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C-H Functionalization

Iridium(III)-Catalyzed Intermolecular C(sp^3)-H Amidation for the Synthesis of Chiral 1,2-Diamines

*Andrea Geraci, Uros Stojiljković, Kevin Antien, Nihad Salameh, and Olivier Baudoin**

Abstract: Chiral 1,2-diamines are privileged scaffolds among bioactive natural products, active pharmaceutical ingredients, ligands for transition-metal-based asymmetric catalysis and organocatalysts. Despite this interest, the construction of chiral 1,2-diamine motifs still remains a challenge. To address this, an iridium(III)-catalyzed intermolecular C(sp^3)-H amidation reaction was developed. This method relies on the design of a new, cheap and cleavable exo-protecting/directing group derived from camphorsulfonic acid, which is directly installed from easily accessible precursors, and furnishes scalemic free 1,2-diamines upon cleavage of both nitrogen substituents. It was found applicable to both α-secondary and α-tertiary-1,2-diamines, for which a two-step protocol involving intermolecular olefin hydroamination and C(sp^3)-H amidation was developed. Kinetic and computational studies provided insights into the observed reactivity difference between pairs of diastereoisomeric substrates.

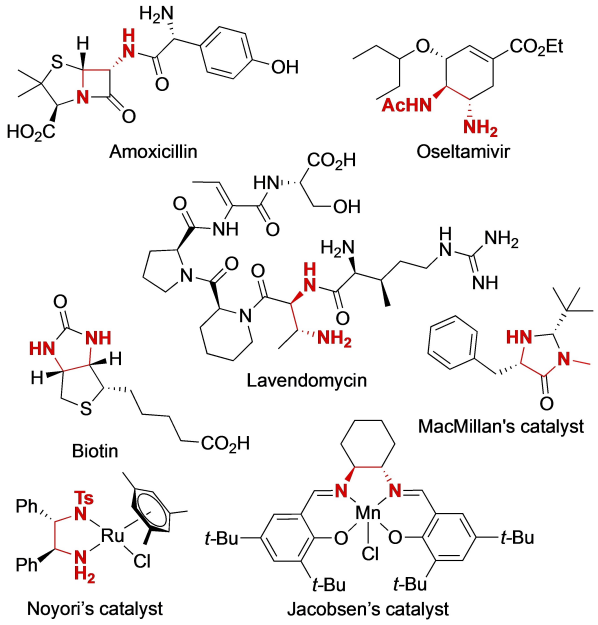

Figure 1. Representative examples of natural products, bioactive molecules, ligands and organocatalysts that contain a chiral 1,2-diamine motif.

Introduction

Chiral 1,2-diamines have been widely recognized as privileged scaffolds among bioactive natural products and active pharmaceutical ingredients (Figure 1).[1] These structural motifs have also found broad application as ligands for transition-metal-based asymmetric catalysis[2] and as organocatalysts.[3] In light of this broad interest, chiral vicinal diamines have been the subject of numerous synthetic studies. Traditional methods include the opening of aziridines with nitrogen nucleophiles,[4] Mannich reaction between α-amino compounds and imines,[5] reduction of α-amino imines,[6] diamination of olefins[7] or multi-step synthetic sequences.[8]

During the last decade, transition-metal-catalyzed C-(sp^3)-H amination reactions proceeding via outer-sphere or inner-sphere mechanisms have witnessed impressive advances, providing powerful, straightforward and unconventional strategies to forge new C(sp^3)-N bonds.[9] Nevertheless, given the ubiquity of C–H bonds in organic molecules, harnessing site-selectivity in C–H bond functionalization remains a significant challenge.[10] This can be addressed by employing an intramolecular C–H activation step that limits the number of accessible sites. In this context, Du Bois and co-workers reported the synthesis of vicinal diamines through Rh^{II}-catalyzed intramolecular nitrene insertion from *N*-sulfamates, followed by reductive cleavage of the corresponding cyclic sulfamate (Scheme 1a).[11] This reaction proceeds via outer-sphere rhodium-nitrene insertion,[9a,b] and therefore displays a higher reactivity toward tertiary and benzylic C–H bonds possessing low bond dissociation energies. An alternative C–H activation-based synthesis of vicinal diamines would involve intermolecular C–H amination of a substrate containing a nitrogen-based directing group. Such reactions proceeding via an inner-sphere, concerted metalation-deprotonation (CMD) mechanism,[9c] preferentially target primary and secondary C–H bonds, and

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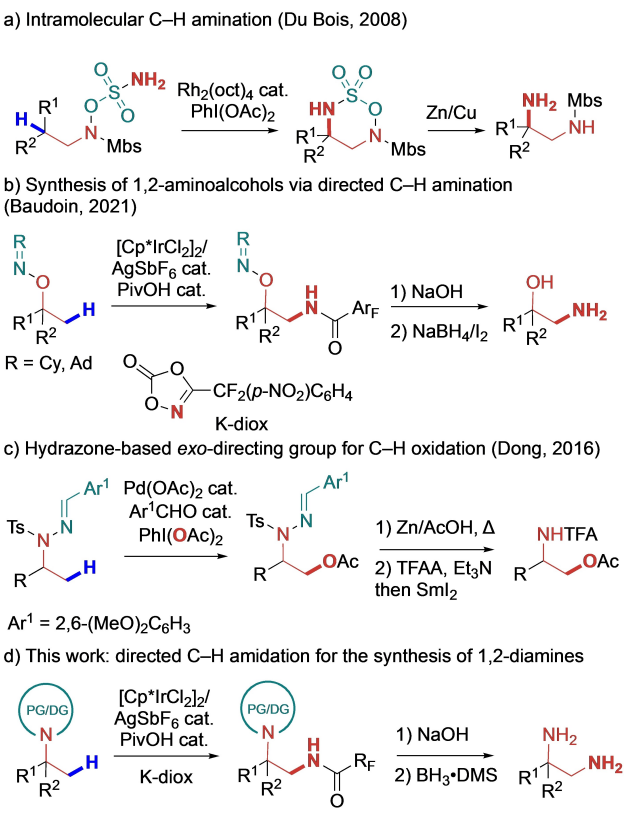
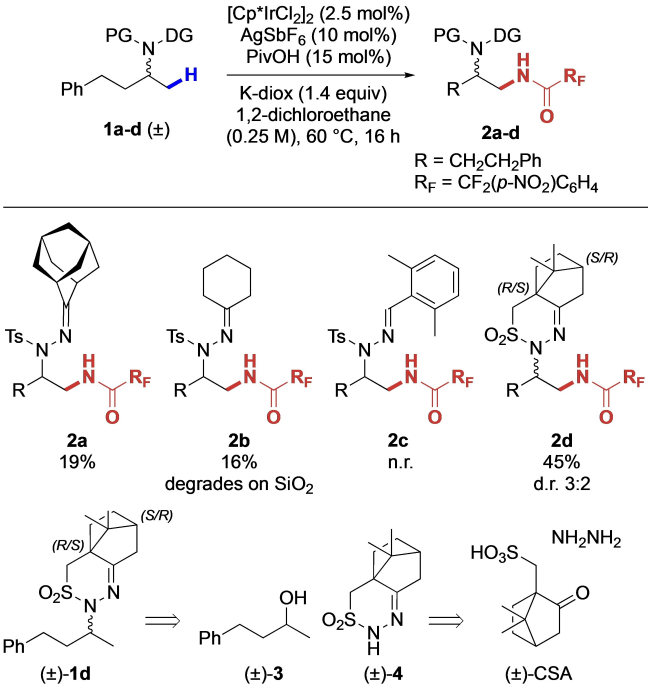


Scheme 1. Synthesis of chiral 1,2-diamines via C(sp^3)-H amination: inspiration and current approach.

are therefore complementary to outer-sphere C–H aminations. Inspired by seminal work using the *exo*-directing group strategy for the metal-catalyzed C–H oxidation and amination of alcohol derivatives,[12] we recently reported the synthesis of 1,2-aminoalcohols via iridium(III)-catalyzed C–H amidation of primary and secondary C–H bonds (Scheme 1b).[13] To this purpose, we used an oxime-based directing group and designed a novel 1,4,2-dioxazol-5-one reagent,[14] K-diox, whose electron-deficient substituent confers both a very good stability of the reagent and a high reactivity of the corresponding iridium nitrene. However, transposing this method to the synthesis of 1,2-diamines is far from trivial. Indeed, this requires the development of a suitable protecting/directing group which 1. disables the coordinating ability of the closest nitrogen atom to the activated C–H bond in order to direct the desired C–H activation process to the C_β-H bond via the formation of a 5-membered metallacycle; 2. is cleavable, to ultimately furnish the free diamine. Studies from the Dong group allowed to identify tosyl-protected hydrazones as promising nitrogen-based *exo*-directing groups for the synthesis of 1,2-aminoalcohol derivatives via Pd-catalyzed C(sp^3)-H oxidation (Scheme 1c).[15] Motivated by the lack of precedents, we developed an iridium(III)-catalyzed C(sp^3)-H amidation to access chiral 1,2-diamines (Scheme 1d). This method relies on the design of a new, cheap and cleavable *exo*-protecting/directing group derived from camphorsulfonic acid and furnishes free diamines upon cleavage of both nitrogen substituents.

Results and Discussion

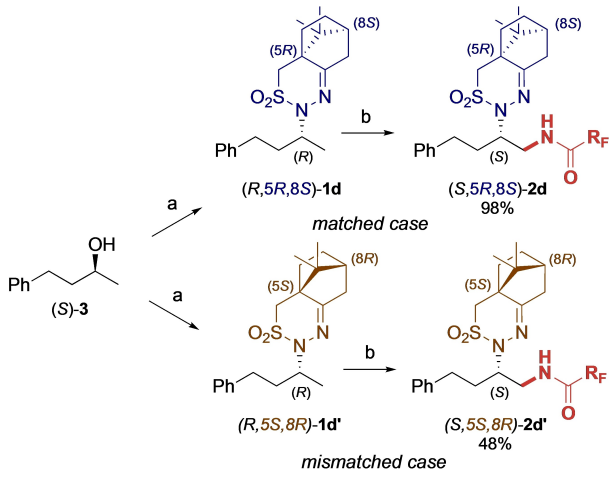
Our initial efforts focused on the design of a suitable protecting/directing group for the C–H amination of α-secondary amines. We hypothesized that a sulfonyl N-protecting group would shut down the Lewis basicity of the proximal nitrogen atom and that a hydrazone possessing bulky substituents would be an appropriate Lewis-basic directing group, favoring coordination to the metal catalyst and activation of the strong C(sp^3)-H bond. We therefore assessed various tosylhydrazone protecting/directing groups under previously reported C(sp^3)-H amidation conditions employing K-diox and a cationic iridium(III) catalyst generated in situ from $[Cp^*IrCl_2]_2/AgSbF_6$ (Scheme 2).[13] We found that simple *N*-tosyl protected adamantyl hydrazone **1a** could be amidated to the corresponding protected 1,2-diamine **2a**, albeit in 19% yield. Unfortunately, optimization of reaction conditions or simple structural modifications of the hydrazone (**1b–c**) did not lead to any satisfactory improvement (see Figure S1 for details). On the other hand, camphorsulfonic acid (CSA) is a very cheap chiral Brønsted acid, routinely used in organic synthesis as reagent, resolution agent, chiral auxiliary or organocatalyst.[16] We envisioned that a CSA-based cyclic hydrazone could be easily installed from secondary alcohols via Mitsunobu reaction, hence serving at the same time as



Scheme 2. Identification of a suitable protecting/directing group for the Ir-catalyzed C(sp^3)-H amidation. Reactions were performed on a 0.2 mmol scale at a concentration of 0.25 M. The shown yields refer to isolated products.

protecting and directing group for the C_β-H amidation of aliphatic amines. We hypothesized that the enhanced rigidity and Lewis basicity of this bicyclic directing/protecting group would lead to a more efficient C–H amination reaction. Hydrolysis of the resulting amide and reductive cleavage would furnish the desired free 1,2-diamine. Gratifyingly, employing a racemic and diastereoisomeric mixture of **1d**, synthesized from racemic alcohol **3** and thiadiazine dioxide **4**, amide **2d** was isolated in 45 % yield as a 3:2 diastereoisomeric mixture.

Independently engaging one enantiomer of the starting alcohol (*S*)-**3** in the Mitsunobu reaction with each enantiomer of the CSA-derived thiadiazine dioxide **4** afforded enantiopure diastereomers (*R*,5*R*,8*S*)-**1d** and (*R*,5*S*,8*R*)-**1d′** (Scheme 3). We were then intrigued to discover that, under the same reoptimized C–H amidation conditions (5 mol% Ir, 1.1 equiv. K-diox), **1d** was converted to the corresponding amide **2d** in 98 % yield (matched case), while **1d′** showed a significantly lower reactivity, delivering the corresponding amide **2d′** in only 48 % yield (mismatched case). Of note, employing other group 9 transition-metal catalysts such as Cp*Co(CO)I_2 or $[Cp^*RhCl_2]_2$ afforded low yields or no reaction at all (Table S2), hence confirming the superior reactivity of Ir^{III} for such reactions.



Scheme 3. Synthesis of stereochemically defined 1,2-diamine derivatives from an enantiopure methyl carbinol. Reaction conditions: a) (5*R*,8*S*)-**4** (top) or (5*S*,8*R*)-**4** (bottom), PPh_3, DIAD, THF, 25 °C; b) $[Cp^*IrCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), PivOH (15 mol%), K-diox (1.1 equiv), 1,2-dichloroethane (*c* 0.25 M), 60 °C, 16 h.

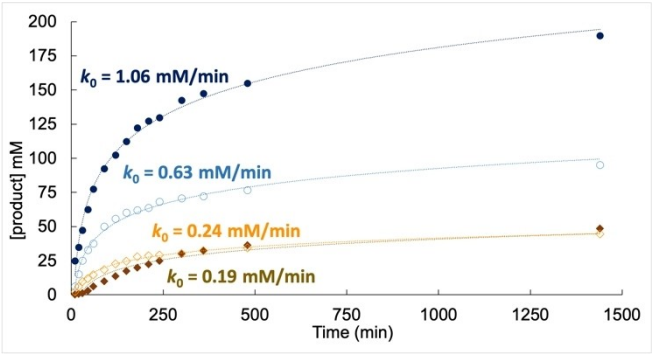
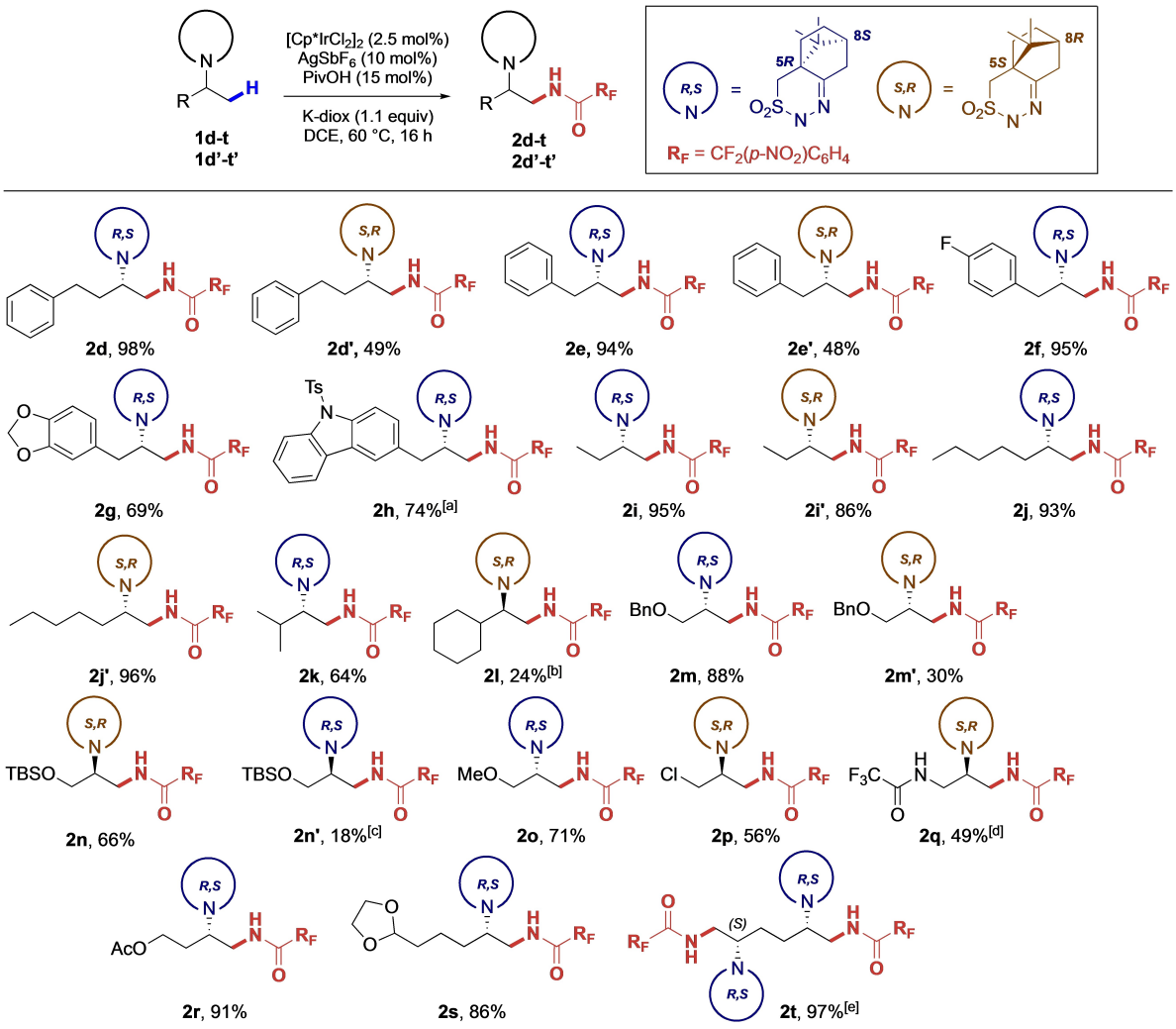


Figure 2. Compared kinetic profiles and initial reaction rates (k_0) for the C–H amidation of (a) **1d** alone (filled circles), (b) **1d′** alone (filled losanges), and (c) **1d** (empty circles) and **1d′** (empty losanges) in a 1:1 mixture of **1d**/**1d′**.

In order to gain a deeper understanding of the reaction kinetics, we monitored the three parallel reactions of isolated diastereoisomers **1d**, **1d′** and a 1:1 mixture of **1d**/**1d′** obtained from (±)-**3** and the enantiopure (5*R*,8*S*)-thiadiazine dioxide (Figure 2, see Scheme 3 for the reactions of **1d** and **1d′**). These experiments showed that **1d** (filled circles) reacts faster (5.5 x) than **1d′** (filled losanges), hence confirming the observed reactivity difference between these two diastereoisomers (see Scheme 3). However, starting from the **1d**/**1d′** mixture the formation of **2d** (empty circles) was strongly slowed down (compare with filled circles), while that of **2d′** was not (empty losanges, compare with filled losanges). As a consequence, the d.r. of **2d** arising from the C–H amidation of the **1d**/**1d′** mixture remained fairly constant (68:32 < d.r. <72:28) throughout the course of the reaction.

Through parallel inhibition experiments (Figures S7–S8), we found that the mismatched amide product **2d′** decelerates the C–H amidation of **1d**, while no significant inhibitory effect was detected when the matched amide **2d** was added to the reaction of **1d′**. This suggests that low concentrations of the minor diastereoisomer **2d′** hamper the formation of **2d**, hence compromising a diastereomeric kinetic resolution scenario. Indeed, modifying common parameters such as temperature, concentration or time in the reaction of the **1d**/**1d′** mixture did not provide any improvement of the d.r. of the matched amide **2d**. Based on the assumption that the energy barrier for the C–H activation step would be notably different for the two diastereomers **1d** and **1d′**, we tested several carboxylic acid additives, which are involved in the CMD mechanism (Table S4). We observed that benzoic acid and decanoic acid improved the d.r. of the resulting amide **2d** to 3:1 (50 % NMR yield of **2d**) and 9:1 (38 % yield), respectively. However, varying the substitution pattern on the Cp* ligand or using bulkier, aliphatic carboxylic acid additives marginally improved the diastereoselectivity of the reaction.

In light of this moderately efficient kinetic resolution from the diastereoisomeric mixture (best d.r. 9:1 with a 38 % yield), we decided to further focus on the highly efficient C–H amidation of matched substrates derived from enantiopure carbinols (see Scheme 3, top). Indeed, the latter are easily accessible via asymmetric synthesis, chiral resolution or from the chiral pool, and would readily furnish enantiopure vicinal diamines through the Mitsunobu/C–H amidation/deprotection sequence. We therefore prepared a range of diastereomerically pure protected secondary amines from enantiopure secondary alcohols and studied their reactivity in the C–H amidation reaction (Scheme 4). In several cases, we prepared both diastereoisomers of reaction substrates to study the generality of the kinetic effect observed with **1d**/**1d′**. We were pleased to observe that most matched substrates performed very well, deliver-

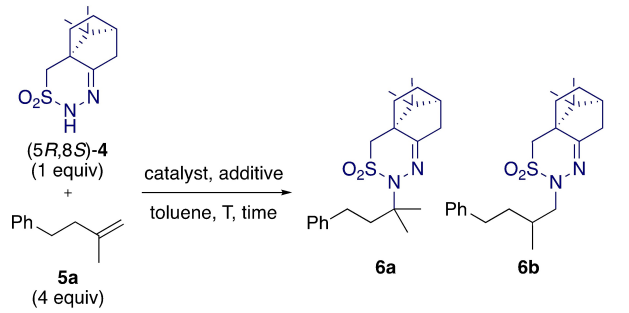


Scheme 4. Scope of the C_β-H amidation reaction of protected diastereomerically pure amines. Reactions were performed on a 0.4 mmol scale at a concentration of 0.25 M. Yields refer to isolated products unless otherwise stated. [a] Reaction carried out at 70 °C. [b] Isolated as a 4:1 diastereoisomeric mixture. [c] NMR yield. [d] $[Cp^*IrCl_2]_2$ 5 mol%, $AgSbF_6$ (20 mol%), PivOH (30 mol%). [e] $[Cp^*IrCl_2]_2$ 5 mol%, $AgSbF_6$ (20 mol%), PivOH (30 mol%), K-diox (2.2 equiv).

ing the corresponding amides in excellent yields. Interestingly, we confirmed the remarkable reactivity difference between matched and mismatched diastereoisomers when the R substituent was rather bulky or rigid (**2d**/**2d**′, **2e**/**2e**′, **2m**/**2m**′, **2n**/**2n**′), with the first series always outperforming the second one. This reactivity trend did not apply to substrates containing linear aliphatic chains **2i**/**2i**′ and **2j**/**2j**′. In these cases, both diastereoisomers displayed excellent yields, indicating that steric bulk probably plays a crucial role in this process. Indeed, branching at the β-position to the amine nitrogen led to reduced yields, as shown with isopropyl and cyclohexyl-containing products **2k**–**l**. Obviously, as illustrated with compounds **2l**, **2n**, **2p** and **2q**, employing a starting secondary alcohol with the opposite absolute configuration required the use of the other enantiomer of the camphorsulfonic-based directing group to remain in the matched case and achieve the highest yields. This is not an issue as both enantiomers of camphorsulfonic acid are commercially available and inexpensive,[17] and the appropriate enantiomer of CSA can thus be chosen based on the availability of the starting alcohol.

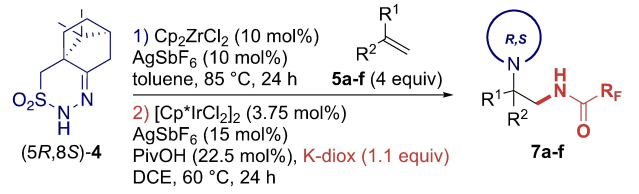
Although one could have expected to observe a competition between the primary C–H bond and the more acidic benzylic position, this was not the case as all homobenzylic amines were regioselectively amidated to yield the corresponding terminal amides (**2e**–**h**), hence further illustrating the influence of steric effects. In this case, in contrast to our previous study,[13] modifying the electronic properties of the aromatic ring affected the outcome of the reaction. Indeed, an electron withdrawing group induced a more facile reaction (**2f**) whereas an electron-rich benzene ring furnished lower yields (**2g**) as compared to **2e**, and this remote electronic effect is somewhat unexpected. Interestingly, the reaction seems compatible with N-protected heterocycles, as illustrated with tosylcarbazole **2h**, although a higher temperature (70 °C) was required in this case. Moreover, the C–H amidation of substrates bearing different functional groups worked well, as shown with products **2m**–**s**. In particular, a

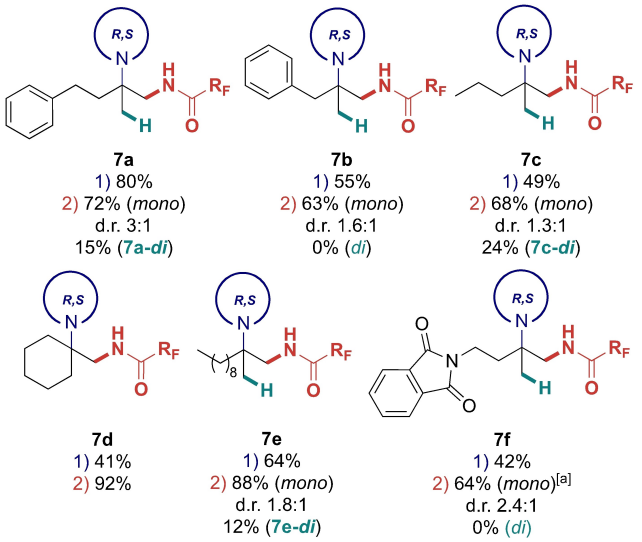
Table 1: Optimization of the Markovnikov-selective intermolecular hydroamidation of olefin **5a** with CSA-derived hydrazone **4**.[a]



entry	catalyst (mol%)	additive (mol%)	T (°C)	time (h)	**6a** (%)[b]	**6a**/**6b**
1	Ph_3PAuCl (10)	AgOTf (10)	85	18	40	96:4
2	$ZrCl_4$ (10)	$AgSbF_6$ (10)	85	16	41	98:2
3	$TiCl_4$ (10)	AgOTf (10)	85	16	0	n.d.
4	Cp_2ZrCl_2 (10)	$AgSbF_6$ (10)	85	16	66	>99:1
5	Cp_2ZrCl_2 (10)	$AgSbF_6$ (10)	85	24	80	>99:1

[a] Reactions were performed at 0.1 mmol scale at a concentration of 0.5 M. [b] NMR yields based on the limiting reagent **4**, using mesitylene as internal standard.

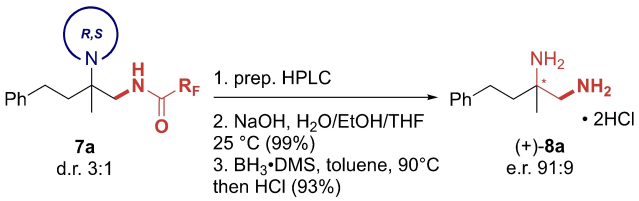




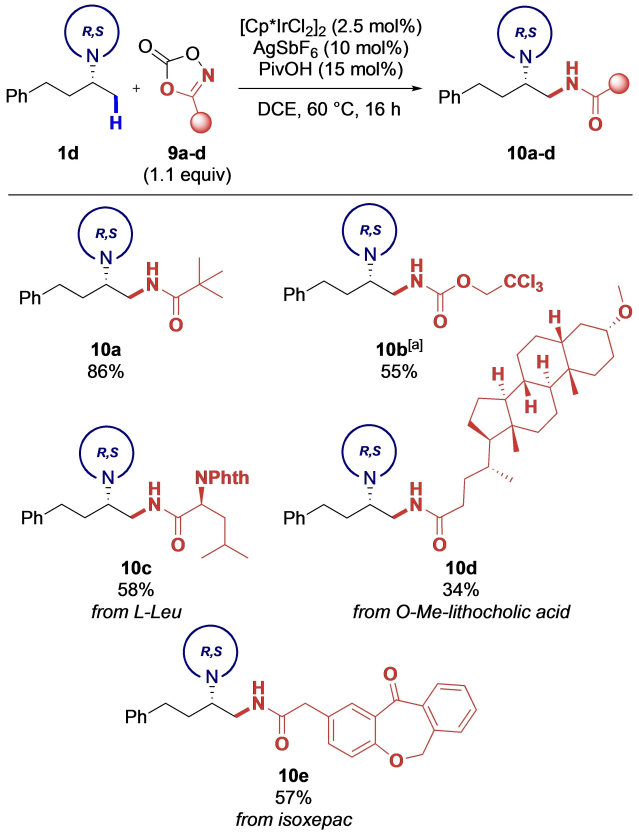
Scheme 5. Two-step synthesis of chiral α-tertiary-1,2-diamines from 1,1-disubstituted alkenes. Reactions were performed on a 0.2 mmol scale at a concentration of 0.25 M. Yields shown refer to isolated products/diastereoisomeric mixtures. D.r. were determined by ^{19}F NMR of the crude mixture. [a] Reaction time: 36 h.

β-chloroamine afforded the protected (*S*)-3-chloropropane-1,2-diamine **2p** in 56% yield, which in turn may be further elaborated to produce more functionalized fragments. In addition, protected primary alcohols (**2m**–**o**, **2r**), a TFA-protected amino group (**2q**) and an acetal (**2s**) all proved compatible with the reaction conditions. For trifluoroacetamide **2q**, a higher catalyst loading was yet necessary, probably due to the stronger coordinating ability of this group. Finally, by doubling the amounts of K-diox and catalysts, it was possible to perform a double C–H amidation from a diamine bearing two directing groups, to furnish the valuable protected tetramine product **2t** in excellent yield. Unfortunately, less reactive secondary C–H bonds were not compatible with the present method.

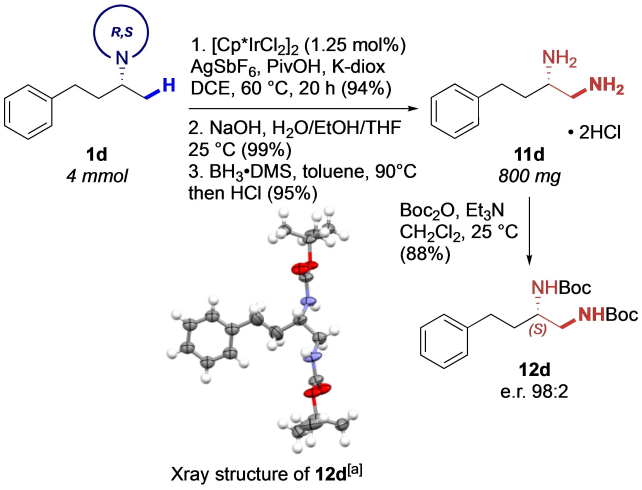
We then investigated the possibility to employ our methodology to construct α-tertiary-1,2-diamines from α-tertiary amines (ATAs), which are commonly found in many bioactive natural products, especially in alkaloids.[18]



Scheme 6. Access to an enantioenriched α-tertiary-1,2-diamine from a C(sp^3)-H amidation product. The e.r. of **8a** was determined on the cyclic urea derivative by HPLC on a chiral stationary phase.



Scheme 7. C(sp^3)-H amidation with other amidation reagents. Reactions were performed on a 0.4 mmol scale at a concentration of 0.25 M. Yields refer to isolated products. [a] $TrocN_3$ was used as amidation reagent.



Scheme 8. Scale-up and global deprotection. [a] Thermal ellipsoids at 50% probability, disordered atoms hidden for clarity.[26] The e.r. was determined on **12d** by HPLC on a chiral stationary phase.

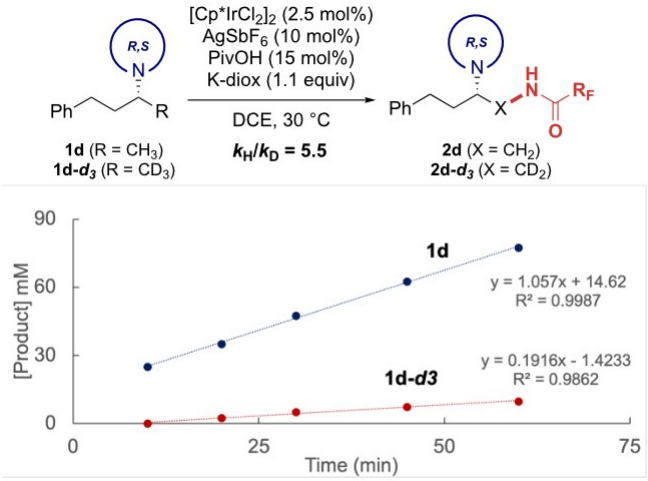


Figure 3. Determination of the kinetic isotope effect. Reactions were run in parallel on a 0.4 mmol scale at a concentration of 0.25 M. See Figure S11 for full kinetic curves.

To this purpose, we set out to install our protecting/directing group onto a suitable ATA precursor. Although ATAs can be synthesized through several approaches based on the formation of a C–C or a C–N bond,[19] we soon realized that in our case this would require a tedious multistep sequence. Looking for simpler alternatives, we turned to the regioselective hydroamination of largely available 1,1-disubstituted olefins, which would provide a straightforward access to the desired C–H amidation precursors, and in turn to chiral α-tertiary-1,2-diamines. Our goal was to develop a practical, intermolecular, regioselective and catalytic hydroamination that would not require pre-functionalization of any starting material. With this in mind, we started to test different catalytic systems reported to promote hydroamination of unactivated olefins (Table 1). We were pleased to find out that the in situ formed cationic gold complex $Ph_3PAu(OTf)$ catalyzes the hydroamination of olefin **5a** with the CSA-based thiadiazine dioxide **4** (used as limiting reagent) to give the corresponding ATA in 40% NMR yield (entry 1).[20] After further screening, we found that other π-acidic catalysts performed well in this reaction (Table S5). In particular, cationic Ti^{IV}- or Zr^{IV}-based catalysts are very appealing, due to the abundant nature of these metals and their excellent Markovnikov selectivity in the considered transformation (Table 1, entries 2–3). Indeed, group-IV metals have been known to promote or catalyze intramolecular hydroaminations of aminoalkenes since the 2000's.[21] Moreover, Ti-catalyzed intermolecular hydroamination of styrenes with electron-deficient anilines was reported by Ackermann and co-workers in 2005.[22] However, known intermolecular hydroaminations that rely on early transition-metal catalysts are dominated by rare-earth metal complexes.[23] Although powerful, these catalysts generally derive from expensive sources and are usually difficult to prepare and store, given their high sensitivity to air and moisture. On the other hand, cationic titanocenes and zirconocenes are isoelectronic to lanthanocenes but considerably cheaper and easier to handle. We were thus pleased to identify Cp_2ZrCl_2 (10 mol%) in combination with $AgSbF_6$ (10 mol%) as the best catalytic system, in toluene at 85 °C for 24 h, to provide the Markovnikov product **6a** exclusively in 80% yield (Table 1, entry 5). To the best of our knowledge, this is the first example of intermolecular hydroamination of an unactivated olefin by group-IV metal catalysis.

With this method in hand, we turned our attention to the two-step synthesis of α-tertiary-1,2-diamines (Scheme 5), where 1,1-disubstituted olefins (**5a–f**) were first regioselectively hydroaminated with **4**, then the resulting protected ATAs **6a–f** were subjected to the C(sp^3)-H amidation reaction under slightly modified conditions - $[Cp^*IrCl_2]_2$ (3.75 mol%), $AgSbF_6$ (15 mol%), PivOH (22.5 mol%), K-diox (1.1 equiv) - to afford the desired α-tertiary-1,2-diamines (**7a–f**). Diamidation was observed in some cases when two methyl groups were present in the C–H amidation substrate, leading to the formation of the unusual α-tertiary-1,2,3-triamine motif (**7a-*di***, **7c-*di***, **7e-*di***). This two-step approach was successfully applied to alkene **5a** to afford the desired α-tertiary-1,2-diamine **7a** in 72% yield, which was isolated as a 3:1 diastereoisomeric mixture, together with the α-tertiary-1,2,3-triamine **7a-*di***, which could be separated upon purification. Interestingly, the same method afforded the protected phenylethylamine derivative **7b**, which could be potentially useful in medicinal chemistry.[24] Olefins **5c** and **5e**, that bear a rather flexible alkyl chain, also underwent hydroamination with total Markovnikov selectivity, and were then smoothly converted to the corresponding amidated products (**7c**+**7c-*di*** and **7e**+**7e-*di***) in good yields under iridium catalysis. Despite the sterically hindered cyclohexyl substituent, protected 1-methylcyclohexan-1-amine **6d** could be synthesized in 41% yield as a single regioisomer, and subsequently C–H amidated to afford **7d** in 92% yield. Gratifyingly, both the Zr-based and Ir-based catalytic systems proved compatible with a protected nitro-

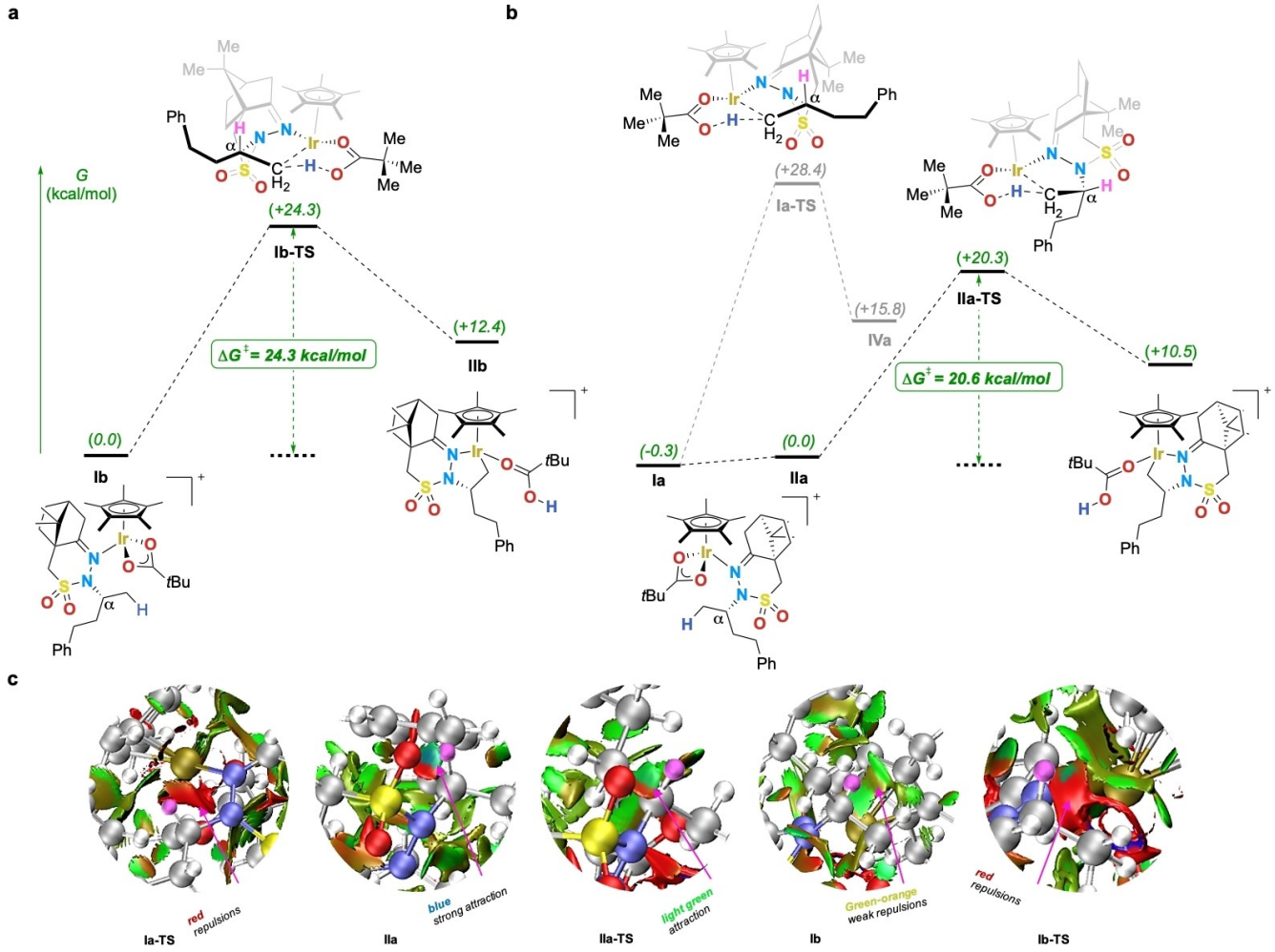


Figure 4. Computational study of the concerted metalation-deprotonation step (CMD). a) Energy diagram of the reaction featuring **1d′** (mismatched reactant). b) Energy diagram of the reaction featuring **1d** (matched reactant). c) NCI plots with highlighted repulsive and attractive interactions. Calculations were performed at ωB97X-D/{6–311++G(d,p)-SDD(Ir)}-SMD(DCE)//B3LYP-D3(BJ)/{6-31G(d,p)-LANL2DZ(Ir)}-(gas) level of theory, in kcal/mol.

gen moiety such *N*-phthalimide, hence producing the interesting orthogonally-protected triamine **7f** in 64 % yield.

Additionally, we were pleased to find out that enantioenriched α-tertiary-1,2-diamine **8a** could be obtained through chromatographic purification (normal phase preparative HPLC) of the diastereomeric mixture **7a** and subsequent stepwise deprotection of terminal and α-tertiary amines with sodium hydroxide and the borane•dimethyl sulfide complex (Scheme 6).

Although the electron-poor dioxazolone K-diox is able to deliver easily cleavable amides (Scheme 6, see also Scheme 8), we wanted to test our C(sp^3)-H amidation reaction protocol with other amidation reagents (Scheme 7). We were pleased to find out that under standard reaction conditions *tert*-butyl-substituted dioxazolone **9a** efficiently delivered the corresponding pivalamide **10a** in 86 % yield. 2,2,2-Trichloroethyl carbonazidate ($TrocN_3$) **9b** is an organic azide commonly used as nitrene source in C–H amination reactions.[25] Gratifyingly, our model substrate was regioselectively functionalized using this reagent, albeit in average yield (**10b**, 55 %). Moreover, the reaction showed compatibility with L-leucine-derived dioxazolone **9c**, which furnished the corresponding amide product **10c** in 58 % yield. Furthermore, more complex dioxazolones bearing a lithocholic acid derivative (**10d**) or the nonsteroidal analgesic isoxepac (**10e**) proved to be competent reaction partners.

With potential applications of our method in mind, we performed the C–H amidation on a 10-fold reaction scale (4 mmol of **1d**), followed with the deprotection sequence (Scheme 8). By reducing the catalyst loading to 1.25 mol% and prolonging the reaction time to 20 h, the corresponding protected 1,2-diamine was isolated in excellent yield (94 %). A mild hydrolysis of the amide was next accomplished quantitatively with sodium hydroxide at room temperature. Then, the protecting/directing group was cleaved under reducing conditions to furnish 800 mg of the highly enantioenriched (e.r. 98:2) 1,2-diamine **11d**, which was isolated as the dihydrochloride salt in 95 % yield. In turn, **11d** was converted to the easier-to-handle bis-carbamate **12d**, which

could serve as precursor to a plethora of useful compounds for diverse applications.

Finally, we conducted mechanistic studies to get additional insights into the C–H amidation reaction. First, by recording the kinetics of the C(sp^3)-H amidation reactions of **1d** and **1d-*d*$_3$** in parallel at 30 °C, a primary kinetic isotope effect ($k_H/k_D = 5.5$) was observed (Figure 3), hence indicating that the C–H activation step is rate-limiting. This result is fully consistent with the value that we obtained in our previous study on the directed C(sp^3)-H amidation of alcohol-derived oximes ($k_H/k_D = 5.0$).[13] A mechanistic proposal based on literature precedents[27] is shown in Figure S12.

We then set out to investigate the difference in reactivity of **1d** and **1d′** by means of a computational study of the CMD, having established experimentally that this is the rate-limiting step of the reaction (Figure 4). We found that **Ib**, the lowest energy conformer of the complex formed from Cp*Ir(κ^2-OPiv) and the mismatched diastereoisomer **1d′**, identified through conformational search, undergoes CMD with a 24.3 kcal/mol free energy barrier (Figure 4a, see the Supporting Information for details). The formation of **Ib-TS** is accompanied by a rotation around the $C_α$-N bond (the $NNC_αH_α$ dihedral angle θ increases from 6.7° to 59.0°), and a repulsive interaction between Ir and $H_α$ (colored in pink, Figure 4c), as indicated by the NCI plot.[28,29] Unexpectedly, **Ia**, the lowest energy conformer of the complex formed from Cp*Ir(κ^2-OPiv) and the matched diastereoisomer **1d**, undergoes C–H activation through transition state **Ia-TS** with a greater barrier of 28.7 kcal/mol. The formation of **Ia-TS** occurs via rotation around the $C_α$-N bond (the $NNC_αH_α$ dihedral angle θ decreases from 7.8° to −64.6°), which induces a repulsive interaction similar to that detected for **Ib-TS**. However, the performed conformational search showed the presence of a slightly higher-lying conformed **IIa** that undergoes the CMD process through **IIa-TS** with a barrier of 20.3 kcal/mol. In this case, only a slight rotation along the $C_α$-N bond ($NNC_αH_α$ dihedral angle θ increasing from 152.3° to 176.9°) is observed, accompanied by a significant shortening of the Ir–N bond (from 2.158 Å in **IIa** to 2.088 Å in **IIa-TS**). This shortening is much less pronounced in **Ib** (from 2.151 Å in **Ib** to 2.133 Å in **Ib-TS**), which indicates that **IIa-TS** exploits a stronger Ir–N interaction. In addition, the NCI plots of both **IIa** and **IIa-TS** reveal a non-classical hydrogen-bonding interaction between $H_α$ and an oxygen atom from the SO_2 group, which might constrain the dihedral angle and prevent $H_α$ from clashing with the iridium atom. This likely contributes to the observed lower energetic barrier for the CMD process. In contrast, such a weak attractive interaction was not found in the NCI plot of **Ib-TS**. When considering the cumulative barrier for the C–H activation of **Ia**→**IIa-TS** ($\Delta G^‡ = 20.6$ kcal/mol), the energy difference $\Delta\Delta G^‡$ between matched and mismatched diastereoisomers is found to be 3.7 kcal/mol in favor of the former, in qualitative good agreement with experimental results (see Figure 2).

Conclusion

We have developed an efficient, robust and scalable method for the synthesis of chiral vicinal diamines via iridium(III)-catalyzed intermolecular C(sp^3)-H amidation. This method relies on the design of a novel, easily accessible and removable CSA-derived N-protecting/directing group. The C–H amidation was performed using the recently introduced dioxazolone reagent K-diox, leading to a readily cleavable amide, but was also compatible with other nitrene sources. A matched/mismatched scenario between the configuration of the protecting/directing group and the starting secondary alcohol was identified and investigated, and the matched case was subsequently exploited to study the reaction scope. In addition, a two-step strategy was elaborated for the synthesis of chiral α-tertiary-1,2-diamines, via Zr^{IV}-catalyzed hydroamination and Ir^{III}-catalyzed C–H amidation. We believe that the current method provides a useful approach to vicinal diamines relevant to synthetic and medicinal chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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