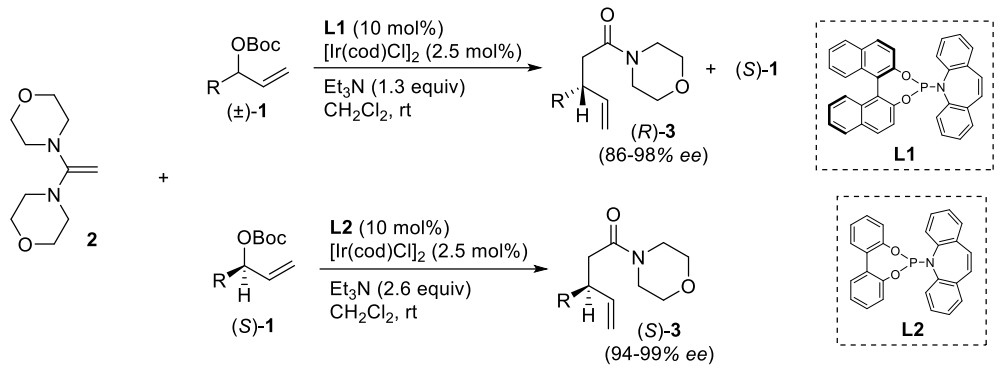
Morpholine Ketene Aminal as Amide Enolate Surrogate in Iridium-Catalyzed Asymmetric Allylic Alkylation

Yeshua Sempere, Jan Alfke, Simon L. Rössler and Erick M. Carreira*

Abstract: Morpholine ketene aminal is employed in iridium-catalyzed asymmetric allylic alkylation reactions as a surrogate for amide enolates to prepare γ,δ-unsaturated β-substituted morpholine amides. Kinetic resolution or, alternatively, stereospecific substitution affords the corresponding products in high enantiomeric excess. The utility of the products generated by this method has been showcased by their further elaboration into amines, ketones or acyl silanes. A putative catalytic intermediate (η^3-allyl)iridium(III) with achiral (P,Olefin)-ligand was synthetized and characterized for the first time.

Iridium-catalyzed asymmetric allylic substitution represents a powerful method for the enantioselective formation of carbon-carbon and heteroatom-carbon bonds.[1] Dating back to the seminal work by Takeuchi and Helmchen,[2] stabilized enolates have been employed as a privileged class of nucleophiles. Despite extensive studies on enolate nucleophiles, examples of amide enolates in iridium catalyzed allylic substitution remain scarce. This paucity originates from the attenuated C–H acidity of amides compared to other carbonyl compounds (dimethyl acetamide pKa≈35 in DMSO),[3] which renders their generation in the presence of reactive allyl-iridium species challenging. Herein, we report the use of morpholine ketene aminal **2** as a simple, easily accessible surrogate for morpholine acetamide enolate in iridium-catalyzed asymmetric alkylation of allylic carbonates **1**. The reaction furnishes γ,δ-unsaturated β-substituted morpholine amides with excellent enantiomeric excess by means of an enantioselective kinetic resolution of racemic allylic carbonates with chiral **L1** as ligand (Scheme 1, top). Alternatively, optically pure allylic carbonates can be employed in a stereospecific allylic alkylation catalyzed by the Ir-complex derived from achiral ligand **L2** (Scheme 1, bottom).

Due to the attenuated C–H acidity of amides, only stabilized amides have been successfully employed in iridium catalyzed allylic substitution. Early approaches have employed oxazolones or thiazolones,[4] which can subsequently be elaborated to substituted amide products. Recently, Hartwig has reported the addition of α-substituted *N*-heterocyclic acetamides (pKa≈27 in DMSO) in stereodivergent fashion with a combination of iridium and copper catalysis.[3,5] The acidity of the α-heteroaryl amides is further enhanced through coordination of the copper-catalyst.[3] To date, unsubstituted amide products have been prepared exclusively through two step procedures. Helmchen and co-workers have reported the use of α-amido esters (pKa≈18 in DMSO)[3] derived from malonates as enolate precursors for the iridium catalyzed substitution of linear allylic carbonates.[6] Subsequent decarboxylation of the corresponding products furnished unsubstituted amides. Notably, unactivated amide enolates have been successfully employed in palladium catalyzed allylic substitution, but due to the intrinsic preference of palladium to furnish linear products, the approach is unable to access products with β-stereogenic centers relative to the amide.[7a] Additional examples catalyzed by Pd include decarboxylative allylations of lactam-derived imides[7b-c] and activated (Cα−F and Cα−Ar) oxindoles (pKa≈18.5 for *N*-methyl-oxindole in DMSO).[3,7d-e]

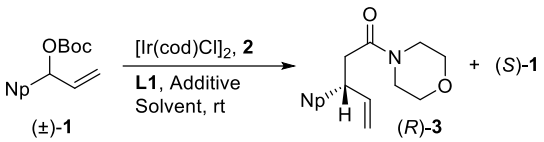


Scheme 1. Morpholine ketene aminals as amide enolate surrogates in iridium-catalyzed asymmetric allylic alkylation reactions and iridium catalyzed allylic alkylations of acetamide enolates.

As part of our ongoing research program on the reactivity of electrophilic η^3-allyl Ir^{III} intermediates in asymmetric transformations,[8] we sought to identify suitable acetamide enolate equivalents. In this respect, we were intrigued by the potential features of morpholine ketene aminal **2**, which has been employed in condensation reactions with aromatic aldehydes by Barton and in a variation of the Eschenmoser-Claisen rearrangement by Trauner.[9] We surmised that it may be sufficiently nucleophilic to undergo reaction with our highly electrophilic η^3-allyl Ir^{III} species and thus function as an unsubstituted amide enolate surrogate.[10]

Morpholine ketene aminal **2** was readily synthesized from the corresponding orthoester and secondary amine following the procedure reported by Baganz and Domaschke in 1962.[11] In initial prospecting experiments with unprotected allylic alcohols as starting material, $[Ir(cod)Cl]_2$ (2.5 mol%), **L1** (10 mol%) and **2** (1.2 equiv.) were found to lead to decomposition of nucleophile. To overcome these issues, allylic carbonates could be employed as suitable substrates for iridium-catalyzed asymmetric allylic alkylation with morpholine ketene aminal. Screening a variety of conditions, including different solvents, underscored dichloromethane as promising (Table 1, entries 2-3).[12]

Table 1. Selected optimization studies of the reaction conditions[a]



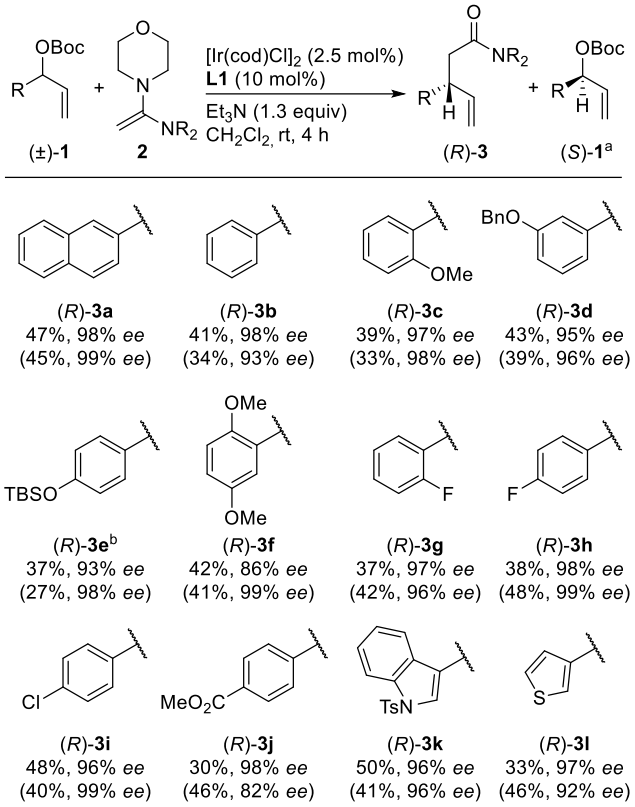
Entry	Solvent	Additive (Equiv)	(*R*)-**3** [%][b]	(*S*)-**1** [%][b]	*ee* (*R*)-**3**[%][c]
1	1,4-dioxane	-	0	76	-
2	$CHCl_3$	-	34	0	58
3	CH_2Cl_2	-	58	31	76
4	CH_2Cl_2	$ZnBr_2$ (0.2)	40	10	32
5	CH_2Cl_2	ZnI_2 (0.2)	27	30	30
6	CH_2Cl_2	$Zn(OTf)_2$ (0.2)	40	5	44
7	CH_2Cl_2	KO^tBu (1.3)	0	0	-
8[d]	CH_2Cl_2	DIPEA (1.3)	35	25	87
9[d]	CH_2Cl_2	Et_3N (1.3)	44	21	97
10[d]	CH_2Cl_2	Et_3N (1.3)	47	45	98

[a] Reaction conditions: (±)-**1** (1.0 equiv), $[Ir(cod)Cl]_2$ (2.5 mol%), **L1** (10 mol%), **2** (1.2 equiv), 0.5 M, rt, 12-18 h. [b] Determined by ^{1}H-NMR analysis of the unpurified reaction mixture using 1,4-dimethoxybenzene as internal standard. [c] Enantiomeric excess determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. [d] Reaction conditions: **2** (0.6 equiv), 4h. Np = 2-naphthyl, Boc = *tert*-butyloxycarbonyl, DIPEA = N,N-diisopropyletylamine.

In contrast to our earlier work,[8g] in which Zinc-based Lewis acids were optimal promoters for the activation of allylic carbonates in asymmetric allylic alkylation reactions, a screening of various Lewis acids failed to yield improved outcomes (Table 1, entries 4–6).[12] Additionally, some decomposition of

the nucleophile was evidenced by the isolation of products stemming from direct allylic substitution of free morpholine. Brønsted acid promoters lead to complete decomposition of nucleophile, furnishing various side products. These observations prompted us to examine the use of bases as additives, which could prevent the decomposition of the nucleophile and the primary product of the reaction (*vide infra*). Triethylamine was identified as an optimal additive for the formation of product in high enantioselectivity (Table 1, entry 9). Furthermore, over the course of our screening experiments, we noted that the *ee* of the product deteriorated if conversion increased over 50% (Table 1, entries 1–7). Optimization efforts in this direction revealed that shorter reaction times and reduced amount of **2** led to highly enantioselective, kinetic resolution (Table 1, entries 8–10).

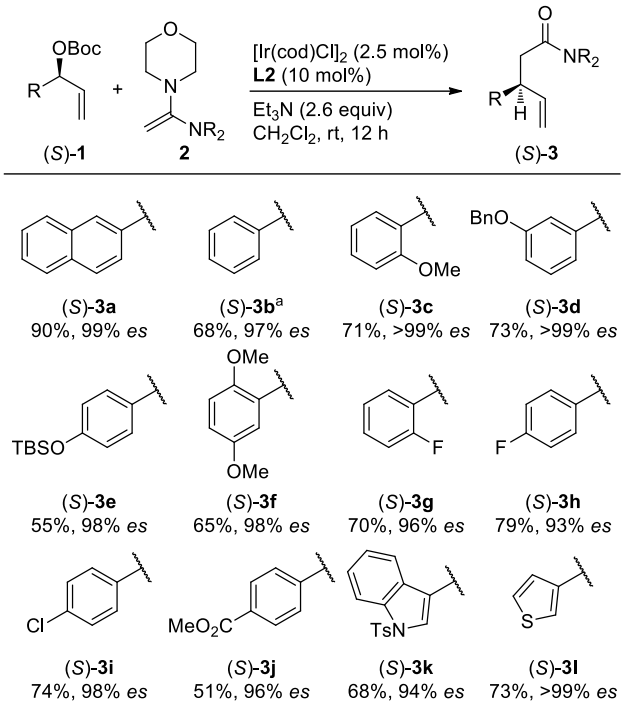
Having identified optimal reaction conditions, the scope of allylic carbonates **1** was evaluated using morpholine ketene aminal **2** (Scheme 2). 2-Napthyl- (**3a**) and phenyl- (**3b**) allylic carbonates furnished the corresponding products in 47% and 41% yield, respectively, and 98% *ee* in both cases. Additionally, the starting material was recovered with good yields and high optical purity. Electron rich substrates performed well under the reaction conditions, yielding the desired amide products in good yields and enantioselectivities (**3c**–**3f**) along with the recovery of optically enriched (96-99% *ee*) allylic carbonates ((*S*)-



Scheme 2. Substrate scope of the enantioselective alkylation of allylic carbonates with morpholine ketene aminal (2). Unless noted otherwise, all reactions were performed on 0.5 mmol scale under the standard reactions conditions (see Table 1, entry 10). Yields refer to isolated products after purification by column chromatography on silica gel. The *ee* values were determined by SFC or GC analysis on a chiral stationary phase. [a]Recovered enantioenriched starting material yields and ee are given in brackets. [b]Absolute configuration determined by X-ray analysis of a derivate.[12] NR_2 = Morpholine, Bn = benzyl, TBS = *t*-$BuMe_2Si$, Ts = *p*-$MeC_6H_4SO_2$.

1c–**1f**). Halogenated aromatic substrates (**1g**-**1i**) were well tolerated and furnished the corresponding amide products with high enantioselectivity (96-98% *ee*). Substrates incorporating electrophilic functional groups, such as ester (**1j**), could be employed without observable competing reactions with the enolate surrogate. Successful conversion of thiophene and indole substituted allylic carbonates to the corresponding amides showcases the use of heteroaromatic substrates (**1k**-**1l**). The kinetic resolution described herein, generally shows a selectivity factor (*s*) of >120, except for substrates **3e** (*s* = 97) and **3f** (*s* = 68).[12,13]

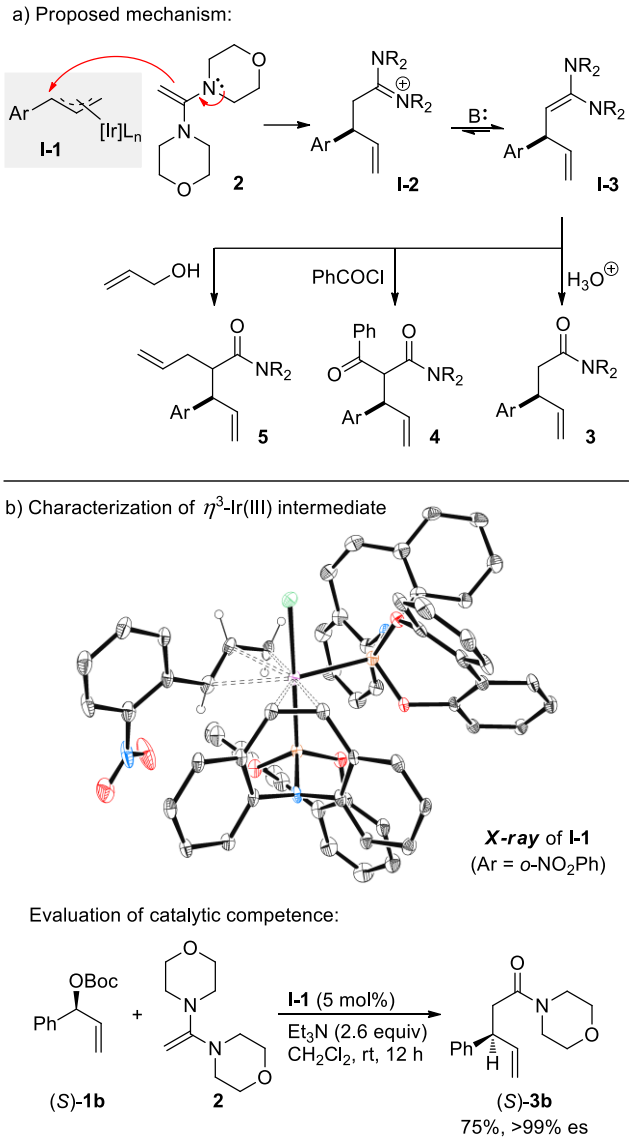
The recovered enantioenriched carbonates (*S*)-**1** proved to be suitable substrates for stereospecific substitution in the presence of **2** and an iridium catalyst derived from achiral ligand **L2** (Scheme 1) providing optically active amide adducts (*S*)-**3** (Scheme 4).[14] All allylic carbonates underwent stereospecific substitution with high enantiospecificity (>93% *es*) and good yields.



Scheme 3. Substrate scope of stereospecific substitution of allylic carbonates with morpholine ketene aminal 2. Unless otherwise noted, all reactions were performed on 0.2 mmol scale, with 1.2 equiv of 2 and 2.6 equiv of Et_3N. Yields refer to isolated products after purification by column chromatography on silica gel. The *es* values were determined by SFC or GC analysis on a chiral stationary phase. [a]Conducted at 2 mmol scale.

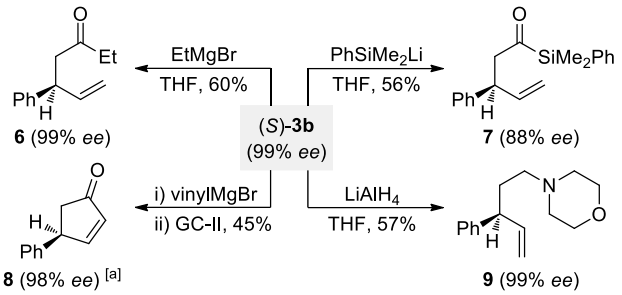
During the course of our studies, we identified an unknown intermediate, which formed during the reaction and ultimately converted to product **3** upon acid work-up. We hypothesized that substituted morpholine ketene aminal **I-3** would form as a primary product.[15] We anticipated such an intermediate **I-3** to be sufficiently nucleophilic to be potentially trapped using an external electrophile. Accordingly, when the standard reaction was terminated through the addition of aromatic acyl chloride, the major product isolated corresponded to the resulting trapped product **4**.[12,16] In a similar fashion, when the reaction is treated with allyl alcohol instead of standard work up, the Eschenmoser-Claisen **5** product is observed, exhibiting that the intermediate generated in our reaction has similar reactivity to the morpholine ketene aminal.[10,12]

To gain further insight into the η^3-allyl Ir^{III} intermediates with achiral ligand **L2**, we formed iridium-**L2** complex in the presence of an allylic alcohol.[17] Subsequent treatment with acid led to the formation of an Ir(III) species **I-1** as evidenced by $^{31}P\{^1H\}$-NMR. The exact nature of this structure could be confirmed by single-crystal X-ray diffraction (Scheme 5). The solid-state structure of **I-1** shows the substrate bound in a η^3-fashion, with two **L2** bound to iridium either in a chelating fashion or solely through phosphorous, respectively. The η^3-allyl is bound with *exo*-configuration. Hence, analysis of the structure leads to a model for understanding the reaction in which equilibration to the corresponding *endo* isomer would be necessary to lead to the configuration of the observed products. To establish the catalytic competence of the isolated intermediate, **I-1** was employed as catalyst under standard reaction conditions. Complex **I-1** effected the stereospecific substitution of allyl carbonate (*S*)-**1b** in yields comparable to catalyst formed in situ from $[Ir(cod)Cl]_2$ and **L2** (Scheme 5b).



Scheme 5. Proposed mechanistic pathway and X-ray of iridium-complex I-1. Compounds 4 and 5 were obtained using allylic carbonate 1a as substrate. I-1 was obtained with *ortho*-nitro substituted substrate.[12] Thermal ellipsoids are shown at 30% probability. Selected hydrogen atoms, non-coordinating counterions, and co-crystallized solvent molecules have been omitted for clarity.

To showcase the synthetic utility of this method we subjected the morpholine amide products to further synthetic manipulations (Scheme 5). In analogy to the corresponding Weinreb amides, morpholine amides can undergo Grignard addition as demonstrated in the formation of ketone **6**.[18,19] Additionally, morpholine amide (*S*)-**3b** (99% *ee*) could be converted to acyl silane **7**, which is a versatile building block that upon addition of a strong nucleophile has been shown to serve as precursors for Brook rearrangements.[20] Moreover, the morpholine amide products can also be smoothly reduced to yield amines with a stereocenter at γ-position (**8**, Scheme 5).[21] Following a procedure described by Helmchen,[6] we synthesized known compound **8** via vinyl Grignard addition and subsequent ring closing metathesis in 45% overall yield and 98% *ee*. Notably, no erosion of enantiomeric excess was observed in any transformation, with the exception of compound **7**.



Scheme 6. Elaboration of morpholine amide products. [a]Absolute stereochemistry determined by comparison with literature [measured: (c = 0.42, $CHCl_3$): –278, reported: (c = 0.51, $CHCl_3$, 97% *ee*): –284].[6b] GC-II = Grubb´s catalyst 2nd generation.

In summary, we have disclosed an asymmetric allylic alkylation that enables the preparation of β-substituted γ,δ-unsaturated amides. Morpholine ketene aminal was shown to be competent nucleophile for the allylic alkylation reaction. This method presents a new approach to the challenging iridium catalyzed allylic alkylation of amide enolates. We have demonstrated that the morpholine amide products can be further transformed to the corresponding ketones, acyl silanes or amines in high enantiomeric excess.

Acknowledgements

ETH Zürich and the Swiss National Science Foundation (200020_152898) are gratefully acknowledged for financial support. We thank Dr. M.-O. Ebert, R. Arnold, R. Frankenstein and S. Burkhardt of the NMR service and Dr. N. Trapp and M. Solar of the X-ray crystallography service for their assistance.

Keywords: Iridium • amide • allylation • enantioselective • synthesis

[1] For selected reviews on the topic, see: *a*) P. Tosatti, A. Nelson and S. P. Marsden, *Org. Biomol. Chem.* **2012**, *10*, 3147; b) W.-B. Liu, J.-B. Xia, S.-L. You, *Top. Organomet. Chem.* **2011**, *38*, 155; c) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675.

[2] a) R. Takeuchi, M. Kashio, *Angew. Chem. Int. Ed.* **1997**, *36*, 263; b) J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025.

[3] a) F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456; b) F. G. Bordwell, H. E. Fried, *J. Org. Chem.* **1981**, 46, 4327; c) F. G. Bordwell, H. E. Fried *J. Org. Chem.* **1991**, *56*, 4218.

[4] a) W. Chen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 377; b) S. E. Shockley, J. C. Hethcox, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2017**, *56*, 11545.

[5] X. Jiang, P. Boehm, J. F. Hartwig, *J. Am. Chem. Soc.* **2018**, *140*, 1239.

[6] a) S. Mathias, D. Pierre, H. Günter, *Angew. Chem. Int. Ed.* **2006**, *45*, 2466; b) P. Dübon, M. Schelwies, G. Helmchen, *Chem.–Eur. J.* **2008**, *14*, 6722.

[7] a) K. Zhang, Q. Peng, X. L. Hou, Y. D. Wu, *Angew. Chem. Int. Ed.* **2008**, *47*, 1741; For examples of other similar nucleophiles such as lactams or oxindoles see: b) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2012**, *4*, 130; c) K. M. Korch, C. Eidamshaus, D. C. Behenna, S. Nam, D. Horne, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2015**, *54*, 179; d) B. M. Trost, M. U. Frederiksen, *Angew. Chem. Int. Ed.* **2005**, *44*, 308; e) K. Balaraman, C. Wolf, *Angew. Chem. Int. Ed.* **2017**, *56*, 1390.

[8] For different examples developed recently in our group see: a) T. Sandmeier, S. Krautwald, E. M. Carreira, *Angew. Chem. Int. Ed.* **2017**, *56*, 11515; b) J. Y. Hamilton, S. L. Rössler, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 8082; c) M. A. Schafroth, S. M. Rummelt, D. Sarlah, E. M. Carreira, *Org. Lett.* **2017**, *19*, 3235; d) T. Sandmeier, S. Krautwald, H. F. Zipfel, E. M. Carreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 14363; e) J. Y. Hamilton, D. Sarlah, E. M. Carreira, *Angew. Chem. Int. Ed.* **2015**, *54*, 7644; f) S. Breitler, E. M. Carreira, *J. Am. Chem. Soc.* **2015**, *137*, 5296; g) Y. Sempere, E. M. Carreira, *Angew. Chem. Int. Ed.* **2018**, *57*, 7654.

[9] D. H. R. Barton, G. Hewitt, P. G. Sammes, *J Chem Soc C* **1969**, 16.

[10] S. N. Gradl, J. J. Kennedy-Smith, J. Kim, D. Trauner, *Synlett* **2002**, 411.

[11] H. Baganz, L. Domaschke, *Chemische Berichte* **1962**, *95*, 2095.

[12] For more details, see Supporting Information.

[13] H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249. For calculated *s*-factors see Supporting Information.

[14] Absolute configuration of recovered starting materials determined by comparison with literature known compounds: J. Štambaský, A. V. Malkov, P. Kočovský, *J. Org. Chem.* **2008**, *73*, 9148; and ref. 8f.

[15] Compound **I-3** has been detected in the crude ^{1}H-NMR of different samples. But our attempts to purify it were never successful due to its prompt hydrolysis to the corresponding amide product.

[16] A. Armati, P. De Ruggieri, E. Rossi, R. Stradi, *Synthesis* **1986**, 573.

[17] For a detailed mechanism study involving chiral phosphoramidite ligand **L1**, see: S. L. Rössler, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2017**, *139*, 3603.

[18] S. Nahm, S. M. Weinreb, *Tetrahedron Letters* **1981**, *22*, 3815.

[19] For some examples of Grignards additions to morpholine amides, see: a) Z. Yu, R. J. Ely, J. P. Morken, *Angew. Chem. Int. Ed.* **2014**, *53*, 9632; b) S. R. Borkar, N. Bokolia, I. S. Aidhen, I. A. Khan, *Tetrahedron Asymmetry* **2017**, *28*, 186; c) Y.-H. Chen, M. Ellwart, G. Toupalas, Y. Ebe, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 4612.

[20] C. T. Clark, B. C. Milgram, K. A. Scheidt, *Org. Lett.* **2004**, *6*, 3977.

[21] N. Assimomytis, Y. Sariyannis, G. Stavropoulos, P. G. Tsoungas, G. Varvounis, P. Cordopatis, *Synlett* **2009**, 2777.