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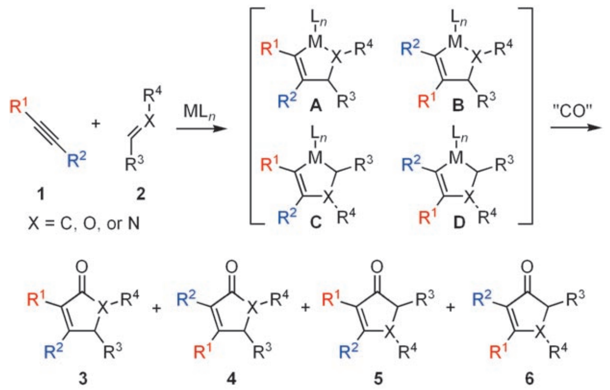
An Alkoxide-Directed Intermolecular [2+2+1] Annulation: A Three-Component Coupling Reaction for the Synthesis of Tetrasubstituted α,β-Unsaturated γ-Lactams**

*Martin McLaughlin, Masayuki Takahashi, and Glenn C. Micalizio**

Metal-mediated [2+2+1] annulations are a powerful class of reactions for the synthesis of functionalized five-membered rings.[1] These processes, which proceed by the initial formation of a metallacyclopentene followed by the insertion of CO, have been described for a variety of functionalized π systems (alkyne–alkene,[2] alkyne–ketone, alkene–ketone,[3] alkene–aldehyde,[3,4] and alkyne–imine[5]), and have been useful for the preparation of functionalized carbocyclic and heterocyclic molecules. The vast majority of these annulation reactions are synthetically useful only in intramolecular contexts, whereby geometrical constraints imposed by a tether between the two reacting π systems dictate the site-selectivity in the C–C bond-forming event. The corresponding bimolecular coupling reaction of unsymmetrically substituted π systems from metal-mediated [2+2+1] annulations has proven much less general as a result of the challenges associated with the control of both reactivity and regioselectivity in the generation of the polysubstituted metallacyclopentene (Scheme 1, **1**+**2**→[**A**–**D**]→**3**–**6**). Here, we describe a highly regioselective process for the bimolecular [2+2+1] annulation that provides a convenient and direct route to tetrasubstituted α,β-unsaturated γ-lactams.

Nitrogen-containing heterocycles are ubiquitous structural motifs in natural products and small molecules of biomedical relevance. Many methods for the convergent assembly of such structures target C–C or C–N bond formation by nucleophilic addition to C=N-based π systems, condensation, or metal-mediated cross-coupling reactions.[6] An alternative and potentially more powerful pathway to functionalized heterocycles is through multicomponent coupling reactions between all-carbon-based π systems, imines, and CO_2 by using [2+2+1] annulation reactions.[5] To date, these annulation processes have been of limited utility in organic synthesis because of the poor levels of regioselection commonly observed in the initial cross-coupling reaction between the internal alkyne and the imine (alkyne+imine→azametallacyclopentene).[7] A general means to control the site- and stereoselective C–C bond formation in these bimolecular coupling reactions would render such processes versatile for the synthesis of highly functionalized nitrogen-containing acyclic and heterocyclic targets. Our recent success in the development of selective cross-coupling reactions of unactivated and differentially functionalized π systems (alkyne–alkyne[8] and alkyne–alkene[9]), in which the unique reactivity of Group IV metal alkoxides was harnessed, led us to question whether we could define such a process for alkyne–imine cross-coupling reactions through the directed carbometalation of an internal alkyne with an azametallacyclopropane.



Scheme 1. Regioisomeric products from bimolecular [2+2+1] annulation reactions. L = ligand.

Our initial results for the regioselective cross-coupling reaction between internal alkynes and imines are shown in Table 1. In short, preformation of an azametallacyclopropane (imine, Ti(O*i*Pr)$_4$, and cyclopentylmagnesium chloride, −78 to −40 °C) was followed by the addition of a homopropargylic alkoxide, and warming the reaction mixture to 0 °C. Protonation of the presumed bicyclic azametallacyclopentene then delivered an unsaturated 1,5-amino alcohol. As illustrated in entry 1 (Table 1), the coupling of imine **7** with the homopropargylic alkoxide **8** provided the unsaturated 1,5-amino alcohol **9**. Importantly, no evidence was found for the production of a minor regioisomer or olefin isomer. This single result represents the first highly regioselective cross-coupling reaction between an unsymmetrically substituted internal alkyne and an imine that proceeds without the requirement of electronic or steric differentiation of the internal alkyne. Although metal-mediated coupling reactions between alkynes and imines have been described, these

[*] M. McLaughlin, M. Takahashi, Prof. G. C. Micalizio
Department of Chemistry, Yale University
225 Prospect St., New Haven, CT 06520-8107 (USA)
Fax: (+1) 203-432-6144
E-mail: glenn.micalizio@yale.edu

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Supporting information for this article (including the characterization of all new compounds) is available on the WWW under http://www.angewandte.org or from the author.

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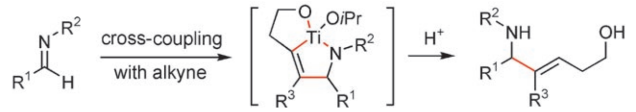
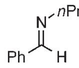
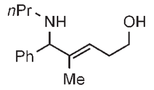
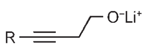
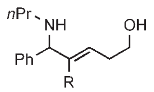
Table 1: Stereoselective synthesis of unsaturated 1,5-amino alcohols.[a]



Entry	Imine	Unsaturated alkoxide	Yield [%]	Major regioisomer
1	 **7**	 **8**	65	 **9**
				
2	**7**	**10**: R = Et	60	**11**: R = Et
3	**7**	**12**: R = *i*Pr	53	**13**: R = *i*Pr
4	**7**	**14**: R = TMS	55	**15**: R = TMS

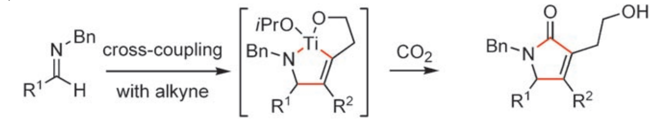
[a] Reaction conditions: Ti(O*i*Pr)$_4$, *c*C_5H_9MgCl, Et_2O, −78 to −40 °C, then unsaturated alkoxide (−40 to 0 °C), quenched with sat. aq NH_4Cl. TMS = trimethylsilyl.

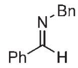
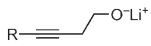
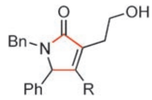
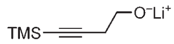
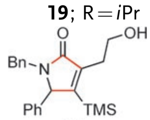
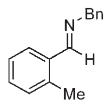
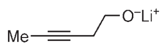
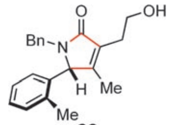
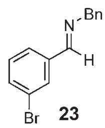
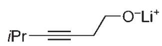
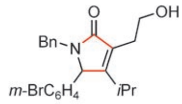
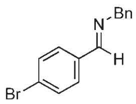
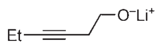
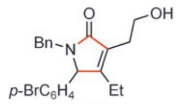
coupling reactions proceed in a regioselective manner with only a small subset of alkynes: terminal, trimethylsilyl (TMS)-substituted, or conjugated alkynes.[5,7]

As observed in our alkyne–alkyne and alkene–alkyne cross-coupling reactions,[8,9] the current process is relatively insensitive to nonbonded steric interactions imposed by substitution at the alkyne. For example, as depicted in entries 2–4 (Table 1), ethyl-, isopropyl-, and TMS-substituted alkynes were all effective cross-coupling partners, and furnished the unsaturated 1,5-amino alcohols **11**, **13**, and **15** as single regioisomeric products—in all cases C−C bond formation occurred distal to the homopropargylic alkoxide, independent of steric considerations. Interestingly, entry 4 (Table 1) demonstrated a complete reversal in regioselectivity with respect to known cross-coupling reactions of TMS-substituted alkynes and imines (C−C bond formation typically occurred β to the TMS substitutent), hence demonstrating that the directing effect of the tethered alkoxide completely overrides the directing effect of the TMS substituent.[10]

With this site-selective alkyne–imine cross-coupling reaction in hand, we focused our attention on developing an intermolecular aza-Pauson–Khand-like annulation reaction for the synthesis of tetrasubstituted γ-lactams (Table 2).[5c] As illustrated in entry 1 (Table 2), coupling of the imine **16** and the methyl-substituted internal alkyne **8**, followed by exposure to CO_2 (20 psi) and heating to 90 °C, furnished the tetrasubstituted γ-lactam **17** as a single regioisomer in 66 % yield. This annulation process was similarly effective with alkyne substrates that possessed more sterically demanding substituents at the terminus of the alkyne (entries 2–4, Table 2), and provided access to the ethyl-, isopropyl-, and TMS-substituted unsaturated γ-lactams **18**–**20** as single regioisomers. Substituted aromatic imines were also effective coupling partners in this reaction; the aromatic imines **21**, **23**, and **25** with *ortho*-methyl, *meta*-bromo, and *para*-bromo substitution, respectively, provided the functionalized lactams **22**, **24**, and **26** in 55–63 % yield (entries 5–7, Table 2).[11] Interestingly, the coupling of the *ortho*-substituted aromatic

Table 2: Stereoselective synthesis of tetrasubstituted α,β-unsaturated γ-lactams.[a]



Entry	Imine	Unsaturated alkoxide	Yield [%]	Major regioisomer
	 **16**			
1	**16**	**8**; R = Me	66	**17**; R = Me
2	**16**	**10**; R = Et	61	**18**; R = Et
3	**16**	**12**; R = *i*Pr	64	**19**; R = *i*Pr
4	**16**	 **14**	49	 **20**
5	 **21**	 **8**	55	 **22** d.r. = 4:1
6	 **23**	 **12**	63	 **24**
7	 **25**	 **10**	59	 **26**

[a] Reaction conditions: Ti(O*i*Pr)$_4$, *c*C_5H_9MgCl, PhMe, −78 to −30 °C, then unsaturated alkoxide (−30 to 0 °C), then CO_2 (20 psi) 90 °C, 48 h. Bn = benzyl.

imine **21** with alkoxide **8** proceeded in a diastereoselective manner and produced the corresponding atropisomeric lactam **22** in a 4:1 ratio.

This [2+2+1] cross-coupling reaction could also be performed in a stereoselective manner. As depicted in Scheme 2, use of a chiral imine **27**[12] in the cross-coupling reaction with alkynes **8** or **12** provided the unsaturated 1,5-amino alcohol products with regioselectivity greater than 95:5 (major/minor regioisomer) in all cases. Interestingly, diastereoselectivity in these reactions appears to be a function of the size of the terminal substituent of the alkyne (90:10 d.r. when R = Me, 75:25 d.r. when R = *i*Pr).

This diastereoselective cross-coupling reaction could be extended to [2+2+1] annulation processes. As depicted in Scheme 2 b, coupling of imine **31**, alkyne **8**, and CO_2 proceeded in a regio- and stereoselective manner to provide the γ-lactam **32** in 48 % yield (≥ 95:5 (major/minor regioisomer); 83:17 d.r.).[13]

In conclusion, we have developed a highly regioselective cross-coupling reaction between internal alkynes and imines that provides convergent access to unsaturated 1,5-amino alcohols or tetrasubstituted α,β-unsaturated γ-lactams.[14] The regiochemical control in these bimolecular coupling reactions

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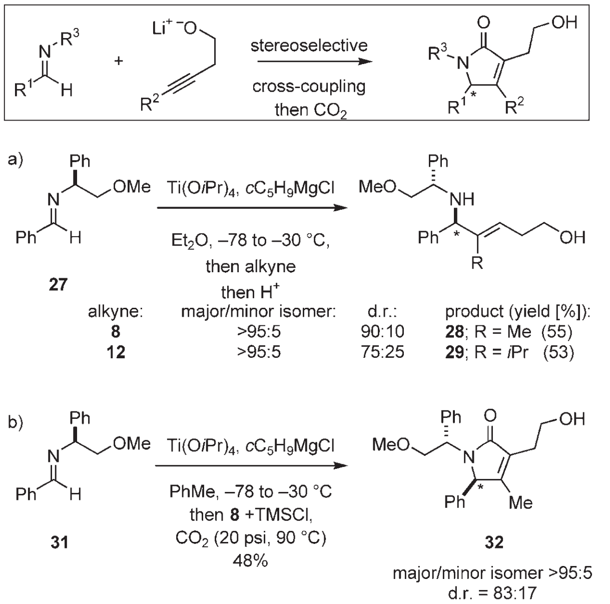

Scheme 2. Stereoselective synthesis of unsaturated 1,5-amino alcohols and tetrasubstituted α,β-unsaturated γ-lactams.

results from alkoxide-directed carbometalation between a preformed azametallacyclopropane and an internal alkyne. The selectivity in these processes was independent of the differential size of substituents around the internal alkyne, and was completely dictated by the presence of a neighboring alkoxide group. Finally, we have demonstrated the potential to employ this coupling reaction in a stereoselective manner whereby absolute stereochemical control is derived from a chiral imine. Further studies focused on the control of related intermolecular [2+2+1] processes are in progress.

Experimental Section

Representative procedure (entry 1, Table 2): Cyclopentylmagnesium chloride (1.8 M in diethyl ether, 2.70 mmol) was added dropwise with a gas-tight syringe to a Schlenk tube charged with a solution of imine **16** (0.292 g, 1.50 mmol) and $Ti(OiPr)_4$ (0.383 g, 1.35 mmol) in toluene (5 mL) at −78 °C. The yellow solution was slowly warmed to −30 °C over 1 h and the brown solution was stirred at −30 °C for a further 2 h. Next, a solution of lithium alkoxide **8**, generated from the deprotonation of the corresponding alcohol (0.028 g, 0.338 mmol) with *n*BuLi (2.5 M in hexanes, 0.371 mmol) in toluene (900 μL) at −78 °C then warming to 0 °C over 20 min, was added dropwise to the brown solution of imine **16** at −30 °C. The reaction was allowed to warm to 0 °C over 1 h and stirred at 0 °C for 4 h. The reaction was then cooled to −30 °C, evacuated, backfilled with CO_2 (20 psi, evacuation and backfilling repeated 3 times), and heated to 90 °C for 48 h. Next, the reaction was removed from the oil bath, the CO_2 was released, and the reaction was quenched with 1 mL of H_2O. The resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The solution was then further diluted with 0.5 M HCl (40 mL) and extracted with diethyl ether. The combined organic phases were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (50 %→66 % EtOAc/hexanes) to yield γ-lactam **17** as an off-white solid (68 mg, 66 %).

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