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Asymmetric Domino Aza-Michael Addition/[3 + 2] Cycloaddition Reactions as a Versatile Approach to α,β,γ-Triamino Acid Derivatives

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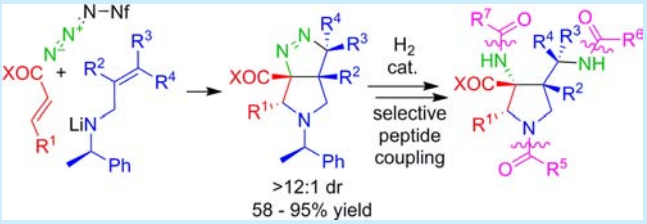
Supporting Information

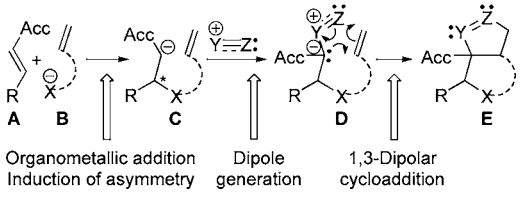
ABSTRACT: Nonproteinogenic amino acids are prepared by an unprecedented domino aza-Michael addition-1,3-dipolar cycloaddition, leading to enantiopure highly substituted pyrrolidinopyrazolines. Nonaflyl azide serves as highly effective diazo transfer reagent, forming the link between the conjugate addition and cycloaddition steps. The resulting pyrrolidinopyrazolines can be rapidly transformed to either α,β,γ-triamino acids or 3,4-methano-β-prolines. Peptide coupling can be regioselectively conducted at each of the amino groups.



Non-natural amino acid derivatives are an important class of organic compounds. They have good potential as functional building blocks in materials chemistry, for example as building blocks for foldamers[1] or dendrimers.[2] They are even more important in medicinal chemistry and attractive in solving biological questions, since they may replace native amino acids in oligopeptides and related structures, altering their hydrolytic stability, conformation, and biological activity.[1b,3] Especially, cyclic amino acids are attractive, since they are conformationally constrained and their properties can thus be easily tuned.[4] However, access to such structures is associated with tedious multistep synthesis, making their use and comprehensive investigation impractical.

We envisaged to provide a one-step approach to cyclic polyfunctional amino acid derivatives by unprecedented tandem organometallic conjugate addition/dipole generation/intramolecular [3 + 2] cycloaddition processes (Scheme 1). Such an approach is attractive, since initial stereochemical information can be set in the addition step (**A** + **B** → **C**),[5] after which the organometallic intermediate serves to generate a dipole **D**, from which the pericyclic process (**D** → **E**) proceeds with high diastereoselectivity. This represents a challenge, since the conditions and rates of organometallic and cycloaddition steps usually differ; therefore, coupling them to domino processes[6] is not trivial.

Scheme 1. Strategic Combination of Organometallic Conjugate Addition Steps with Dipolar [3 + 2] Cycloadditions to a Domino Process



This analysis indicated that the aza-Michael addition is a suitable step for the asymmetric introduction of nitrogen functionality.[7] For the subsequent dipole generation from the organometallic intermediate **C** the diazo functionality is very promising, since it gives access to pyrazoline derivatives.[8] Whereas Regitz diazo transfer[9] using sulfonyl azides is well established for β-dicarbonyl compounds, it is currently limited in scope and selectivity for simple enolates, since azidation usually competes. Although Evans' results can be used as a guideline that electron-rich sulfonyl azides, such as triisopropylbenzenesulfonyl azide ($TrisylN_3$), react by α-azidation, whereas *p*-nitrobenzenesulfonyl azide (PNBSA)[10] or diphenylphosphoryl azide (DPPA)[11] afforded predominately diazo compounds, no generally applicable selective diazo transfer protocol to simple enolates exist.

We report here a short and efficient approach to cyclic amino acid scaffolds **3** based on an unprecedented domino aza-Michael addition/diazo transfer/1,3-dipolar cycloaddition process from simple starting materials **4**, **5**, and **6** (Scheme 2). Central bicycles **3** provide the basis for an efficient synthesis of cyclic triamino acid derivatives **1** and bicyclic β-prolines **2**, which are important structural motifs in medicinal chemistry.[12]

Initially the critical diazo transfer, which links the polar and cycloaddition steps, had to be established with high selectivity. Therefore, β-amino ester **7** served as a model. It was deprotonated with LDA at −78 °C and treated with several sulfonyl azides **6a**−**e** (Table 1). After 30 min, acetic acid (3 equiv) was added to the cooled solution and the mixture was

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Scheme 2. Domino Approach to α,β,γ-Triamino and Cyclic β-Amino Acid Derivatives 1 and 2

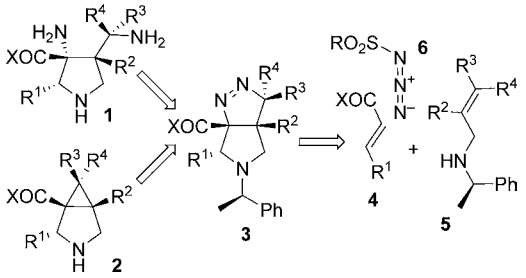
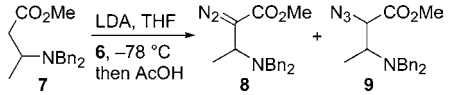


Table 1. Enolate Azidation vs Diazo Transfer Using Different Sulfonyl Azides 6a–e



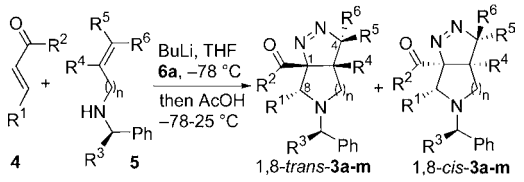
entry	6	yield (%)	8 (%)[a]	9 (%)	7 (%)
1	**a** $F_9C_4SO_2N_3$	82	99	0	0
2	**b** PNBSA	89	73	27	0
3	**c** DPPA	53	85	0	15
4	**d** $AcNHC_6H_4SO_2N_3$	N.d.[b]	33	11	56
5	**e** $TrisylN_3$	78	11	83	6

[a]The ratio of products was determined by ^{1}H NMR spectroscopy. Compounds **7**, **8**, and **9** were inseparable by column chromatography. [b]Not determined. The product ratio was determined from the crude reaction mixture.

warmed to rt overnight. Nonaflyl azide **6a**,[13] which was not employed for diazo transfer to enolates so far, turned out to be the reagent of choice for the selective synthesis of α-diazo ester **8** (entry 1). In contrast, reagents **6b–e** provided mixtures, which reflect the known reactivity trends (entries 2–5).[10]

These results enabled the exploration of the proposed domino strategy (Table 2). Lithium amides of **5** were generated by deprotonation of the parent amine with *n*-butyllithium at −78 °C. Their conjugate addition to α,β-unsaturated esters or amides **4** followed by addition of nonaflyl azide led to almost instantaneous diazo transfer at −78 °C, and the cyclized products 1,8-*trans*-**3a–l** and 1,8-*cis*-**3a–l** were observed in the reaction mixture (entries 1–12). Quenching with acetic acid completed the conversion of the intermediate triazenes to bicyclic products **3**. The domino reaction was less efficient when using methyl esters and less hindered *N*-allylbenzylamine, because 1,2-addition of the lithium amide was competitive (entry 2 vs 1), whereas application of *tert*-butyl esters suppressed the 1,2-addition completely. When the allylic unit was unsubstituted ($R^4 = R^5 = R^6 = H$), the uncyclized α-diazo ester was not observed as an intermediate, suggesting that the 1,3-dipolar cycloaddition was faster than formation of the diazo compound (entries 1–5, 10–12). In more substituted allylic amines ($R^4 = H$, R^5, $R^6 = Me$, or $R^4 = Me$, entries 6–9) the cycloaddition was slower, but the conversion was complete within hours. Michael acceptors having alkyl or aryl substituents in the β-position are tolerated equally well in the tandem process. The domino reactions are not limited to esters as Michael acceptors, an amide, and even a Weinreb amide reacted similarly effectively (entries 11, 12). A homoallylic amine was also applicable in good yield, thus providing an efficient access to piperidinopyrazolines **3m** with high diastereoselectivity (entry 13). Remarkably, all domino reactions proceeded with more than 12:1 1,8-*trans*/1,8-*cis* selectivity. No other diastereomer of **3** was observed. The application of enantiopure α-methylbenzylamines **5** leads to enantiopure products **3d–m** (entries 4–13). The stereochemical information from the double bond geometry in crotylamines was completely transferred into the configuration at C4 of products **3g,h** (entries 7, 8). The structure and relative configuration of bicycles **3f** and **3m** was unequivocally proven by X-ray crystallography (Figure 1; see Supporting Information).

Table 2. Scope of Domino Aza-Michael Addition/Diazo Transfer/[3 + 2] Cycloaddition Reactions



	4		5						
entry	R^1	R^2	R^3	R^4	R^5	R^6	*n*	**3** (%)	*trans*/*cis*-**3**[a]
1	Me	O*t*Bu	H	H	H	H	1	**a** 77	12:1
2	Me	OMe	H	H	H	H	1	**b** 37[b]	14:1
3	Ph	O*t*Bu	H	H	H	H	1	**c** 72	15:1
4	Me	OMe	Me	H	H	H	1	**d** 95	15:1
5	Me	O*t*Bu	Me	H	H	H	1	**e** 91	14:1
6	Me	O*t*Bu	Me	Me	H	H	1	**f** 58	15:1
7	Me	O*t*Bu	Me	H	Me	H	1	**g** 85	12:1
8[c]	Me	O*t*Bu	Me	H	H	Me	1	**h** 70	50:1
9	Me	O*t*Bu	Me	H	Me	Me	1	**i** 62	>20:1
10	Ph	O*t*Bu	Me	H	H	H	1	**j** 90	15:1
11	Me	NMe_2	Me	H	H	H	1	**k** 76	>20:1
12	Me	NMe (OMe)	Me	H	H	H	1	**l** 71	17:1
13	Me	O*t*Bu	Me	H	H	H	2	**m** 71	>20:1

[a]Determined from the ^{1}H NMR spectra of the crude reaction mixtures. [b]The product of double 1,2- and 1,4-addition was also isolated in 37% yield. [c]The opposite enantiomer of **5h** than depicted in the equation was used, resulting in the corresponding enantiomer of **3h**.

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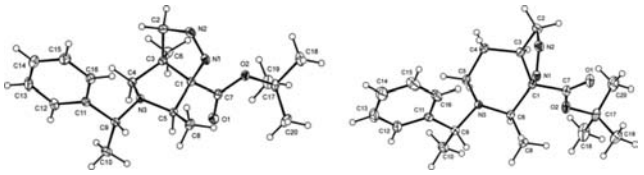
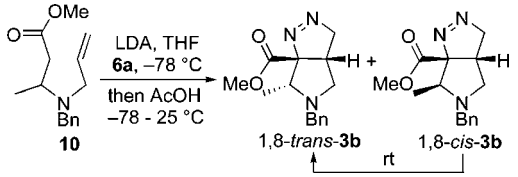
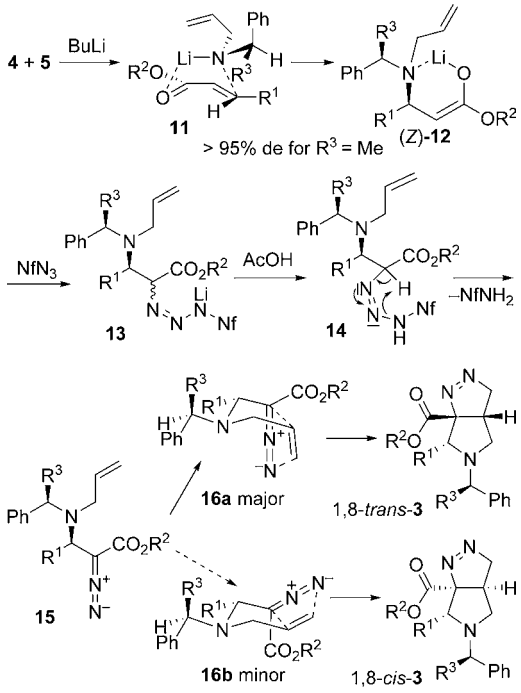


Figure 1. X-ray crystal structures of 1,8-*trans*-**3f** and 1,8-*trans*-**3m**. Thermal ellipsoids are drawn at the 30% probability level.

Scheme 3. Diazo Transfer/[3 + 2] Cycloaddition of 10



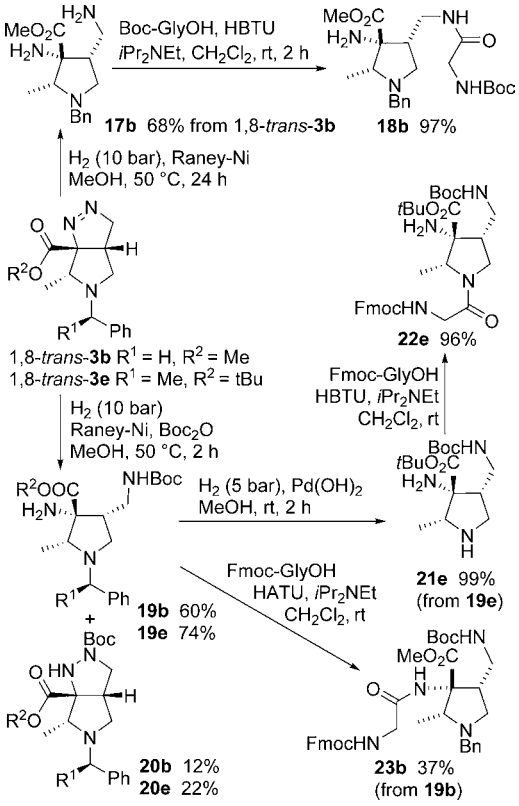
Scheme 4. Mechanism and Stereochemical Rationale of the Domino Process



The isolated *β*-amino ester **10** underwent the diazo transfer/intramolecular cycloaddition sequence similarly, giving pyrrolidinopyrazolines 1,8-*trans*- and 1,8-*cis*-**3b** in 79% and 2% yield, at gram scale (Scheme 3). The diastereomeric ratio of the crude mixture was 11:1, similar to that before. Interestingly, the minor diastereomer 1,8-*cis*-**3b** converted slowly to more stable 1,8-*trans*-**3b** at rt over several weeks.

The stereoselectivity of the reaction sequence can be described by initial precoordination of the lithium amide generated from amine **5** to the carbonyl group of **4**, followed by transfer of the amide group to the *β*-position via transition state **11** with the least steric interaction (Scheme 4).[7a] Thus generated (*Z*)-enolate **12** couples subsequently with NfN_3 leading to unstable triazenide **13**. Its protonation to **14** triggers the formation of diazo intermediate **15**. The high diastereoselectivity of the cycloaddition step is explained by a strongly preferred *trans*-diequatorial orientation of R^1 and the ester group in the transition state **16a**, which collapses to 1,8-*trans*-**3**, whereas the minor isomers 1,8-*cis*-**3** result via **16b**. Alternative transition states with axial orientation of R^1 suffer from unfavorable interactions with the phenylethyl group (not shown).

Scheme 5. *α,β,γ*-Triamino Acids and Their Selective Peptide Coupling



Bicyclic pyrazolines 1,8-*trans*-**3b** and 1,8-*trans*-**3e** served as examples for diversification of the scaffold. Hydrogenolytic ring opening of the pyrazoline ring provided a facile access to orthogonally protected *α,β,γ*-triamino acid derivatives (Scheme 5). Using 1,8-*trans*-**3b** and Raney nickel under 10 bar of hydrogen yielded diaminopyrrolidinecarboxylate **17b**, which underwent selective peptide coupling with Boc-protected glycine at the primary amine function furnishing dipeptide **18b**. A similar hydrogenolysis of either 1,8-*trans*-**3b** or 1,8-*trans*-**3e** with Raney nickel in the presence of Boc_2O afforded a separable mixture of ring opened **19b** or **19e** protected at the primary amine function and small amounts of bicyclic **20b,e**. Further hydrogenolysis of **19e** using $Pd(OH)_2$ removed the benzylic protecting group. The resulting pyrrolidine **21e** underwent peptide coupling to dipeptide **22e** in high yield. Finally, even the amine function at the quaternary stereocenter of **19b** was subject to peptide coupling affording dipeptide **23b**. The yield must, however, be further optimized.

Selective diversification of the bicyclic ring system was also possible (Scheme 6). Reduction of the N=N double bond of 1,8-*trans*-**3b** by zinc in acetic acid and subsequent Boc protection provided the corresponding orthogonally protected pyrrolidinopyrazolidine **20b** in good yield without cleavage of the N–N bond. Hydrogenolysis of 1,8-*trans*-**3b** or 1,8-*trans*-**3e** and treatment with Boc_2O gave the diprotected bicyclic derivatives **24b,e** in good yields. The 1-pyrazoline ring can be tautomerized[14] to thermodynamically more stable 2-pyrazoline **25b** by treatment with DBU (or tetramethylguanidine). Et_3N

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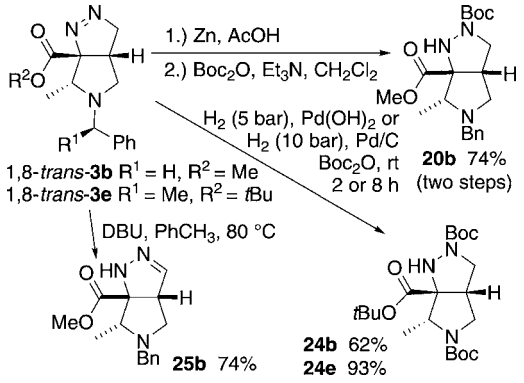
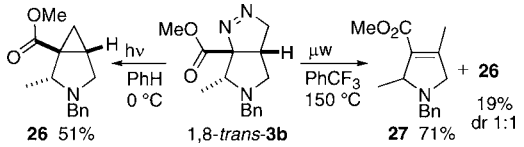
Scheme 6. Modification of the Bicyclic Ring System



Scheme 7. Nitrogen Extrusion Reactions of 1,8-*trans*-3b



failed to promote this reaction, whereas K_2CO_3 in MeOH[14b] led to selective saponification of the ester group (not shown).

1-Pyrazolines are known to undergo extrusion of molecular nitrogen under either thermal or photochemical conditions.[14,15] Irradiation of a benzene solution of 1,8-*trans*-**3b** by a low-pressure mercury lamp gave the cyclopropane **26** as a single diastereomer in 51% yield, another attractive structural pattern occurring in pharmaceuticals[12] and alkaloids[16] (Scheme 7). In contrast, 2,4-dimethylpyrrolinecarboxylate **27** was obtained under microwave irradiation resulting from a 1,2-hydrogen shift accompanying N_2 elimination in good yield together with a diastereomeric mixture of bicyclic amino acid **26**.

In conclusion, α,β,γ-triamino acids and bicyclic β-prolines were effectively approached by the combination of anionic aza-Michael additions with dipolar cycloadditions. Nonaflyl azide was identified as an excellent reagent for converting non-stabilized ester and amide enolates to the corresponding α-diazo derivatives, enabling construction of scaffolds **3** in a rapid modular manner from easily accessible starting materials. Topologically, the reported method corresponds to a 1,2-diamination/cycloaddition strategy, in which three C−N bonds and a C−C bond are formed in one pot. Employment of chiral α-methylbenzylamines leads to enantiopure products containing four stereocenters. It was demonstrated that these scaffolds can be deeply diversified to afford highly substituted mono- and bicyclic chiral α,β,γ-triamino acids, which are applicable in peptide synthesis. Multiple applications in medicinal chemistry, oligo- and polypeptide chemistry, new materials, and toward the total synthesis of natural products can be foreseen.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data of all compounds and X-ray structure determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Reviews: (a) Martinek, T. A.; Fülöp, F. *Chem. Soc. Rev.* **2012**, *41*, 687. (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (d) Bouillère, F.; Thétiot-Laurent, S.; Kouklovsky, C.; Alezra, V. *Amino Acids* **2011**, *41*, 687.

(2) Reviews: (a) Guillot-Nieckowski, M.; Eisler, S.; Diederich, F. *New J. Chem.* **2007**, *31*, 1111. (b) Scholl, M.; Kadlecova, Z.; Klok, H.-A. *Prog. Polym. Sci.* **2009**, *34*, 24. (c) Sadler, K.; Tam, J. P. *Rev. Mol. Biotechnol.* **2002**, *90*, 195.

(3) Recent reviews: (a) Heck, T.; Geueke, B.; Kohler, H.-P. E. *Chem. Biodiversity* **2012**, *9*, 2388. (b) Jamieson, A. G.; Boutard, N.; Sabatino, D.; Lubell, W. D. *Chem. Biol. Drug Des.* **2013**, *81*, 148. (c) Kwon, I.; Lim, S. I. *Macromol. Chem. Phys.* **2013**, *214*, 1295. (d) Vasudev, P. G.; Chatterjee, S.; Shamala, N.; Balaram, P. *Chem. Rev.* **2011**, *111*, 657.

(4) (a) Kiss, L.; Fülöp, F. *Chem. Rev.* **2014**, *114*, 1116−1169. (b) Singh, R.; Vince, R. *Chem. Rev.* **2012**, *112*, 4642. (c) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323. (d) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181.

(5) (a) Galeštoková, Z.; Šebesta, R. *Eur. J. Org. Chem.* **2012**, 6688. (b) *Catalytic Asymmetric Conjugate Reactions*; Cordova, A., Ed.; Wiley-VCH: Weinheim, 2010.

(6) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(7) (a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833. (b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.

(8) Recent review: Léavai, A. *J. Heterocycl. Chem.* **2002**, *39*, 1.

(9) Reviews: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Maas, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 8186.

(10) (a) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(11) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708.

(12) (a) Wang, W.; Simovic, D. D.; Di, M.; Fieber, L.; Rein, K. S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1949. (b) Frauli, M.; Hubert, N.; Schann, S.; Triballeau, N.; Bertrand, H.-O.; Acher, F.; Neuville, P.; Pin, J.-P.; Prézeau, L. *Mol. Pharmacol.* **2007**, *71*, 704. (c) Mukhopadhyaya, J. K.; Kozikowski, A. P.; Grajkowska, E.; Pshenichkin, S.; Wroblewski, J. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1919. (d) Medda, A.; Lee, H.-S. *Synlett* **2009**, 921.

(13) Different applications of NfN_3: (a) Chiara, J. L.; Suárez, J. R. *Adv. Synth. Catal.* **2011**, *353*, 575 and cited references. (b) Mitcheltree, M. J.; Konst, Z. A.; Herzon, S. B. *Tetrahedron* **2013**, *69*, 5634.

(14) Precedence: (a) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P. J.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (b) Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *73*, 9479.

(15) Precedence: Santos, B. S.; Nunes, S. C. C.; Pais, A. A. C. C.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2012**, *68*, 3729.

(16) (a) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704. (b) MacMillan, K. S.; Nguyen, T.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 1187.

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