (albeit impure).[9] On the basis of this result, dichlorodienamides were not evaluated further. Cyclization of **21c** proceeded in the same manner as the analogous **13d**, albeit in a better yield. In addition to the two products **24** and **25**, a trace amount of the 3° chloride **22b** was isolated (5%), indicating that the diene **24** is probably produced via thermal elimination of HCl from **22b**.

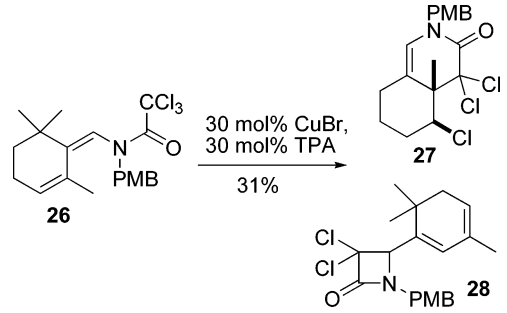
Encouraged by the higher yields obtained in the cyclization of the trichloro derivative **21b**, we briefly explored the scope of cyclization onto the hindered derivative **26** (obtained from *β*-cyclocitral). Reaction yielded the 6-*exo* product **27** (as one diastereomer as determined by NOE) and the 4-*exo* product **28** in a 3:2 ratio in poor combined yield (31%; Scheme 7). The rest of the mass balance was baseline material.

Surprised by the regiochemical outcome of cyclization of **26** (where the 6-*exo* product predominated), we next investigated the regiochemical outcome and relative rate of cyclization onto the dieneamide functionality **29** in a competition experiment (Scheme 8). In this case, cyclization onto the diene **29** would be competitive with a traditional 5-*exo* cyclization. We also compared the outcome of this reaction with that of the 3,3-disubstituted alkene **30**. While cyclization of **30** at room temperature furnished an inseparable mixture of the products (**33**:**32**, 5:1, 97%), the only product arising from reaction of **29** was the corresponding 5-*exo* product **31** (91%), indicating that cyclization onto the 4-*exo* position of the diene fragment is slower than both the 5-*exo* reaction and the 4-*exo* cyclization

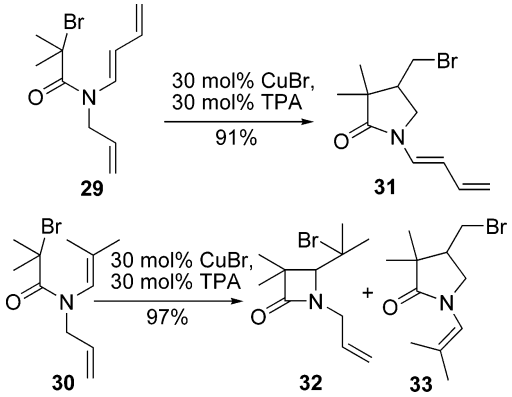
(8) Presumably caused by oxidation of the CuCl/TPA complex to the corresponding Cu(II) peroxo complex: Chishiro, T.; Shimazaki, F.; Tani, F.; Tachi, Y.; Naruka, Y.; Karasawa, S.; Hayani, S.; Maeda, Y, *Angew. Chem., Int. Ed.* **2003**, *42*, 2788.

(9) Gani, V.; Viout, P. *Tetrahedron* **1978**, *34*, 1337.

SCHEME 7. Cyclization of 26



SCHEME 8. Competition Experiments



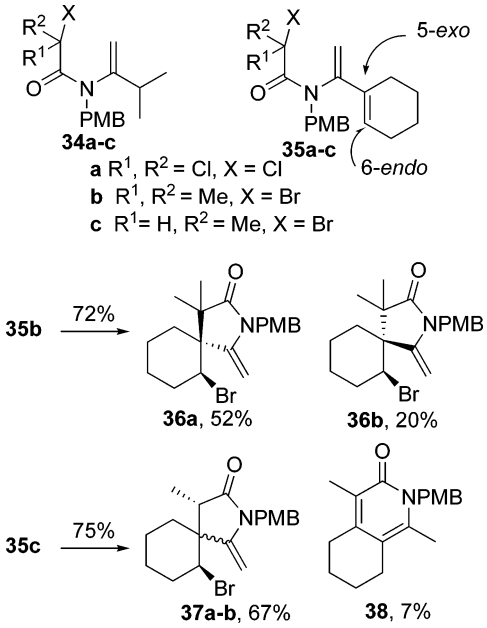
of an analogous 3,3-disubstituted alkene. Cyclization of **30** at reflux furnished the thermodynamic product **33** only (95%).

Reaction of 2-Substituted Dieneamides: Trichloro derivatives with substituents at the 2-position in enamides (e.g., **34a**) have been reported to undergo cyclization exclusively in the 5-*endo* mode, while analogous compounds with less activated initiating functionality (e.g., **34b**) fail to undergo any cyclization.[4b] Thus we next investigated the cyclization reactions of **35a**−**c** (Scheme 9), and in order to potentially increase the bias toward the 5-*endo* mode of cyclization, we introduced substituents at the 5-*exo* and 6-*endo* positions to retard competitive reaction at these points. Cyclization of the bromide **35b** furnished a 72% yield of the 5-*exo* cyclization product **36** (5:2 mixture of diastereomers) with no 5-*endo* products being detected.

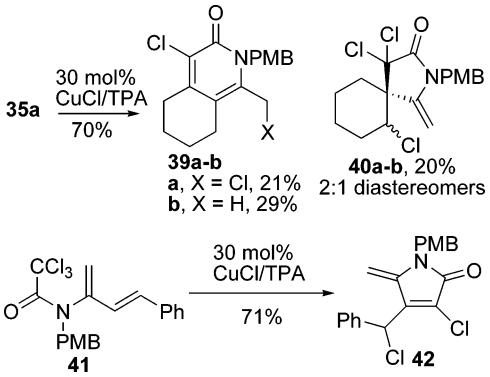
Cyclization of the 2° bromide **35c** also delivered the 5-*exo* product **37** (2:1 mixture of diastereomers, 67%) but with a minor amount (7%) of the formal 6-*endo* product **38**. Two of the four possible diastereomers of **37** were produced and tentatively assigned as **37a**,**b** based upon NOE data. In both cases, the expected 5-*endo* cyclization mode was not observed. This was surprising in light of the exclusive 5-*endo* cyclization of **34a** which has a similar steric demand. While reports of 6-*endo* cyclizations have appeared in the literature,[7] they are relatively rare.[10] So it was interesting to observe that these were the major products arising from the cyclization of **35a** (50%). Finally we investigated the cyclization of the dienamide **41** which was found to convert to a single product **42** in 71% yield when treated with CuCl and TPA in toluene at reflux (Scheme 10).

(10) Cyclization onto imines: (a) Tajino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* **2006**, *128*, 7712. (b) Cyclization of vinyl radicals: (c) Quirante, J.; Vila, X.; Palona, L.; Guiu, J. M.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 1372.

SCHEME 9. Cyclization of 2-Substituted Dienamides



SCHEME 10. Cyclization of 2-Substituted Dienamides



In conclusion, we have investigated the regiochemical outcome of Cu(I)-mediated cyclization of 2- and 3-substituted dienamides. For 3-dienamides derived from aldehydes (**11a**−**d**, **21a**−**b**) cyclization proceeds via a 4-*exo* cyclization mode mirroring the observed outcome of the related 3,3-disubstituted enamides (e.g., **1a**). Termination of the reaction via a 1° radical generally leads to halogen atom transfer, while termination by a 2° radical leads to mixtures of atom transfer, elimination, and oxygen trapping, making the reactions less synthetically useful. Cyclization leading to 3° radicals leads to elimination and dimerization. On the other hand, reaction of 2-substituted dienamides (**35b**,**c** and **41**) derived from ketones did not proceed via the expected 5-*endo* mode of cyclization (based upon precedence with the reaction of **1b**), instead proceeding via the 5-*exo* mode predominantly. The nature of the initiating radical functionality in **35a**−**c** had a profound outcome on the regiochemistry with **35a** proceeding via the 6-*endo* cyclization mode.

Experimental Section

General Procedure for the Synthesis of Dienamides 11a−d, 21a,b, 26, 29, 31, and 32 Derived from Aldehydes. The amine (4-methoxybenzylamine or allylamine) (40 mmol) was added to the appropriate aldehyde (40 mmol) at 0 °C. After 15 min, the mixture was dissolved in diethyl ether (100 mL), dried over $MgSO_4$,

filtered, and concentrated in vacuo to give a crude imine that was used without further purification. To this imine (4 mmol) at 0 °C in anhydrous CH_2Cl_2 (20 mL) under nitrogen was added either trichloroacetyl chloride (4 mmol) or 2-bromoisobutyryl bromide (4 mmol) followed by triethylamine (4 mmol). After stirring at 0 °C for 3 h, the reaction mixture was washed with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by column chromatography.

General Procedure for the Synthesis of Dienamides 37a−c and 47 Derived from Ketones. A mixture of 4-methoxybenzylamine (15 mmol), the appropriate ketone (15 mmol), and anhydrous $ZnCl_2$ (100 mg) in dry toluene (60 mL) was heated at reflux for 16 h with azeotropic removal of water. Filtration followed by removal of the solvent in vacuo furnished a crude imine that was used without further purification. To this imine (4 mmol) at 0 °C in anhydrous CH_2Cl_2 (20 mL) under nitrogen was added over 10 min either trichloroacetyl chloride (4 mmol), 2-bromopropionyl bromide (4 mmol), or 2-bromoisobutyryl bromide (4 mmol) followed by *N*,*N*-diethylaniline (4 mmol). After stirring for 16 h at room temperature, the reaction mixture was washed with 1 N HCl (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by column chromatography.

General Procedure for Cyclization Reactions. To a solution of the cyclization substrate in dry toluene (0.012 M) under nitrogen were added CuCl or CuBr (0.3 equiv) and tripyridylamine (0.3 equiv). The mixture was heated at reflux (between 2 and 16 h), cooled, and filtered through silica with elution with EtOAc. The combined filtrate was concentrated in vacuo, and the residue was purified by column chromatography.

Acknowledgment. We acknowledge AstraZeneca for a studentship (J.V.G.).

Supporting Information Available: Selected experimental procedures and characterization data for all compounds and representative ^{1}H NMR for **11**, **13**−**33**, and **35**−**42** (the inseparable mixture of **32** and **33**), and ^{13}C NMR data for **14**−**20**, **22**−**25**, **27**, **28**, **31**, **33**, and **36**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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