Published in final edited form as:

J Am Chem Soc. 2017 July 12; 139(27): 9164–9167. doi:10.1021/jacs.7b05778.

Asymmetric Radical Bicyclization of Allyl Azidoformates via Cobalt(II)-Based Metalloradical Catalysis

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Abstract

Cobalt(II)-based metalloradical catalysis has been successfully applied to radical bicyclization of allyl azidoformates to construct aziridine/oxazolidinonefused bicyclic structures. The Co(II) complex of D_2-symmetric chiral amidoporphyrin 3,5-Di^{t}Bu-QingPhyrin has been identified as an effective metalloradical catalyst for the intramolecular radical aziridination of this type of carbonyl azides, allowing for high-yielding formation of synthetically useful chiral [3.1.0]-bicyclic aziridines with high diastereo- and enantioselectivity.

Radical chemistry has been increasingly explored for the development of new synthetic tools to construct molecular structures.[1,2] Despite tremendous advances, formidable challenges, such as control of enantioselectivity, remain largely unaddressed for many radical reactions. Among recent strategies,[3] metalloradical catalysis (MRC) presents a conceptually new approach in that metal-centered radicals are exploited as open-shell catalysts for initiating as well as controlling homolytic radical processes.[4,5] As stable 15e-metalloradicals, Co(II) porphyrin complexes have recently been demonstrated with the unusual ability in activating diazo compounds and organic azides to generate the unprecedented α-Co(III)-alkyl radicals (also known as Co(III)-carbene radicals)[6] and α-Co(III)-aminyl radicals (also known as Co(III)-nitrene radicals), [7] respectively. These metal-stabilized organic radicals are competent for both H atom abstraction and radical addition, leading to new catalytic radical processes for C–H amination,[8] C–H alkylation,[9] C=C aziridination,[10] and C=C cyclopropanation. [11] With D_2-symmetric chiral porphyrins as supporting ligands,[11a,c] the Co(II)-based MRC (Co(II)-MRC) enables control of reactivity as well as stereochemistry of

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05778.

Experimental details and analytical data for all new compounds (PDF)

Crystallographic data for **3e** (CIF)

Crystallographic data for **7a** (CIF)

these radical processes, including enantioselectivity.[9–11] In particular, through α-Co(III)-alkyl radicals as intermediates, asymmetric intramolecular radical bicyclization of allyl diazoacetates was achieved to afford bicyclic cyclopropanes (Scheme 1A).[11c] By parallel thinking, we were attracted to the possibility of the equivalent process through α-Co(III)-aminyl radicals as intermediates (Scheme 1B). In addition to the prerequisite for metalloradical activation of this type of carbonyl azides, this proposed catalytic process would require the control of stereochemistry of two consecutive radical cyclization steps: (i) enantioselective 5-*exotrig* cyclization of the α-Co(III)-aminyl radical **I** and (ii) diastereoselective 3-*exo-tet* cyclization of the γ-Co(III)-alkyl radical **II** (Scheme 1C). If achieved, this type of asymmetric intramolecular aziridination would be synthetically useful since the resulting chiral [3.1.0]-bicyclic aziridines are versatile intermediates for the synthesis of chiral oxazolidinone and vicinal amino alcohol derivatives, which are key structural motifs in many biologically important molecules (see Figure S1 in Supporting Information (SI)).

Catalytic intramolecular olefin aziridination represents one of the most attractive approaches for the construction of fused bicyclic aziridines.[12] While diastereoselective catalytic systems have been developed,[13] allyl azidoformates have not been successfully employed for catalytic intramolecular aziridination. [14] The challenge is attributed to the inertness of this type of carbonyl azides toward catalytic activation.[13a,14a–d,15] As a novel alternative involving the catalytic activation of *N*-tosyloxy-carbamates, Lebel and co-workers developed a nonoxidative approach for the intramolecular aziridination process.[14a–d] In all the previous systems, however, the control of enantioselectivity has not been addressed. As a new application of Co(II)-MRC, we wish to report herein the development of the first catalytic system for asymmetric intramolecular aziridination of allyl azidoformates through a stepwise radical bicyclization pathway without the need for bases or oxidants. Using D_2-symmetric chiral amidoporphyrin as the ligand, the Co(II)-catalyzed process allows for efficient construction of 3-oxa-1-azabicyclo[3.1.0]-hexan-2-one structures in high yields with excellent diastereo- and enantioselectivity. The resulting optically active bicyclic aziridines can serve as useful intermediates for the preparation of chiral oxazolidinone and vicinal amino alcohol derivatives with retention of the original enantiopurity.

At the outset of this project, cinnamyl azidoformate (**1a**) was selected as the model substrate to explore both the reactivity and stereoselectivity of intramolecular radical aziridination via Co(II)-MRC (Scheme 2). After optimization of reaction conditions, the first-generation Co(II) complex of D_2-symmetric chiral amidoporphyrin [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-ChenPhyrin) [11a] was shown to be effective in catalyzing the reaction, affording the desired bicyclic aziridine **2a** in quantitative yield. While the diastereoselectivity was excellent, it displayed a low but significant level of enantioselectivity. When the second-generation catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-QingPhyrin) was used,[11c] the enantioselectivity was increased dramatically, affording **2a** as essentially a single enantiomer while maintaining the excellent yield and diastereoselectivity (Scheme 2).

Under the same conditions, the [Co(**P2**)]-based system could effectively catalyze asymmetric intramolecular radical aziridination of a broad range of allyl azidoformates **1** (Table 1). Due to the high reactivity associated with the strain of 3-oxa-1-

azabicyclo[3.1.0]hexan-2-one structures, some of the resulting bicyclic aziridines **2** were difficult to isolate in high yields. Taking advantage of the reactivity, aziridines **2** could be directly transformed to the corresponding 2-oxazolidinones **3** via in situ ring-opening reactions by nucleophiles. For example, although **2a** was not stable enough for high-yielding isolation (Scheme 2), it could be directly converted, upon subsequent in situ reaction with $TMSN_3$, to oxazolidinone **3a** in 92% yield while preserving the original excellent stereochemistry (entry 1). Similarly, allyl azidoformates containing aryl substituents with varied electronic and steric properties were all suitable substrates for the aziridination process and the subsequent in situ ring-opening reaction, forming 2-oxazolidinones **3b**–**3f** in high overall yields for the two steps with excellent diastereo- and enantioselectivity (entries 2–6). The absolute configuration of **3e** (entry 5) was established as (3*R*, 4*S*). In addition, this combined aziridination and ring-opening system could tolerate substrates with sterically more hindered 2-substituted groups, leading to high-yielding formation of **3g**–**3i** with excellent diastereo- and enantioselectivity (entries 7–9). Furthermore, the Co(II)-catalyzed bicyclization could even be applied for trisubstituted alkenes as demonstrated for the reaction of **1j**, affording **2j** in full conversion but in 62% isolated yield due to its instability during purification (entry 10). It is remarkable that both the relative and absolute configurations of the two newly generated contiguous chiral centers in the ring structure, including one quaternary stereogenic center, could be completely controlled. In addition, the aziridination/ring-opening protocol worked equally well with vinyl-substituted allyl azidoformates as exemplified with the high-yielding transformation of **1k** to **3k** as a single diastereomer with high enantioselectivity (entry 11). Likewise, acyl-substituted allyl azidoformates such as **1l** could be bicyclized to **2l** in an excellent yield with complete control of diastereoselectivity but with lower enantioselectivity (entry 12). It is noted that the olefin, ketone, and other functionalities were well tolerated by the catalytic radical process.

To further demonstrate the versatility of the resulting optically active [3.1.0]-bicyclic aziridines as chiral building blocks for stereoselective organic synthesis, ring-opening reactions by different types of nucleophiles were performed with the use of the enantiopure aziridine **2a** as the representative reactant (Scheme 3). In addition to stereoselective formation of oxazolidinone **3a** with $TMSN_3$, the aziridine ring in **2a** could be regioselectively opened at the *exo*-position by N-, O-, C-, and S-based nucleophiles, leading to high-yielding formation of **3a**–**7a**, respectively, as single diastereomers without erosion of the original enantiopurity.[15b,c] In addition to the *exo*-ring openings, the *endo*-ring opening of aziridine **2a** was achieved selectively via 1,3-dipole addition with benzaldehyde in the presence $AgSbF_6$ as a Lewis acid.[16] The [3 + 2] cycloaddition product **8a** with a bridged bicyclic structure was formed in quantitative yield with full retention of the original enantiopurity. Moreover, the resulting oxazolidinones from the regioselective ring-opening reactions could be further transformed to the corresponding vicinal amino alcohol derivatives through simple decarbonylation (Scheme 3). For example, upon treatment with 1,3-diaminopropane under reflux, **5a** and **6a** were readily converted to chiral vicinal amino alcohols **9a** and **10a**, respectively, in high yields with complete retention of the original optical activity.

To probe the underlying stepwise radical mechanism, two pairs of (*E*)- and (*Z*)-allyl azidoformates with different olefin substitution patterns were employed as the substrates for the Co(II)-based intramolecular aziridination (Scheme 4). Under the standard conditions, both reactions of the disubstituted allyl azidoformates (*E*)-**1a** and (*Z*)-**1a′** were found to produce the same (*E*)-aziridine **2a** as the single diastereomer in similar yields but with different enantioselectivities (Scheme 4A). While the difference in enantioselectivity indicates that the first radical cyclization (Scheme 1C: **I**→**II**) is likely the enantio-determining step, the observed diastereoconvergence is attributed to the facile interconversion between the corresponding intermediates **II** generated from **1a** and **1a′**, respectively, due to the low-barrier rotation of the α-C–C bond of the C-centered radical (Scheme 1C), leading to the formation of the more stable (*E*)-aziridine **2a** after the second radical cyclization. In contrast, when the sterically more congested trisubstituted allyl azidoformates (*E*)-**1j** and (*Z*)-**1j′** were used as the substrates, the stereospecific formation of aziridines (*E*)-**2j** and (*Z*)-**2j′**, respectively, were observed (Scheme 4B), indicating restricted rotation of the α-C–C bond of the corresponding intermediates **II** even at 80 °C as a result of the increased steric hindrance. Furthermore, as detailed in the SI, the α-Co(III)-aminyl radical **I** with a dangling olefin moiety from the reaction of (*E*)-**1a** with [Co(**P2**)] could be directly detected by both EPR spectroscopy (Figure S2)[7a,d] and HRMS (Figure S3).[7d] Collectively, these observations convincingly support the proposed stepwise radical bicyclization mechanism (Scheme 1C).

In summary, metalloradical catalysis (MRC) has been successfully applied to develop the first catalytic system that is highly stereoselective for asymmetric intramolecular olefin aziridination of allyl azidoformates through a unique stepwise radical bicyclization pathway. The Co(II)-based metalloradical system can effectively activate this type of carbonyl azides, which are known to be inert toward activation by existing close-shell metal systems, under mild conditions without the need for bases or oxidants. The [Co(**P2**)]-catalyzed intramolecular radical aziridination has a broad scope and can be applicable to various allyl azidoformates, leading to stereoselective construction of 3-oxa-1-azabicyclo[3.1.0]hexan-2-one derivatives in high yields with both high diastereo- and enantioselectivity. Through both *exo*- and *endo*-regioselective ring-opening reactions, the resulting enantioenriched oxazolidinone-fused bicyclic aziridines have been demonstrated to be versatile synthetic intermediates for the preparation of the biologically important chiral oxazolidinone and vicinal amino alcohol derivatives with preservation of the original enantiopurity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful for financial support by NIH (R01-GM102554).

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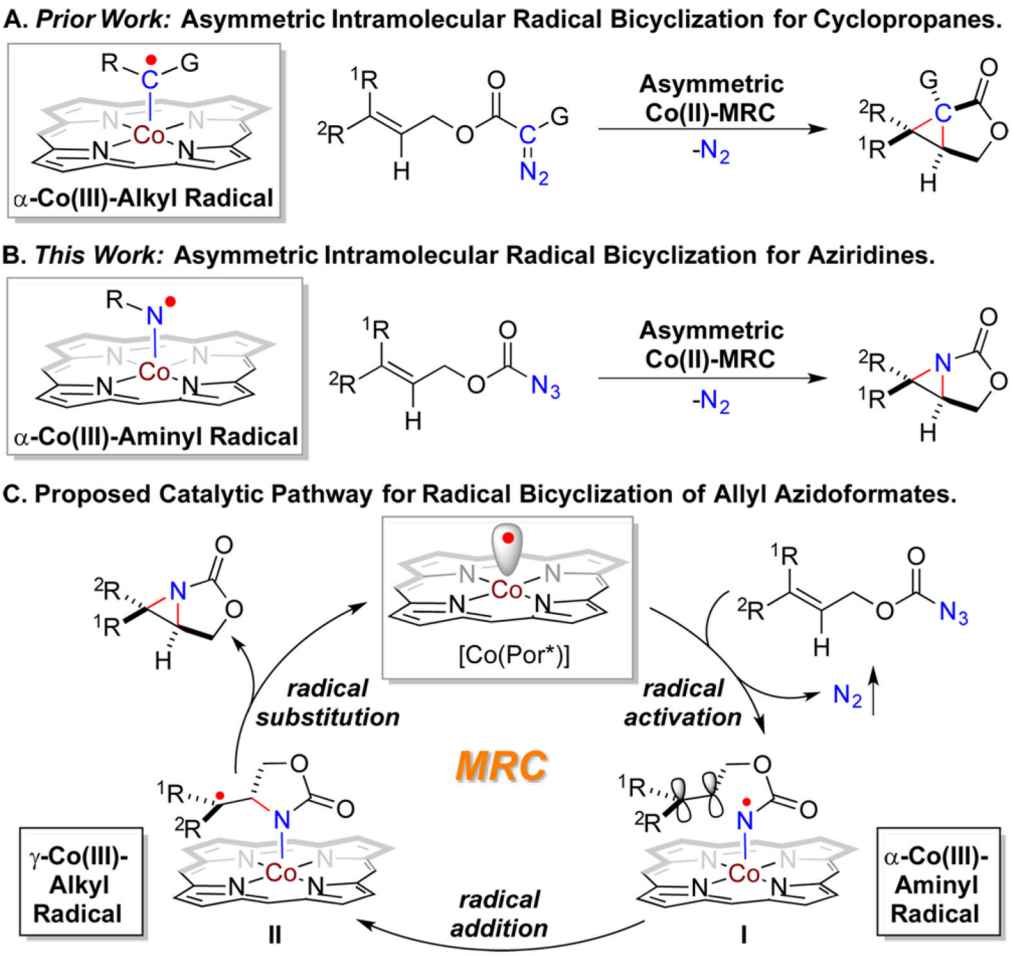
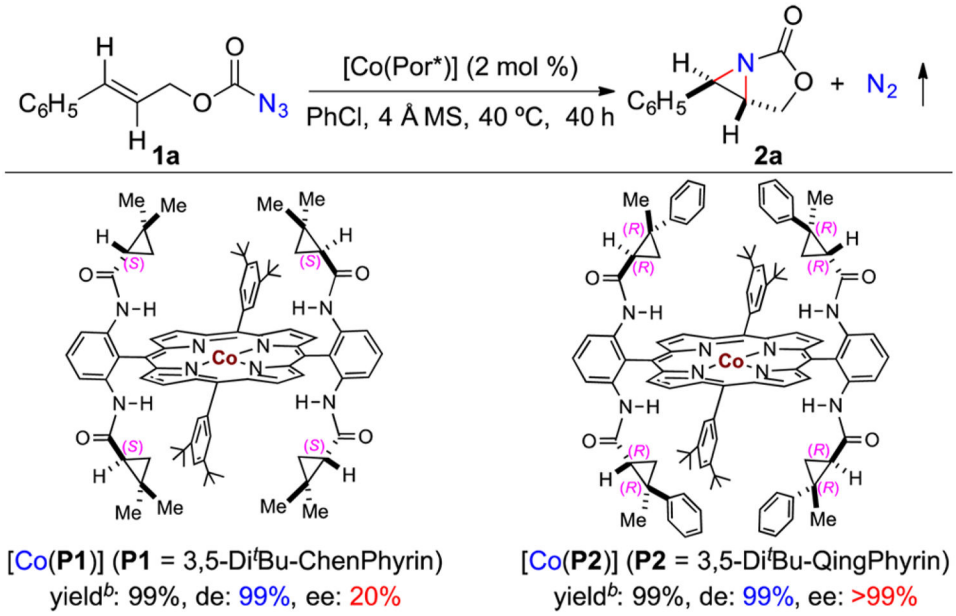


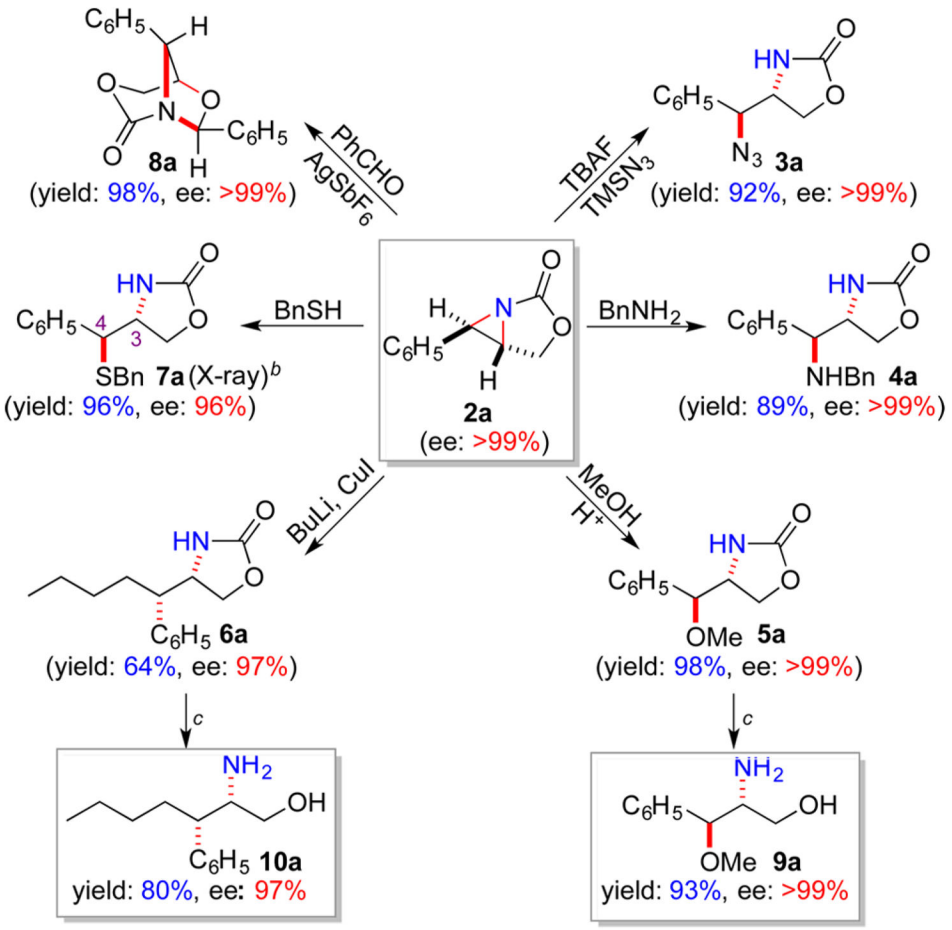
Scheme 1.

Asymmetric Intramolecular Radical Bicyclization Processes via Co(II)-Based Metalloradical Catalysis



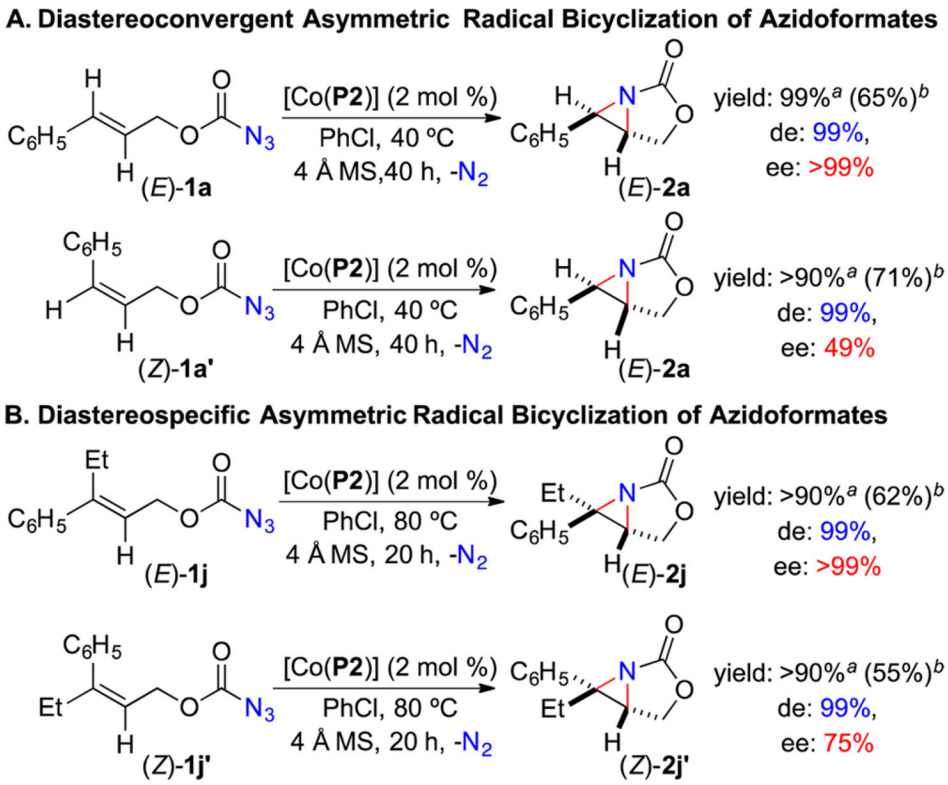
Scheme 2. Ligand Effect on Co(II)-Catalyzed Asymmetric Radical Bicyclization of Cinnamyl Azidoformate[a]

[a]Performed in PhCl at 40 °C for 40 h using 2 mol % [Co(Por*)] under N_2 in the presence of 4 Å MS; [azide **1a**] = 0.1 M. [b]Yields were based on ^{1}H NMR.



Scheme 3. Regioselective Ring-Opening of Enantiopure [3.1.0]-Bicyclic Aziridine and Further Decarbonylation[a]

[a]Isolated yields. [b]Absolute configuration was determined by X-ray as (3*R*, 4*S*). [c]Refluxed in $NH_2(CH_2)_3NH_2$ for 0.5 h.

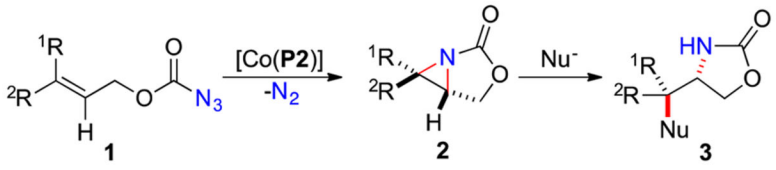


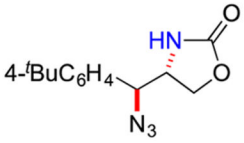
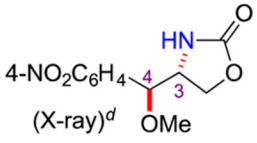
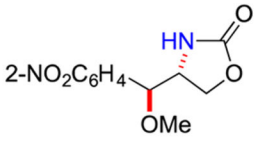
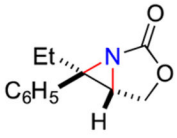
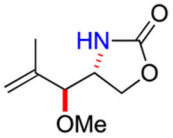
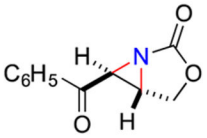
Scheme 4. Catalytic Reactions of (*E*)- and (*Z*)-Allyl Azidoformates to Probe Radical Bicylization Mechanism

[a]NMR yields. [b]Isolated yields. Note: Aziridines were unstable toward workup.

Table 1

Asymmetric Intramolecular Radical Bicyclization of Allyl Azidoformates by [Co(P2)][a]



 entry 1[b]: (**3a**); yield: 92% de: 99%, ee: >99%	 entry 2[b]: (**3b**); yield: 95% de: 99%, ee: 97%	 entry 3[b]: (**3c**); yield: 84% de: 99%, ee: 95%
 entry 4[b]: (**3d**); yield: 95% de: 99%, ee: 93%	 entry 5[c]: (**3e**); yield: 89% de: 99%, ee: 91%	 entry 6[b]: (**3f**); yield: 71% de: 99%, ee: 95%
 entry 7[b]: (**3g**); yield: 99% de: 99%, ee: >99%	 entry 8[c]: (**3h**); yield: 99% de: 99%, ee: 94%	 entry 9[b]: (**3i**); yield: 89% de: 99%, ee: 94%
 entry 10[e]: (**2j**); yield: 62%[f] de: 99%, ee: >99%	 entry 11[c]: (**3k**); yield: 94% de: 99%, ee: 93%	 entry 12: (**2l**); yield: 95% de: 99%, ee: 70%

[a]Performed in PhCl at 40 °C for 40 h using 2 mol % [Co(**P2**)] under N_2 in the presence of 4 Å MS; [azide **1**] = 0.1 M; isolated yields.

[b]In situ addition of $TMSN_3$ (1.1 equiv) and TBAF (1.1 equiv).

[c]In situ addition of MeOH (2.0 mL) and H_2SO_4 (30 mol %).

[d]Absolute configuration was determined by X-ray as (3*R*, 4*S*).

[e]At 80 °C for 20 h.

[f]100% conversion; >90% NMR yield.