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Teichert, Johannes F.; Fañanás-Mastral, Martín; Feringa, Bernard

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Iridium-Catalyzed Asymmetric Intramolecular Allylic Amidation: Enantioselective Synthesis of Chiral Tetrahydroisoquinolines and Saturated Nitrogen Heterocycles**

Johannes F. Teichert, Martín Fañanás-Mastral, and Ben L. Feringa*

Tetrahydroisoquinolines represent a large class of natural compounds with interesting and diverse biological properties.^[1,2] Therefore, these heterocycles are important targets for organic synthesis and much effort has been directed towards the development of efficient enantioselective routes to prepare chiral tetrahydroisoquinolines.^[3–8] The methods investigated thus far include palladium-catalyzed C–H activation of arylethylamines,^[9] transition-metal-catalyzed hydrogenation of imines^[10] or heteroaromatic compounds^[7], as well as Lewis acid promoted ionic cyclizations,^[11] and organocatalytic Mannich reactions.^[12] However, these procedures are limited by the fact that either electron-rich phenylethylamine derivatives are required, or only alkyl groups can be introduced at the stereogenic center, or a number of steps are required to reach the unprotected tetrahydroisoquinoline.

The iridium-catalyzed asymmetric allylic substitution^[13–18] with phosphoramidites^[19–23] as chiral ligands represents a powerful synthetic method, which has found application in a wide variety of natural product syntheses.^[13,19] One major advantage of asymmetric iridium-catalyzed allylic substitution is its tolerance towards a large variety of nucleophiles, including ammonia.^[24–28] The use of amides as nucleophiles for these transformations has only been reported for potassium trifluoroacetamide as ammonia surrogate^[24] or in allylic amidation reactions through decarboxylative pathways.^[29,30] Furthermore, using amides as nucleophiles has the advantage that alkylamine chains can be introduced at a stereogenic center through iridium-catalyzed allylic amidation.

Herein, we report a new catalytic asymmetric approach towards chiral tetrahydroisoquinolines and saturated chiral nitrogen heterocycles. Specifically, a synthetic protocol for an intramolecular iridium-catalyzed allylic amidation reaction to construct chiral tetrahydroisoquinolines is presented (Scheme 1). This transformation should serve as a reliable method to access these valuable chiral building blocks for the synthesis of natural products, as it furnishes a terminal olefin as well as a secondary amine after removal of the trifluoro-

Scheme 1. Retrosynthetic approach and twofold use of the trifluoroacetamide group.

acetic acid group. Both of these functionalities serve as the basis for further facile functionalization.

The usefulness of the trifluoroacetamide group in our approach is twofold. First, it serves as a protecting group during the synthesis of the allylic carbonates, whose key step depends on a palladium-catalyzed cross-coupling reaction that leads to the introduction of the allylic moiety (Scheme 1).^[31] Here, unprotected amines are generally not accepted. Second, the amide serves as the actual nucleophile of the iridium-catalyzed allylic substitution, which furnishes the tetrahydroisoquinoline core. An important property of the trifluoroacetamide group is that the secondary amine moiety can easily be deprotected without jeopardizing the adjacent sensitive allylic–benzylic stereocenter.^[32]

We set off to investigate the influence of bases on the catalytic system, which comprised of preformed iridacycle **3**^[15] in THF at 50 °C. The choice of base was found to be highly influential for the conversion and enantioselectivity of allylic carbonate **1**^[33] into the corresponding protected chiral tetrahydroisoquinolines **2** (Table 1). The use of DBU resulted in 70 % conversion and 81 % *ee* (Table 1, entry 1),^[34] while other organic bases such as TBD and DABCO, which have been used earlier in combination with Ir catalysts for allylic substitutions,^[35,36] led to significantly lower conversions and enantioselectivities (Table 1, entries 2 and 5). Inorganic bases such as K₃PO₄ and Cs₂CO₃ (Table 1, entries 3 and 4) performed similarly, with disappointingly low conversions and enantioselectivities.

We then went on to optimize the catalytic system. With the preformed iridacycle **3**, at elevated temperatures (50 °C) the reaction did not reach full conversion overnight, and the desired tetrahydroisoquinoline **2** was isolated in only 33 % yield (Table 2, entry 1). However, we were delighted to find that the in situ formed iridacycle, which was prepared from catalytic amounts of the phosphoramidite ligand **L1** and [Ir(cod)Cl]₂, showed a higher activity and led to full conversion with similar enantioselectivities (83 % *ee*;

[*] J. F. Teichert, Dr. M. Fañanás-Mastral, Prof. Dr. B. L. Feringa
Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 4, 9747 AG, Groningen (The Netherlands)
Fax: (+31) 50-363-4296
E-mail: b.l.feringa@rug.nl

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Table 1: Base screening.^[a]

Entry	Base	Conversion [%] ^[b]	ee [%] ^[c]
1	DBU	70	81
2	TBD	0	n.d.
3	K ₃ PO ₄	10	19
4	Cs ₂ CO ₃	15	22
5	DABCO	10	31

[a] Reaction conditions: **1** (1.0 equiv, 16.9 mg, 0.05 mmol), **3** (5.0 mol%, 3.45 mg, 0.0025 mmol), and base (1.0 equiv, 0.05 mmol) were dissolved in THF (1 mL) and stirred under N₂ at 50 °C for 20 h. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral stationary phase; see the Supporting Information. DABCO = 1,4-Diazabicyclo[2.2.2]octane, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene.

Table 2: Catalyst optimization.^[a]

Entry	R	Catalyst	T [°C]	Yield [%] ^[b]	ee [%] ^[c]
1	CF ₃ (1)	3	50	33 ^[e]	81
2	CF ₃ (1)	Ir/L1	50	73	83
3	CF ₃ (1)	Ir/L1	RT	55 ^[d]	80
4	CF ₃ (1)	Ir/L2	50	82	94
5	CF ₃ (1)	Ir/L2	RT	90	95
6	CH ₃ (4)	Ir/L2	50	n.d.	n.d.

[a] Reaction conditions: **1** or **4** (1.0 equiv, 0.05 mmol), Ir catalyst (5.0 mol%, 0.0025 mmol), and DBU (1.0 equiv, 8 μL, 0.05 mmol) were dissolved in THF (1 mL) and stirred under N₂ at the indicated temperature until full conversion (as evidenced by TLC). [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase; see the Supporting Information. [d] Reaction did not reach full conversion.

Table 2, entry 2). Lowering the temperature (RT) did not affect the enantioselectivity but again resulted in incomplete conversion (Table 2, entry 3). Turning to the related methoxy-substituted phosphoramidite **L2**,^[37] we found the product of the intramolecular asymmetric allylic amidation in excellent enantioselectivities (95% ee), with an even higher yield

observed at room temperature (Table 2, entries 4 and 5). Notably, when the corresponding acetamide was subjected to the optimized reaction conditions, no allylic amidation occurred even at elevated temperatures (Table 2, entry 6), thus indicating that trifluoroacetamides possess ideal electronic and/or acidic requirements for the asymmetric transformation envisaged.

To probe the substrate scope of the catalytic system, a collection of chiral tetrahydroisoquinolines was synthesized, which carried the most common substitution patterns seen in natural products.^[1,2] Furthermore, the method was extended to a number of saturated nitrogen heterocycles of various ring sizes (Table 3). Tetrahydroisoquinolines with donor substitu-

Table 3: Product scope of intramolecular allylic amidation.^[a]

Entry	Product	T [°C]	Yield [%] ^[b]	ee [%] ^[c]
1	2	RT	97	95
2	5	RT	89	94
3	6	RT	92	91
4	7	RT	78	94
5	8	50	56 ^[d] (100% conv.) ^[e]	96
6	9	50	68 ^[d] (100% conv.) ^[e]	88
7 ^[f]	10	50	25 ^[d] (100% conv.) ^[e]	92

[a] See the Experimental Section. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase; see the Supporting Information. [d] Products are volatile. [e] Determined by ¹H NMR spectroscopy. [f] A side reaction was observed, see Scheme 2.

ents, such as methoxy, dioxo, and methyl groups (**2**, **5**, and **6**; Table 3, entries 1–3) were all synthesized in very good yields and with excellent enantioselectivities ranging from 91–95%.^[38,39] Furthermore, the unsubstituted tetrahydroisoquinoline **7** could be isolated with similarly good results (78%, 94% ee; Table 3, entry 4).

We were interested in expanding the method of the asymmetric intramolecular allylic amidation to the synthesis of other chiral nitrogen-containing heterocycles. Along these lines, five-, six-, and seven-membered chiral heterocycles **8–10** were synthesized (Table 3, entries 5–7). For these reactions to proceed smoothly, elevated temperatures of 50 °C were needed to ensure full conversion. In all cases, however, very good to excellent enantioselectivities (up to 96% ee) were found, thus demonstrating the versatility of our new catalytic transformation.

Notably, when we investigated the synthesis of chiral azepane **10** (Table 3, entry 7), an unexpected side reaction occurred. When allylic carbonate **11** was reacted under the optimized reaction conditions (Scheme 2), chiral azepane **10** was found along with linear diene **12** as the major product. The product distribution seemed to be independent of temperature and amounts of DBU employed.^[40] This side reaction was only observed for **10** and not in the synthesis of piperidine **9** or pyrrolidine **8**, thus indicating that the mechanism of the formation of the seven-membered ring involves special spatial constraints.^[41]

Scheme 2. Observed side reaction. cod = 1,5-cyclooctadiene.

The ease of protecting-group removal, that is, the chiral secondary trifluoroacetamide, was demonstrated with the conversion of **2** into **13** (Scheme 3). The product was simply stirred at room temperature in the presence of an excess

Scheme 3. Deprotection of trifluoroacetamide.

amount of K_2CO_3 in MeOH/H₂O (7:1) to give the corresponding chiral tetrahydroisoquinoline **13** in excellent yield, without loss of enantiomeric excess. Through the terminal olefin and the secondary amine functional groups, **13** is a highly versatile chiral building block for the synthesis of tetrahydroisoquinoline-derived structures.

In conclusion, we have developed a new asymmetric synthesis of chiral nitrogen-containing heterocycles, especially tetrahydroisoquinolines, which are important building blocks for the synthesis of biologically active products. Our approach is based on the first intramolecular asymmetric iridium-catalyzed allylic amidation, and the desired products are accessible in excellent yields and enantioselectivities. The trifluoroacetamide group serves two purposes in this approach; initially it is used as a protecting group during the synthesis stage of the starting materials, but later on its enhanced nucleophilicity is exploited for the key asymmetric allylic amidation. We have also demonstrated that the deprotection required to form the corresponding amine can be readily executed.

Experimental Section

General procedure for the asymmetric allylic amidation reaction (Table 3): $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.5 mol%, 3.36 mg, 5.0 μmol) and **L2** (5.0 mol%, 6.00 mg, 10.0 μmol) were dissolved in dry THF (1 mL) under N_2 . Then, DBU (1.00 equiv, 0.03 mL, 0.20 mmol) was added and the reaction mixture was heated at 50 °C for 30 min. Then, it was brought to the appropriate temperature and the allylic carbonate (1.0 equiv, 0.20 mmol) was added. The reaction mixture was stirred until full conversion was achieved (as evident by TLC). All volatile components were removed under reduced pressure to yield the crude product as an orange oil. This was purified by column chromatography on silica gel to yield the desired trifluoroacetamide.

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- [39] The absolute configuration of the products was determined by comparison of the optical rotation of compound **2** with the literature value (Ref. [8]). The absolute configuration of the other products was assigned by analogy.
- [40] In the absence of the Ir catalyst, no reaction was observed, thus indicating that the Ir catalyst is essential for this transformation to take place.
- [41] For a discussion of possible mechanisms for this transformation, see the Supporting Information.