Published in final edited form as:

European J Org Chem. 2017 January 3; 2017(1): 45–48. doi:10.1002/ejoc.201601283.

Diastereoselective Intramolecular Cyanoamidation with Alkenes

Ashley M. Dreis^{a,†}, Sadie C. Otte^a, Matthew S. Eastwood^a, Elizabeth R. Alonzi^a, Jason T. Brethorst^a, and Christopher J. Douglas^{a,*}

^aDepartment of Chemistry, University of Minnesota–Twin Cities 207 Pleasant St. SE, Minneapolis, MN 55155, USA

Abstract

Reported herein is a diastereoselective intramolecular alkene cyanoamidation, wherein high d.r. values are imparted by chiral directing groups. Lactams with an α -all-carbon quaternary stereocenter are readily synthesized, which may enable access to structures frequently found in biologically active molecules and natural products.

Keywords

Cyanoamidation; Diastereoselectivity; Bond Activation; Palladium; Homogeneous catalysis

Introduction

The stereoselective formation of all-carbon quaternary centers is a significant synthetic challenge that is particularly important for the synthesis of complex molecules. Cyanoamidation, one of several emerging C–CN bond activation methods, involves the activation of a C–CN bond and subsequent addition of the cyanoformamide carbonyl and nitrile groups to a double bond. In particular, cyanoamidation with 1,1-disubstituted alkenes enables efficient formation of all-carbon quaternary stereocenters while forming two new C–C bonds.

Asymmetric construction of ring systems is one achievement of C–CN bond activation methods. Since various therapeutic alkaloids and/or synthetic drug targets often contain highly-functionalized cyclic amines, C–CN bond activation (e.g., cyanoamidation) may be employed to easily streamline the synthesis of such scaffolds. For example, C–CN bond activation has proven to be a rapid complexity-building tool, as showcased in the total syntheses of esermethole^[1,2] and vincorine.^[3]

A decade ago, Takemoto^[4,5] disclosed the formation of 3,3-disubstituted oxindoles through intramolecular cyanoamidation and later developed an asymmetric version of this reaction (Scheme 1a).^[6,7] An aliphatic-tethered alkene derivative (Scheme 1b) did not cyclize with

cdouglas@umn.edu, <http://www1.chem.umn.edu/groups/douglas/>.

[†]Current address: Benesch, Friedlander, Coplan, & Aronoff LLP, 41 South High Street, Suite 2600, Columbus, OH 43215, USA

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <http://dx.doi.org/10.1002/ejoc.201601283>.

the same efficiency as the aromatic-tethered substrates.^[7] High levels of stereocontrol have been limited to cyanoamidation reactions that form oxindoles. However, intramolecular cyanoamidation with aliphatic-tethered alkynes to give α -alkylidene lactams was successful.^[1]

Herein, we report the first catalytic diastereoselective cyanoamidation of cyanoformamides with aliphatic-tethered alkenes (Scheme 1c). A facile synthesis of lactams bearing an α -all-carbon quaternary stereocenter is achieved. The high stereoselectivity is attributed to the strategic placement of a chiral directing group, which is an underutilized strategy in metalcatalyzed transformations. Our approach reduces the dependency on synthetically complex or expensive chiral ligands. Further, we expand the scope of lactams that can be prepared by stereoselective cyanoamidation, which should further broaden its utility in the synthesis of complex molecules.

Results and Discussion

We have discovered that *N*-benzyl protected aliphatic-tethered alkenylcyanoformamide derivatives successfully undergo cyanoamidation in the presence of Lewis acids.^[8] Previous work suggests that Lewis acids effectively promote C–CN bond activation reactions in other contexts;^[9–11] mechanistic studies regarding this effect in cyanoamidation are ongoing in our laboratory.^[12] Therefore, we began our studies on diastereoselective cyanoamidations with chiral *N*-benzyl and *N*-naphthyl derivatives.

Cyanoformamide **1a** was heated to 130 °C in the presence of Pd₂dba₃, triphenylphosphine, and triphenylborane for 48 h, which resulted in full consumption of the starting material **1** to the desired piperidinone product **2a**. The d.r. of the reaction was determined to be 3.8:1 (Table 1, entry 1). We were encouraged because this selectivity was achieved in the absence of a chiral catalyst; the chiral directing group alone was sufficient to impart diastereoselectivity. Other achiral phosphine ligands were examined in order to probe their stereoelectronic effects. Ligand parameters such as cone angle and electron-donating ability did not appear to significantly influence the reaction and we were unable to make correlations between the ligand structure and the stereoselectivity (entries 2–4). Decreasing the temperature resulted in only 67 % consumption of **1** (as determined by the ratio of **1**:**2** in the ¹H NMR) and did not affect the diastereoselectivity (entry 5).

Chiral phosphoramidite ligands were added to the reactions in an attempt to enhance the stereoselectivity. Ligands **4–6** had been reported by Takemoto et al.^[7] as being effective in the enantioselective synthesis of oxindoles through cyanoamidation. Reaction of **1a** with ligand **4** provided **2a** with a d.r. of 1:1.6, in favor of the minor diastereomer that was obtained when achiral phosphine ligands were employed (entries 1–5 vs. entry 6). In addition, a new byproduct **3a** was observed in a ratio of 1.5:1, **2a**:**3a**. The five-membered lactam **3a**, being void of a nitrile and including an exocyclic olefin, likely formed through 1) isomerization of the olefin, 2) migratory insertion of the C–C bond across the *gem*-dimethyl olefin, and 3) β -hydride elimination to release HCN.^[12] We hypothesized that a substrate-ligand stereochemical mismatch between **1a** and **4** may have been responsible for the observed change in diastereoselectivity and chemoselectivity. Accordingly, we prepared the

enantiomer of ligand **4**. As expected, ligand **5** (*ent-4*) gave an increased d.r. of 6.3:1 and formation of byproduct **3a** decreased (7.2:1, **2a:3a**; entry 7). Introducing methyl substituents on the 1,1'-bi-2-naphthol (BINOL) backbone (ligand **6**) further improved the diastereo- and chemoselectivity. In order to preserve the matched relationship between ligand and substrate, we investigated the enantiomer of **1a** (**1b**, *ent-1a*) in the reaction with ligand **6**; product **2b** was obtained in a d.r. of 8.1:1 along with **3b** in a ratio of 14.6:1 (entry 8). A diastereomer of ligand **6**, ligand **7**, further raised the d.r. to 8.7:1 and byproduct **3b** was not observed (entry 9).

We next prepared substrate **1c**, which contains the bulkier (*S*)-naphthyl(ethyl) directing group. In the presence of an achiral catalyst, product **2c** was formed selectively as a 4.1:1 mixture of diastereomers (entry 10). Therefore, the inherent selectivity for the naphthyl(ethyl) directing group is comparable to the phenyl(ethyl) analogue. Reaction of **1c** in the presence of the catalyst produced from Pd₂dba₃ and ligand **4** gave product **2c** in the highest d.r. observed in this study (10.2:1); however, a significant amount of byproduct **3c** was also formed (1.5:1, **2c:3c**; entry 11). Ligand **5**, the enantiomer of **4**, resulted in a significant decrease of the d.r. (2.3:1, entry 11 vs. 12). These results suggest that ligand **5** is mismatched with **1c** whereas ligand **4** is matched with **1c**. Unlike the phenyl substrate **1a**, the naphthyl substrate **1c** favored the same diastereomer with both matched and mismatched ligands (entries 6 and 7 vs. entries 11 and 12). Ligands **4** and **5** were not able to override the stereochemical influence of the naphthyl group in **1c**, unlike the reactions with **1a**. While the naphthyl group of **1c** induces lower chemoselectivity than the analogue phenyl group of **1a** in the matched cases (entry 7 vs. 11), it induces higher chemoselectivity in the mismatched cases (entry 6 vs. 12). Reaction of **1c** in presence the larger ligand **7** resulted in complete suppression of byproduct formation and an 8.3:1 d.r. (entry 13).

With these promising results for synthesizing δ -lactams in hand, we turned our attention to γ -lactams. Subjection of cyanoformamide **1d** to Pd(PPh₃)₄ yielded the desired γ -lactam **2d** as a 2:1 mixture of diastereomers (Table 2, entry 1). The corresponding naphthyl substrate **1e** reacted under identical conditions to provide **2e** in similar diastereoselectivity (entry 2). Interestingly, the omission of BPh₃ diminished the diastereoselectivity (entry 2 vs. 3). Surprisingly, replacing Pd(PPh₃)₄ with Pd₂dba₃ and chiral ligand **4** or its enantiomer **5** resulted in a lower d.r. for the reaction of **1d** (entries 4 and 5). Because the d.r. was slightly higher with PPh₃ than with chiral phosphoramidites **4** and **5**, we suggest that matched/mismatched effects are no longer operative. Substitution of the BINOL backbone in ligand **6** provided a stereoselectivity comparable to that of the reaction without a chiral ligand (entry 1 vs. 6). A diastereomer of ligand **6**, ligand **7**, did not significantly affect the diastereoselectivity of the reaction (entry 7).

The increased steric bulk of naphthyl analogue **1e** did not improve the selectivity in the presence of chiral ligands, and diastereomeric BINOL ligands **6** and **7** both gave **2e** with a d.r. of 1.7:1. This suggests that the relative stereochemistry of the amine moiety of the ligand does not heavily influence the stereochemical outcome (entries 8 and 9). A preliminary substrate scope was explored (Table 3). Cyanoformamides **1f–1h** were subjected to Pd(dba)₂, BPh₃, ligand **7**, and toluene at 130 °C for 48 h. The reaction tolerated ethyl

substitution to provide δ -lactam **2f** in 61 % isolated yield and gave a d.r. of approximately 6:1. The reaction was less effective with the isopropyl-substituted substrate; δ -lactam **2g** was prepared in 38 % isolated yield and a d.r. of approximately 5:1. The d.r. was slightly lower in both cases in comparison to the d.r. obtained for the methyl analogue. Unfortunately, cyanoformamide **1h** bearing an allylic benzyloxy group provided δ -lactam **2h** in only 5 % isolated yield, albeit in a d.r. of > 20:1. The mass balance was a complex mixture of other products.^[13] Although ϵ -lactam **2i** was not observed when cyanoformamide **1i** was subjected to the reaction conditions, cyanoformamide **1j** was successfully transformed to β -lactam **2j** with modest conversion and 43 % isolated yield. However, the cyclization to form β -lactam **2j** was not stereoselective. It is interesting to note that even with our limited sample size, it was observed that the d.r. increased with ring size, as our best results were obtained with the six-membered ring products.

Products **2a–2g** and **2j** were obtained in isolated yields between 28 and 61 %. The major diastereomer of piperidinone **2a** was obtained by medium pressure liquid chromatography (MPLC). Although we were able to obtain the major diastereomer of piperidinone **2b** by MPLC, we succeeded to isolate the minor diastereomer by semi-preparative HPLC. Isolation and separation of the five-membered ring products **2d** and **2e** was achieved with simple flash chromatography. Semi-preparative HPLC was required to separate the diastereomers of lactam **2f**, **2g**, and **2j** after initial purification by flash column. Successful reactions on a 100 mg scale were accomplished for three different ring sizes; yields and diastereomeric ratios were similar to those reported for the smaller scale reactions [compare δ -lactam **2a** (entry 9, Table 1); γ -lactam **2e** (entry 2, Table 2); β -lactam **2j** (Table 3)].

Optimization for removal of the directing group is ongoing in our laboratory. Preliminary results with **2a** suggest that oxidation with ceric ammonium nitrate may selectively cleave the directing group from the nitrogen atom.^[14] Along these lines, we may pursue the use of other directing groups and Lewis acids in the future.

Conclusions

Diastereoselective cyanoamidation with aliphatic-tethered alkenes to provide δ -, γ -, and β -lactams bearing α -all-carbon quaternary stereocenters was accomplished by using a chiral directing group with both chiral and achiral catalysts. By using an achiral catalyst, we determined that the directing group alone imparted diastereoselectivity. Our results indicate that the triphenylborane affects the diastereoselectivity in some reactions, but we do not have a mechanistic explanation yet as to how Lewis acids impact the diastereo-determining step. In some cases the selectivity could be further enhanced by using chiral ligands, which revealed matched/mismatched relationships with the different directing groups on the cyanoformamide substrates. This strategy was effective for the stereocontrolled synthesis of lactams bearing α -all-carbon quaternary stereocenters.

Acknowledgments

This work was funded by the National Institute of Health (R01 GM095559). NMR spectra were recorded on an instrument purchased with support from the National Institute of Health (S10 OD011952). E. R. A. thanks the University of Minnesota for support through the Undergraduate Research Opportunities Program (UROP) award.

We also thank Dr. Letitia Yao (UMN) for NMR assistance and Zhongda Pan (UMN) for constructive conversations and purification of chemical reagents.

References

1. Kobayashi Y, Kamisaki H, Takeda H, Yasui Y, Yanada R, Takemoto Y. *Tetrahedron*. 2007; 63:2978–2989.
2. Nakao Y, Ebata S, Yada A, Hiyama T, Ikawa M, Ogoshi S. *J. Am. Chem. Soc.* 2008; 130:12874–12875. [PubMed: 18778055]
3. Yasui Y, Kinugawa T, Takemoto Y. *Chem. Commun.* 2009:4275–4277.
4. Kobayashi Y, Kamisaki H, Yanada R, Takemoto Y. *Org. Lett.* 2006; 8:2711–2713. [PubMed: 16774238]
5. Yasui Y, Takemoto Y. *Chem. Rec.* 2008; 8:386–394. [PubMed: 19107868]
6. Yasui Y, Kamisaki H, Takemoto Y. *Org. Lett.* 2008; 10:3303–3306. [PubMed: 18582078]
7. Yasui Y, Kamisaki H, Ishida T, Takemoto Y. *Tetrahedron*. 2010; 66:1980–1989.
8. Dreis, AM. Ph. D. Dissertation. University of Minnesota; 2015.
9. Rapoport, M. E. I. Du Pont De Nemours And Company. US4371474. 1982.
10. Swartz BD, Reinartz NM, Brennessel WW, García JJ, Jones WD. *J. Am. Chem. Soc.* 2008; 130:8548–8554. [PubMed: 18540608]
11. Nakao, Y. C–C Bond Activation, *Topics in Current Chemistry*. Dong, G., editor. Vol. 346. Springer; Berlin: 2014. p. 33–58.
12. Ogilvie JM, Serratore NA, Frost GB, Douglas CJ. Manuscript in Preparation.
13. One side-product was isolated (**3h**; see Supporting Information). The side product **3h** resulted from the substitution of the benzyloxy group for a phenyl group. Upon increasing the BPh₃ loading to 2.0 equiv., **3h** became the major product over **2h**.
14. Gautam LN, Su Y, Akhmedov NG, Petersen JL, Shi X. *Org. Biomol. Chem.* 2014; 12:6384–6388. [PubMed: 24933675]

Scheme 1.
Intramolecular cyanoamidation with alkenes.

Optimization of diastereoselective cyanoamidation to form α,α -disubstituted δ -lactams.

[a]_D Determined by quantitative ¹H NMR spectroscopy.

Table 2Optimization of diastereoselective cyanoamidation to form 3,3-disubstituted γ -lactams.

	Product	Catalyst	Ligand	Additive	Consumption of 1	d.r.
1	1d	Pd(PPh ₃) ₄	none	BPh ₃	100 %	2:1
2	1e	Pd(PPh ₃) ₄	none	BPh ₃	100 %	1.9:1
3	1e	Pd(PPh ₃) ₄	none	none	100 %	1.1:1
4	1d	Pd ₂ dba ₃	4	BPh ₃	100 %	1.7:1
5	1d	Pd ₂ dba ₃	5	BPh ₃	100 %	1.3:1
6	1d	Pd ₂ dba ₃	6	BPh ₃	100 %	2:1
7	1d	Pd ₂ dba ₃	7	BPh ₃	100 %	1.8:1
8	1e	Pd ₂ dba ₃	6	BPh ₃	100 %	1.7:1
9	1e	Pd ₂ dba ₃	7	BPh ₃	100 %	1.7:1

Table 3

Substrate scope of diastereoselective cyanoamidation.

^[a] Conditions: Pd(dba)₂ (0.08 equiv.), BPh₃ (1 equiv.), **7** (0.16 equiv.), toluene (130 °C), 48 h.^[b] Single diastereomer detected by ¹H NMR spectroscopy.^[c] Conditions: Pd(PPh₃)₄ (0.08 equiv.), BPh₃ (1 equiv.), toluene (130 °C), 48 h.^[d] Incomplete conversion.