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Titanium and Cobalt Bimetallic Radical Redox Relay for the Isomerization of *N*-Bz Aziridines to Allylic Amides

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Abstract

Herein a bimetallic radical redox-relay strategy is employed to generate alkyl radicals under mild conditions with titanium(III) catalysis and terminated via hydrogen atom transfer with cobalt(II) catalysis to enact base-free isomerizations of *N*-Bz aziridines to *N*-Bz allylic amides. This reaction provides an alternative strategy for the synthesis of allylic amides from alkenes via a three-step sequence to accomplish a formal transpositional allylic amination.

Graphical Abstract

Bimetallic Radical Redox-Relay Catalysis:

Keywords

radical redox relay; titanium catalysis; cobalt catalysis; bimetallic; aziridines; allylic amines; allylic amides

Allylic amines are valuable synthetic intermediates for the preparation of pharmaceutically active compounds. The construction of allylic amines and their derivatives remains an active research area for methodological development. Traditionally, access to allylic amine scaffolds can be achieved via classical routes such as transition-metal-catalyzed amination of allylic acetates and carbonates (via Pd¹ or Ir² catalysis; Scheme 1A) and the Overman rearrangement by treating allylic trichloroacetimidates with a transition metal catalyst (e.g.,

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Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

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Primary Data

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Hg,^{3a} Au,^{3b} or Pd^{3c}) (Scheme 1B). Alternatively, alkenylation of protected amines via α -C–H activation or decarboxylation provides another route to allylic amine derivatives. For example, MacMillan demonstrated that iridium was competent in the C–H activation of pyrrolidines and the functionalization of amino acids, leading to allylic amines after capture of an alkene equivalent (Scheme 1C).⁴ Additionally, rhodium complexes were shown to be capable of catalyzing hydroamination of 1,3-dienes in a regioselective fashion, giving rise to allylic amines (Scheme 1D).⁵ Several other methods are available for accessing specific types of functionalized allylic amines. For instance, the aza-Morita–Baylis–Hillman reaction employing chiral lanthanum catalysts provides allylic phos-phorylamides derived from methyl acrylate.⁶ Recently, an electrochemical method was developed to achieve an intra-molecular aza-Wacker-type cyclization, furnishing oxazo-lidinones with allylic amine fragments.⁷ Also, zirconium-catalyzed hydroalkylation of alkynes via α -C–H activation of amines was reported to provide the same type of products.⁸

This diverse collection of methods provides synthetic chemists with various options for the synthesis of allylic amines and their derivatives. Nevertheless, most of these transformations start with a specific type of pre-functionalized alkenes (e.g., allylic alcohol derivatives, vinyl sulfones, dienes, and alkynes). In contrast, the installation of an amine group at the allylic position of an alkene represents another attractive alternative strategy given the abundance of C=C bonds in feedstock chemicals and complex bioactive compounds. In this regard, seminal work in transition metal catalysis made possible the synthesis of allylic amines via direct or indirect allylic C–H oxidation (Scheme 2A) in the presence of copper,⁹ palladium,¹⁰ iridium,¹¹ rhodium,¹² ruthenium,¹³ or cobalt¹⁴ catalysts.

We aimed to provide a complementary approach for the synthesis of allylic amine derivatives starting from simple alkenes. To this end, we envisioned a three-step synthetic sequence entailing alkene aziridination, acylation, and ring-opening rearrangement (Scheme 2B). Comparing with the allylic C–H amination strategy, this sequence gives rise to selective transposition of the alkene during formation of allylic amines. Therefore, from the same starting alkenes, our approach will deliver different regioisomeric products. The success of our desired strategy will be based in part on the recent developments in alkene aziridination chemistry by Kürti et al., which led to a series of reaction methods that can convert simple alkenes to NH aziridines using Rh, Cu, or an organocatalyst.¹⁵ Thus, the missing piece in this synthetic plan lies in an efficient and selective ring-opening rearrangement that transforms the *N*-acylaziridines to the desired allylic amides. We note that a seminal contribution in this regard was made by Scheffold, who disclosed enantioselective synthesis of allylic amine scaffolds from cyclic aziridine precursors employing cob(I)alamin as catalyst¹⁶ (Scheme 2C). However, this reaction was only applicable to aziridines derived from cyclopentene and cyclohexene; cycloheptene- and cyclooctene-derived substrates could not undergo isomerization, and no examples of aziridines from acyclic alkenes were reported.

In our previous research, we developed a Ti/Co dual catalytic¹⁷ rearrangement of epoxides to allylic alcohols via a radical redox-relay mechanism (Scheme 2D). This work was inspired by key prior research in the areas of Ti and Co radical catalysis. Since initial reports of trivalent titanium by Wilkinson,¹⁸ Ti(III) species have demonstrated a remarkable

capacity to act as oxophilic single electron reductants and found a great degree of synthetic utility in the catalytic epoxide ring opening (ERO) as demonstrated by RajanBabu and Nugent,¹⁹ Gansäuer,²⁰ and later ourselves.^{21,22} In addition, Co(II) complexes have been shown to be excellent catalysts for hydrogen-atom transfer (HAT) to organic substrates in both directions (i.e., HAT from Co to C²³ or from C to Co²⁴). Our work harnessed both reactivities in the same catalytic system: titanocene promotes the reductive radical ring opening of an epoxide substrate, which then undergoes HAT to Co(salen) to complete the formation of an allylic alcohol product. Importantly, the resultant Ti and Co intermediates proceed through a single-electron transfer (SET) process to return both catalysts to their active oxidation states, thereby closing both catalytic cycles. In works published independently by us and Gansäuer, *N*-acylaziridines have been shown to undergo Ti(III)-mediated radical ring opening in the context of [3+2] cycloaddition²⁵ and Giese-type reactions,²⁶ respectively. This parallel reactivity is in part owing to the similar ring strain of aziridines (~26 kcal/mol) in comparison to epoxides.²⁷ These precedented results led us to hypothesize that the desired rearrangement of aziridine to allylic amides could be achieved by means of a radical redox relay process in the presence of a pair of Ti/Co catalysts under mild, base-free conditions.

We set out to evaluate this hypothesis by subjecting *N*-protected aziridines to the Ti/Co-cocatalysis conditions used in the epoxide isomerization reaction reported by our group (Scheme 2D).²⁸ The catalyst combination of Cp*TiCl₃ and Co(salen) **6** (Figure 1) was used initially because the former has been shown to promote aziridine ring-opening (ARO) in our previously reported [3+2] cycloaddition reaction²⁵ and the latter was shown to be an excellent HAT catalyst in the epoxide isomerization. A key to realizing this new protocol was to determine a suitable protecting group that can readily undergo coordination and reduction by a Ti(III) species, while also minimizing the inherent proclivity for Ti(IV)-mediated 2e-chemistry that would lead to undesired side products. Thus, we surveyed several common protecting groups as well as the free NH aziridine (Table 1, entries 1–8). Not surprisingly, unprotected aziridine **1a^H** showed no conversion in the presence Cp*TiCl₃ and Co(salen) **6** because this substrate does not contain an O-based coordination site for oxophilic Ti (entry 1). Acetyl and tosyl-protected aziridines were also fully recovered after the reaction (entries 2 and 5). Pivaloyl group provided predominantly the nucleophilic ring-opening product with Cl[−] (**4^{Piv}**) (entry 3). Boc-protected substrate was consumed unproductively to **4^{Boc}** in addition to unidentified products (entry 4). Notably, benzoyl and 3,5-bis(trifluoromethyl)benzoyl groups exhibited promising reactivity (entries 6, 7), with the former providing the desired allylic amide **2a** in 88% yield and a small amount (12%) of fully reduced alkyl-amide **3a**. The more electron-withdrawing 3,5-bis(trifluoromethyl)benzoyl group led to product **4a^{CF3}** (17%) via a Lewis acid promoted pathway in addition to a diminished yield of desired **2a^{CF3}** (79%). However, more electron-rich 4-methoxy benzoyl group was inert to the conditions, likely owing to its more negative reduction potential (entry 8).

We further discovered that with the optimal substrate **1a**, the reaction could be carried out without any Et₃N·HCl, which also led to marginally improved yield and selectivity (93% **2a** + 6% **3a**; Table 1, entry 9). Finally, a control experiment was conducted using in situ

generated Cp*Ti(OTf)₃, which was reported to show enhanced stability of Ti(III) in less coordinating solvents.²⁹ However, the Lewis acid mediated rearrangement to oxazoline **5a** was observed instead, which was likely a result of Zn(OTf)₂ catalysis as reported previously.³⁰

Using **1a** as the substrate, we assessed the reaction solvents and cobalt catalysts. Co(salen) **6** with *p*-CF₃ and *o*-^tBu substituents on the salicylaldehyde groups was shown as an excellent catalyst using Et₂O or EtOAc as the solvent (Table 2, entries 1 and 2). As previously mentioned, when EtOAc was used as the solvent, Et₃N·HCl was not necessary (entry 3). It has been postulated that additives similar to Et₃N·HCl can form supramolecular adducts that activate Ti(III) species toward reductive chemistry in Et₂O;³¹ it is possible that this activation mechanism is unnecessary in a more coordinating solvent such as EtOAc. Increasing the concentration of the reaction by two-fold further improved the reaction selectivity, with **2a** isolated in effectively quantitative yield without formation of **3a** (entry 4); this system was thus identified as the optimal conditions for following substrate scope studies. Other solvents such as MeCN, THF, and toluene gave much reduced reactivity and chemoselectivity (entries 5–7). Co(salen) **7** with *p*-Cl and *o*-Me groups (Figure 1) was also found to facilitate the desired transformation in Et₂O, yielding **2a** in 95% without any reduced side product **3a** (entry 8). However, two equivalents of Et₃N·HCl were necessary in this case (entry 8), and purification of the product can be more challenging than with catalyst **6** due to the similar polarity of **7** to allylic amide **2a**.

Notably, no rearrangement reaction occurred when Zn⁰, Cp*TiCl₃, or [Co] **6** was omitted (Table 2, entries 9–11). It has been shown that Ti alone can catalyze the isomerization of epoxides to allylic alcohols by trapping the carbon-centered radical (e.g., **I_A** in Scheme 2D) followed by β-hydride elimination³² or β-hydrogen atom abstraction.³³ Nevertheless, a similar mechanism cannot be operating under our aziridine rearrangement reaction given that no reaction was observed with just Cp*TiCl₃ and Zn⁰, thus emphasizing the role of the cobalt catalyst.

Under the optimal conditions, we sampled a range of alkyl *N*-Bz aziridines in addition to model substrate **1a** (Scheme 3). Various aziridines synthesized from cyclic alkenes with an *exo* or *endo* C=C unit were converted to the desired allylic amides **2a**, **2b**, **2d–f**, **2i**, **2j** in good to excellent yields. Importantly, aziridines **1c**, **1g**, **1h** derived from acyclic alkenes (monosubstituted or 1,1-disubstituted) also proved to be suitable substrates for the isomerization reaction. In contrast, such substrates are typically poorly reactive in our previously published epoxide rearrangement reaction.²⁸ For all substrates, the regioselectivity for the aziridine ring opening step universally favored the formation of the more substituted C-centered radical. When the regioselectivity of the Co-mediated HAT process is concerned, the outcome is substrate dependent. 3-Carene-derived substrate **1e** gave predominantly *endo* olefin product **2e**, whereas linear substrate **1h** yielded terminal alkene **2h** as the major species. In the case with α-cedrene-derived aziridine **1j**, the *exo*-olefin **2j** was observed as the only product, which was as expected according to Bredt's rule.

Our group previously demonstrated that secondary and tertiary alkyl chlorides could be reduced to alkyl radicals by Ti(III) catalysts.³⁴ Given that we have observed β-chloroamides

as by-products in the isomerization of aziridines, presumably via a Lewis acid mediated nucleophilic ring opening, we sought to assess the possibility of these chloroamides as key reactive intermediates (Scheme 4). Thus, we carried out two experiments using control substrates: a secondary chloroamide **4a** and a tertiary chloroamide **4k** (for details, see SI). Compound **4a** failed to react under the standard conditions under Ti/Co catalysis and the starting material was re-isolated quantitatively. In the case of the tertiary chloroamide **4k**, it was found that the substrate was active under standard conditions. However, **4k** did not lead to the same product distribution as compared to the corresponding aziridine **1k** under the same conditions. Specifically, **4k** underwent sluggish reaction to form allylic amide **2k** in 6% yield in addition to a new product, enamide **2k'**, in 41% yield, with **4k** recovered in 52%. In contrast, the corresponding aziridine **1k** was fully consumed under identical conditions and led to the formation of allylic amide **2k** as the major product along with 22% of **2k'**. We hypothesize that the reactions with **4k** and **1k** proceed through different radical intermediates; specifically, the former gives a free C-centered radical after Cl-atom abstraction by Ti(III), whereas the latter gives a C-centered radical that is also tethered to a Ti-bound azaenolate (similar to **I_D** in Scheme 5). Therefore, in the reaction with **1k**, the subsequent HAT with Co will predominantly take place at the less hindered C–H site (giving rise to **2k**) due to the steric repulsion between the Ti and Co catalysts. A control experiment showed that **2k** can be converted to **2k'** possibly via a Co-mediated process,³⁵ which could explain the formation of **2k'** as a minor product in the reaction with **1k**. The disparate reaction outcome suggested that the aziridine rearrangement to allylic amides is unlikely to be mediated by sequential nucleophilic ring opening by Cl[–] followed by reductive elimination of the resultant chloroamides.

Further, we noticed that in reactions with Cp*Ti(OTf)₃ as the precatalyst (see Table 1, entry 10), an oxazoline product **5a** could be observed, likely arising from a Lewis acid catalyzed rearrangement.³⁰ This type of product could also be formed upon eluting certain *N*-Bz aziridines that are prone to ring opening through silica gel. To assess the plausibility of this species as an intermediate in the rearrangement reaction, we subjected oxazoline **5a** to the model reaction conditions. No new species were formed and 87% of **5a** was reisolated after 24 hours.

With this information in hand, we propose a catalytic cycle that is analogous to the epoxide reaction we reported previously. Cp*TiCl₃ is first reduced by half of an equivalent of Zn⁰ to form the active catalyst, [Cp*TiCl₂] (Scheme 5). [Cp*TiCl₂] then engages in coordination and inner-sphere electron transfer with **1a**, which triggers the homolysis of the more substituted aziridine C–N bond (ARO) to relieve ring strain. The incipient radical intermediate **I_C** has a weakened γ C–H bond,³⁶ which permits the HAT to take place with cobalt catalyst **3** to form **I_D**. At this point, proton transfer (PT) occurs between resultant Co(III)–H and **I_D** to liberate the allylic amide **2a** from azaenolate intermediate **I_D**. We then propose that the Co(I) [*E*_{p/z}(Co^{II/I}) = –1.76 V vs Fc^{+/0}] and Ti(IV) [*E*_{1/2}(Ti^{IV/III}) = –1.13 V vs Fc^{+/0}] species turn over each other via a thermodynamically favored electron transfer to reform Co(II) and Ti(III) to complete the cycle (For cyclic voltammograms see SI Figure S2).

In summary, we have presented a three-step method for the preparation of allylic amides from alkenes that is complementary to current methods by providing net transposition of the alkene moiety through a Ti/Co-cocatalyzed aziridine rearrangement. Our method relies on the capacity for titanium and cobalt to operate together towards radical redox relay chemistry, which encompasses several electron transfer, proton transfer, and other radical elementary reactions to be harnessed in the same catalytic cycle in a productive manner. This design permits mild, base-free isomerization reactions to occur. Additionally, we have demonstrated that even with more activated starting materials, namely *N*-Bz aziridines, radical Ti(III) chemistry can pre-dominate over traditional Ti(IV) Lewis acid reactivity with the appropriate combination of catalysts and aziridine protecting group. This transformation further enriches the synthetic toolbox that Ti(III) and Co(II) radical chemistry provides.

¹H and ¹³C (complete proton decoupling) spectra were recorded on Inova-400 (400 MHz), Inova-500 (500 MHz), and Inova-600 (600 MHz) spectrometers. Chemical shifts for protons are reported in parts per million downfield from TMS and are referenced to residual protium in the NMR solvent (CHCl₃, δ = 7.26). Chemical shifts for carbon are reported in ppm downfield from TMS and are referenced to the carbon resonances of the solvent (CDCl₃, δ = 77.16). Data are represented as follows: chemical shift, multiplicity (standard abbreviations), coupling constants in hertz (Hz), integration. IR spectra were obtained using a Bruker Hyperion Tensor 27 FTIR spectrophotometer. HRMS were obtained on a ThermoFisher Scientific Exactive series DART Mass Spectrometer.

Preparation of starting aziridines **1** is described in detail in SI.

Ti/Co-Catalyzed Isomerization of *N*-Bz Aziridines to Allylic Amides (Tables 1 and 2 and Scheme 3); General Procedure

To an oven-dried screw-topped vial that was transferred to a glovebox was added Cp*TiCl₃ (5.8 mg, 0.02 mmol, 10 mol%), Zn (6.5 mg, 0.1 mmol, 50 mol%), and EtOAc (1.0 mL, 0.2 M). The mixture was stirred until the solution became green. Then, {Co[(Me₄)salen(CF₃, *t*Bu)]; [(Me₄)salen(CF₃, *t*Bu)] = *N,N'*-bis(2-*tert*-butyl-4-trifluoromethylsali-cylidene)-2,3-dimethyl-2,3-diaminobutane} (**6**; 12.9 mg, 0.02 mmol, 10 mol%), and *N*-Bz aziridine **1** (0.2 mmol, 1.0 equiv) were added and the reaction mixture was stirred at rt for 24 h. Upon completion (as indicated by TLC), the solution was transferred to a vial using DCM, concentrated, and purified directly by flash chromatography.

N-(Cyclohex-2-en-1-yl)benzamide (**2a**)

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (30% DCM:hexanes, then 0–30% EtOAc:hexanes); *R*_f = 0.13 (30% EtOAc:hexanes); white solid; yield: 39.8 mg (99%, 197 μmol); mp 105–107 °C.

IR (neat): 3353, 2966, 1633, 1530, 1330 cm⁻¹.

^1H NMR (500 MHz, CDCl_3): δ = 7.81–7.71 (m, 2 H), 7.48 (t, J = 7.3 Hz, 1 H), 7.41 (t, J = 7.5 Hz, 2 H), 6.10 (d, J = 8.5 Hz, 1 H), 5.90 (ddd, J = 9.6, 4.6, 2.6 Hz, 1 H), 5.74–5.65 (m, 1 H), 4.69 (dtt, J = 8.5, 5.6, 2.9 Hz, 1 H), 2.06–1.97 (m, 3 H), 1.77–1.60 (m, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 166.7, 134.8, 131.3, 131.3, 128.5, 127.6, 126.9, 45.1, 29.5, 24.8, 19.7.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{NO}^+$: 202.1226; found: 202.1230.

***N*-[(1-Tosyl-1,2,3,6-tetrahydropyridin-4-yl)methyl]benzamide (2b)**

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (30% DCM:hexanes, then 0–40% EtOAc:hexanes); R_f = 0.18 (50% EtOAc:hexanes); yellow gum; yield: 65.1 mg (88%, 175 μmol).

IR (neat): 3300, 3059, 2860, 2246, 1639, 1531, 1333, 1157, 910 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.75 (d, J = 7.3 Hz, 2 H), 7.65 (d, J = 8.0 Hz, 2 H), 7.50 (t, J = 7.4 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 6.27 (s, 1 H), 5.55 (t, J = 3.7 Hz, 1 H), 3.97 (d, J = 5.9 Hz, 2 H), 3.58 (q, J = 2.8 Hz, 2 H), 3.19 (t, J = 5.7 Hz, 2 H), 2.41 (s, 3 H), 2.22 (d, J = 6.0 Hz, 2 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 167.62, 143.82, 134.27, 133.69, 133.22, 131.82, 129.80, 128.79, 127.83, 127.03, 118.47, 44.78, 42.75, 26.86, 21.65.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3\text{S}^+$: 371.1424; found: 371.1423.

Methyl (*E*)-11-Benzamidoundec-9-enoate (2c)

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (30% DCM:hexanes, then 0–35% EtOAc:hexanes); R_f = 0.05 (30% EtOAc:hexanes); yellow oil; yield: 61.4 mg (quant, 194 μmol); E/Z = 3:1.

IR (neat): 3328, 2928, 2855, 1737, 1640, 1533, 1371, 1237, 1046 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.77 (d, J = 7.6 Hz, 2 H), 7.48 (t, J = 7.3 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 6.20 (s, 1 H), 5.74–5.57 (m, 1 H), 5.53 (dt, J = 15.4, 6.1 Hz, 1 H), 4.02 (d, J = 6.2 Hz, 2 H), 3.65 (s, 3 H), 2.29 (t, J = 7.5 Hz, 2 H), 2.02 (q, J = 7.1 Hz, 2 H), 1.61 (d, J = 7.2 Hz, 1 H), 1.40–1.24 (m, 9 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 174.44, 134.26, 131.49, 128.64, 127.03, 125.68, 125.09, 51.56, 42.10, 37.29, 34.17, 32.31, 29.51, 29.13, 27.49, 24.99.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{NO}^+$: 318.2063; found: 318.2064.

(E)-N-(Cyclododec-1-en-1-ylmethyl)benzamide (2d)

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (30% DCM:hexanes, then 0–25% EtOAc:hexanes); R_f = 0.26 (30% EtOAc:hexanes); white solid; yield: 46.2 mg (72%, 144 μ mol); mp 120–123 °C.

IR (neat): 3313, 2919, 2855, 1629, 1521, 1277, 1050 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.48 (t, J = 7.4 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 5.95 (s, 1 H), 5.60 (t, J = 7.9 Hz, 1 H), 4.13 (d, J = 5.1 Hz, 2 H), 2.18 (dt, J = 18.7, 6.9 Hz, 4 H), 1.52 (dq, J = 8.9, 5.5, 4.3 Hz, 4 H), 1.38 (q, J = 5.9 Hz, 2 H), 1.29 (d, J = 8.8 Hz, 10 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 167.66, 134.83, 134.06, 133.03, 131.51, 128.71, 127.02, 38.09, 34.61, 27.80, 26.89, 26.82, 25.97, 25.69, 24.70, 24.56, 24.52, 23.83.

HRMS (DART): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{20}\text{H}_{30}\text{NO}^+$: 300.2321; found: 300.2322.

N-[(1R,3R,6S)-4,7,7-Trimethylbicyclo[4.1.0]hept-4-en-3-yl)benzamide (2e)

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (30% DCM:hexanes, then 0–30% EtOAc:hexanes); R_f = 0.25 (30% EtOAc:hexanes); white solid; yield: 36.4 mg (72%, 143 μ mol); mp 88–91 °C.

IR (neat): 3391, 2965, 2892, 1627, 1521, 1383, 1133, 948 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.79 (d, J = 7.0 Hz, 2 H), 7.52 (t, J = 7.3 Hz, 1 H), 7.46 (t, J = 7.4 Hz, 2 H), 6.16 (d, J = 8.5 Hz, 1 H), 5.67 (d, J = 1.8 Hz, 1 H), 4.32 (ddd, J = 8.4, 4.9, 3.2 Hz, 1 H), 2.20 (ddd, J = 15.0, 9.0, 3.2 Hz, 1 H), 1.79 (s, 3 H), 1.78–1.74 (m, 1 H), 1.12 (s, 3 H), 1.07 (ddd, J = 8.7, 3.5, 1.7 Hz, 1 H), 0.93 (s, 3 H), 0.90 (dt, J = 8.7, 4.4 Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 167.15, 136.72, 135.06, 131.47, 128.69, 127.03, 124.07, 46.83, 27.92, 26.41, 23.50, 23.41, 21.73, 17.12, 15.13.

HRMS (DART): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{NO}^+$: 256.1695; found: 256.1697.

N-[1-(1,2,3,6-Tetrahydro-[1,1'-biphenyl]-4-yl)ethyl]benzamide (2f)

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (30% DCM:hexanes, then 0–35% EtOAc:hexanes); R_f = 0.12 (30% EtOAc:hexanes); white solid; yield: 54.9 mg (90%, 180 μ mol); mp 177–180 °C.

IR (neat): 3373, 2958, 2857, 1633, 1539, 1490, 1374, 1120, 951 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.79 (d, J = 8.4 Hz, 2 H), 7.50 (t, J = 6.7 Hz, 1 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.30 (t, J = 7.6 Hz, 2 H), 7.23–7.18 (m, 3 H), 6.14–6.03 (m, 1 H), 5.80 (d, J = 16.2 Hz, 1 H), 4.70 (pent, J = 7.4 Hz, 1 H), 2.78 (td, J = 11.6, 5.4, 3.1 Hz, 1 H), 2.40–2.26 (m, 2 H), 2.25–2.12 (m, 3 H), 2.03–1.96 (m, 1 H), 1.84–1.75 (m, 1 H), 1.38 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 166.78, 166.76, 146.96, 146.92, 138.63, 138.47, 135.00, 134.95, 131.53, 131.51, 128.71, 128.70, 128.53, 128.53, 127.01, 126.98, 126.97, 126.21, 121.90, 121.21, 50.27, 49.92, 40.24, 40.16, 33.44, 33.36, 29.97, 29.89, 26.70, 26.53, 19.84, 19.69.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{NO}^+$: 306.1852; found: 306.1851.

***N*-{2-[(3*r*,5*r*,7*r*)-Adamantan-1-yl]allyl}benzamide (2g)**

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (0–20% EtOAc:hexanes); R_f = 0.36 (30% EtOAc:hexanes); white solid; yield: 34.1 mg (57%, 114 μmol); mp 100–104 $^\circ\text{C}$.

IR (neat): 3358, 2962, 2905, 2840, 1613, 1540, 1300, 897 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.82–7.75 (m, 2 H), 7.49 (dd, J = 8.5, 6.2 Hz, 1 H), 7.43 (t, J = 7.5 Hz, 2 H), 6.09 (s, 1 H), 4.97 (d, J = 5.2 Hz, 2 H), 4.11 (d, J = 5.4 Hz, 2 H), 2.05–2.01 (m, 3 H), 1.78–1.71 (m, 9 H), 1.68 (d, J = 11.7 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 167.1, 154.8, 134.7, 131.4, 128.6, 126.8, 108.5, 41.0, 40.4, 37.4, 36.8, 28.5.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{NO}^+$: 296.2008; found: 296.2010.

(*Z*)-*N*-(2-Methyl-4-phenylbut-2-en-1-yl)benzamide (2h)

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (0–20% EtOAc:hexanes); R_f = 0.16 (30% EtOAc:hexanes); white solid; yield: 32 mg (53%, 106 μmol); 1:0.2 ratio of terminal/internal alkene.

IR (neat): 3383, 2965, 1627, 1563, 1261, 1180, 950 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.77 (d, J = 7.6 Hz, 2 H), 7.51 (t, J = 7.3 Hz, 1 H), 7.44 (t, J = 7.7 Hz, 2 H), 7.28 (d, J = 7.7 Hz, 2 H), 7.19 (dd, J = 11.1, 7.2 Hz, 3 H), 6.12 (s, 1 H), 4.98 (d, J = 26.5 Hz, 2 H), 4.09 (d, J = 6.0 Hz, 2 H), 2.83 (t, J = 8.1 Hz, 2 H), 2.42 (t, J = 8.0 Hz, 2 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 167.36, 145.46, 141.64, 134.50, 131.55, 128.64, 128.40, 126.90, 125.98, 111.19, 44.52, 35.82, 34.19.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{NO}^+$: 266.1539; found: 266.1540.

***N*-(Cyclopent-2-en-1-yl)benzamide (2i)**

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (0–20% EtOAc:hexanes); R_f = 0.12 (30% EtOAc:hexanes); white solid; yield: 36.9 mg (99%, 198 μmol); mp 130–131 $^\circ\text{C}$.

IR (neat): 3345, 2965, 2850, 1719, 1519, 1260, 1057 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.76 (d, J = 7.0 Hz, 2 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 2 H), 6.04 (d, J = 15.8 Hz, 1 H), 6.01 (dt, J = 6.0, 2.2 Hz, 1 H), 5.79 (dq, J = 4.5, 2.2 Hz, 1 H), 5.22 (tp, J = 7.2, 2.3 Hz, 1 H), 2.53–2.44 (m, 2 H), 2.43–2.32 (m, 1 H), 1.73–1.63 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 166.98, 135.28, 134.88, 131.50, 131.20, 128.68, 127.01, 56.23, 31.72, 31.38.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{NO}^+$: 188.1069; found: 188.1063.

***N*–[(3*R*,3*aR*,5*S*,7*R*,8*aS*)-3,8,8-Trimethyl-6-methyleneoctahydro-1*H*-3*a*,7-methanoazulen-5-yl]benzamide (2j)**

Synthesized according to general procedure on a 0.2 mmol scale and isolated after column chromatography (0–20% EtOAc:hexanes); R_f = 0.15 (30% EtOAc:hexanes); pale yellow oil; yield: 34.9 mg (54%, 108 μmol).

IR (neat): 3288, 2923, 2252, 1639, 1533, 1446, 1274, 1024 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.82 (d, J = 6.9 Hz, 2 H), 7.51 (t, J = 7.3 Hz, 1 H), 7.45 (t, J = 7.4 Hz, 2 H), 6.07 (d, J = 9.2 Hz, 1 H), 5.02 (q, J = 10.0, 9.1 Hz, 1 H), 4.80–4.71 (m, 2 H), 2.41 (d, J = 4.3 Hz, 1 H), 2.13 (ddd, J = 10.9, 7.4, 2.8 Hz, 1 H), 2.03 (t, J = 8.1 Hz, 1 H), 1.92–1.83 (m, 2 H), 1.77 (q, J = 6.9 Hz, 1 H), 1.62 (ddd, J = 12.8, 6.4, 2.7 Hz, 1 H), 1.49–1.43 (m, 1 H), 1.39–1.33 (m, 1 H), 1.21 (t, J = 11.4 Hz, 2 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.86 (d, J = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 166.82, 151.29, 134.82, 131.60, 128.76, 127.03, 107.33, 60.64, 56.89, 54.93, 49.04, 44.89, 42.69, 42.61, 42.00, 37.08, 26.87, 26.29, 25.99, 15.58.

HRMS (DART): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{NO}^+$: 324.2321; found: 324.2323.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Co(salen) catalysts **6** and **7**

A. Allylic substitution **B. Overman Rearrangement** **C. C–H Alkenylation** **D. Hydroamination** **Scheme 1.**

Examples of current methods towards allylic amine synthesis

A. Previous work on allylic C–H amination

B. Proposed three-step synthesis of allylic amides

C. Previous work on aziridine isomerization

D. Previous Ti/Co bimetallic catalysis for epoxide rearrangement

Scheme 2.
Synthetic design and literature precedence

Scheme 3.

Substrate scope. *Reagents and conditions:* Cp*TiCl₃ (10 mol%), [Co] **6** (10 mol%), Zn⁰ (0.5 equiv), EtOAc (0.2 M). Amide **2h** was isolated as an inseparable mixture of 3 products; for the internal allylic amide, *E/Z* ratio = 1.2:1 (absolute stereochemistry not assigned).

A. Secondary β -chloroamide as starting material

B. Tertiary β -chloroamide as starting material

C. Oxazoline as starting material

Scheme 4.

Potential Lewis acid intermediates. Yields of the products from **4k** were calculated based on isolated mass of the mixture and the product ratio was determined by ^1H NMR analysis.

Scheme 5.
Proposed catalytic cycle

Table 1Assessment of Aziridine Protecting Group and Titanium Catalyst^a

Entry	1	R	[Ti]	2 (%)	3 (%)	4 (%)	5 (%)
1 ^b	1a ^H	H	Cp*TiCl ₃	-	-	-	-
2	1a ^{Ac}	Ac	Cp*TiCl ₃	-	-	-	-
3 ^b	1a ^{Piv}	Piv	Cp*TiCl ₃	-	17	52	-
4	1a ^{Boc}	Boc	Cp*TiCl ₃	-	-	25	-
5	1a ^{Ts}	Ts	Cp*TiCl ₃	-	-	-	-
6	1a	Bz	Cp*TiCl ₃	88	12	-	-
7	1a ^{CF₃}	3,5-(CF ₃) ₂ Bz	Cp*TiCl ₃	79	-	17	-
8	1a ^{OMe}	4-MeOBz	Cp*TiCl ₃	-	-	-	-
9 ^b	1a	Bz	Cp*TiCl₃	93	6	-	-
10 ^b	1a	Bz	Cp*Ti(OTf) ₃ ^c	-	-	-	57

^aAll yields are isolated unless otherwise noted.^bWithout Et₃N·HCl.^cGenerated in situ by treatment of Cp*TiCl₃ with 0.3 equiv AgOTf.

Table 2

Assessment of Cobalt Catalyst and Solvent

Entry	[Co]	Solvent	x (equiv)	2a (%)	3a (%)	4a (%)
1	6	Et ₂ O	2	93	7	-
2	6	EtOAc	2	88	12	-
3	6	EtOAc	0	93	6	-
4^a	6	EtOAc	0	99	-	-
5	6	MeCN	2	43	5	-
6	6	THF	2	47	13	-
7	6	PhMe	2	50	8	-
8	7	Et₂O	2	95	-	-
9	7	Et ₂ O	0	-	-	-
10 ^b	7	Et ₂ O	2	-	-	-
11 ^c	7	Et ₂ O	2	-	-	-
12 ^d	7	Et ₂ O	2	-	-	26

^a Carried out using 0.2 M concentration of **1a** in EtOAc.^b No Co.^c No Ti.^d No Zn.