CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Transition-metal-free stereoselective borylation of allenamides

Authors: Elena Fernández, Jose Luis Vicario, Jordi Carbo, Lorena Garcia, Jana Sendra, Nuria Miralles, and Efraim Reyes

To be cited as: *Chem. Eur. J.* 10.1002/chem.201803004

Link to VoR: http://dx.doi.org/10.1002/chem.201803004

Supported by
ACES

WILEY-VCH

10.1002/chem.201803004

WILEY-VCH

COMMUNICATION

Transition-metal-free stereoselective borylation of allenamides

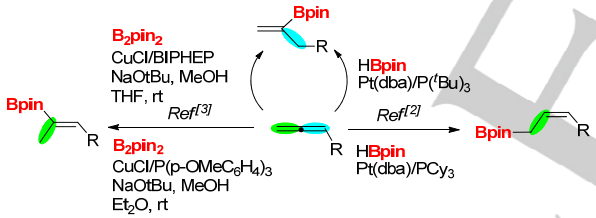
Lorena García,[b] Jana Sendra,[a] Núria Miralles,[a] Efraim Reyes,[b] Jorge J. Carbó,*[a] Jose L. Vicario,*[b] Elena Fernández*[a]

Dedication ((optional))

Abstract: Complete stereocontrol on the transition-metal-free hydroboration of the distal double bond of allenamides can be achieved when allenamides contain acyl substituents, providing exclusively the *Z*-isomer. The consecutive Pd-catalyzed cross coupling reaction allowed the straightforward formation of tri-substituted enamides, with total control on the stereoselectivity.

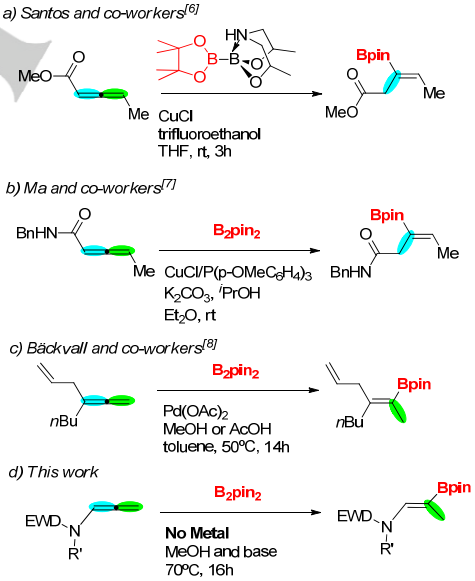
Hydroboration of allenes to afford stereodefined alkenyl boronates represents an efficient synthetic strategy to prepare polysubstituted olefins with total control on the stereoselectivity.[1] The first challenge is the regiocontrol of the C-B and C-H formation along the allene system, which depends on the transition metal catalyst used, the ligands involved and the substrate itself.

From the original proof of concept by Miyaura and co-workers,[2] the hydroboration of alkoxyallenes with HBpin catalyzed by $Pt(dba)_2/PCy_3$ generated exclusively allylboranes, while the hydroboration of alkyl- and aryl-substituted allenes with HBpin catalyzed by $Pt(dba)_3/P(^tBu)_3$ ocurred at the internal double bond to selectively provide 1-alken-2-yl boronates (Scheme1).[2] The copper-catalyzed hydroboration of allenes with bis(pinacolato) diboron (B_2pin_2) forms 2-alken-2-yl or 1-alken-2-yl boronates by applying also a ligand effect.[3-5]



Scheme 1. Synthetic approaches towards divergent transition metal catalyzed hydroboration of allenes with HBpin and B_2pin_2

Alternatively, substrate directing effect to control the regioselective hydroboration has been pursued by electrophilic allenoates that react with PDIPA diboron (pinacolato diisopropanolaminato diboron) in the presence of a copper(I)catalyst, to install a boron moiety on the β-position, via hydroboration of the internal double bond (Scheme 2a).[6] Similarly, the effect of the amide group in 2,3-disubstituted allenamides influenced that the copper-catalyzed hydroboration with B_2pin_2 took place regioselectively producing β-borylated β,γ-unsaturated enoamides via a plausible intramolecular interaction between the carbonyl group and the organocopper intermediates (Scheme 2b).[7] Contrarily, an efficient olefin-directed palladium-catalyzed regioselective hydroboration of allenes containing an allyl moiety, promotes the hydropalladation and subsequent borylation to hydroborate the terminal double bond with B_2pin_2.[8] Now, we planned to conduct in this work, the borylation of the unexplored allenamides to identify the influence of the amine group on the chemo- and regioselective addition of the boryl moiety (Scheme 2d), but also to give access to stereodefined trisubstituted alkenes.



Scheme 2. Substrate directed transition-metal catalyzed hydroboration of allenes with B_2pin_2 (a,b,c) and transition-metal-free hydroboration of allenamides in this work (d).

In order to explore this new piece of chemistry we avoided the use of any transition-metal complexes as catalysts and instead we selected the alkoxide activation of B_2pin_2 to form the nucleophilic boryl moiety in the acid-base Lewis adduct [MeO-Bpin-Bpin]$^-$[Hbase]$^+$.[9] This system has already shown to be efficient in the borylation of C=C bonds,[10] C=N bonds,[11] electron deficient C=C bonds[12] and tertiary allylic or propargylic alcohols.[13] The addition of the acid-base Lewis adduct [MeO-Bpin-Bpin]$^-$[Hbase]$^+$ to aliphatic allenes was previously explored

[a] Dr. E. Fernández, Dr. J. J. Carbó, Dr. N. Miralles, Ms. J. Sendra, Author(s)
Department Química Física I Inorgànica
University Rovira i Virgili
C/ Marcel·lí Domingo s/n
E-mail: mariaelena.fernandez@urv.cat
[b] Dr. J. L. Vicario, Dr. E. Reyes, Ms. L. García
Department of Organic Chemistry II
University of the Basque Country (UPV/EHU)
P.O. Box 644, 48080 Bilbao (Spain)
joseluis.vicario@ehu.es

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

10.1002/chem.201803004

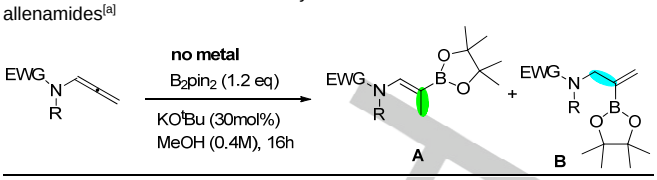
WILEY-VCH

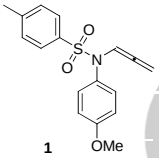
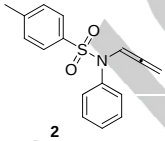
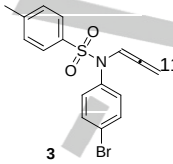
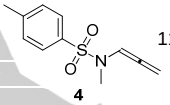
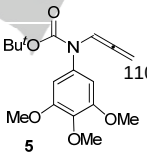
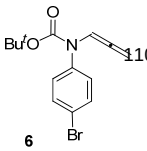
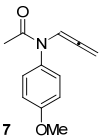
COMMUNICATION

giving access to the 1,2-diboration of the terminal double bond.[10] Since replacing the aliphatic group in allenes by the amine group, renders the allenamine more electronically enriched and consequently very reactive and sensitive towards hydrolysis and polymerization, we focussed the study on the electronic deficient variants of allenamides, diminishing therefore the electron-donating ability of the nitrogen atom, providing superior stability as substrates.[14] Therefore we prepared *N*-(4-methoxyphenyl)-4-methyl-*N*-(propa-1,2-dien-1-yl)benzenesulfonamide (**1**)[15] as the model substrate to test the transition-metal-free borylation with B_2pin_2 and MeOH/base. We selected KO^{t}Bu as the most efficient base versus Cs_2CO_3 and NaO^{t}Bu, with an optimized 30 mol% loading. The reaction temperature was explored in a range from 70ºC to 110ºC and we found that the highest temperature favoured the major conversion towards a mixture of two hydroborated products that have in common that the boryl moiety is located at the central carbon of the allenamide but with a 2/1 ratio in favour of the hydroboration along the terminal double bond (Table 1, entry 1). Similar effect was observed for a series of *N*-Ts substituted amines, with electron donating or electron withdrawing aryl substituents, but no significant differences were detected in the reaction outcome or in the regioselectivity (Table 1, entries 1-3). When the aryl substituent was replaced by a methyl group in the amine moiety (allenamide **4**), the reaction was less efficient (60% NMR Yield) but the ratio between the 2-pinacolboryl prop-1-en-1-amine keeps being double than the 2-pinacolboryl prop-2-en-1-amine (Table 1, entry 4). The replacement of Ts by Boc in the amine functional group, showed that the electron withdrawing substituents on the phenyl group of the substrate might favour the borylation reaction (90% NMR yield, Table 1, entry 6) versus the electron donating substituents in the substrate (75% NMR yield, Table 1, entry 5). However, the regioselectivity was again a mixture of the two hydroborated products with a 2/1 ratio in favour of the hydroboration along the terminal double bond. Interestingly, when the acyl group was introduced as the electron withdrawing group in the allenamide, substrate **7**, we were able to perform the reaction with total conversion and exclusive formation of the 2-pinacolboryl prop-1-en-1-amine **7A**, even at 70ºC (Table 1, entry 7).

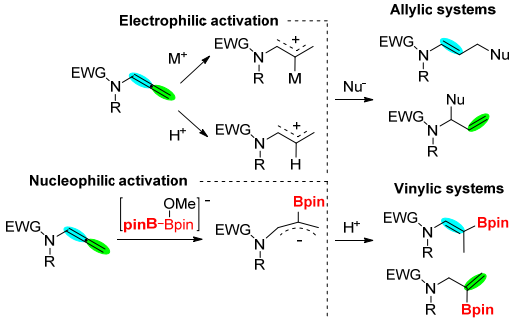
The complete regioselectivity observed requires a deep understanding of the factors that might control it, particularly as no transition-metal catalysts or ligands are involved in such control. But also, in terms of chemical behaviour, we observe an umpolung on the natural reactivity trend of the allenamide reagent. Allenamides with electron withdrawing groups are known to conduct electrophilic activation[16] assisted by transition-metal complexes or Brønsted acids, to generate a stabilized carbocation that eventually reacts with nucleophilic reagents either at the α or γ position, involving the proximal or distal C=C bond, respectively (Scheme 3, top).[17] Interestingly, the products formed in all these cases are allylic systems. However, in our transition-metal free hydroboration of the same allenamides, we realized that the *in situ* generated nucleophilic Bpin moiety exerts a nucleophilic attack on the C=C=C π system forming the C-B bond on the central carbon and generating the corresponding carbanion with a relative stabilized energy (Scheme 3, bottom). Furthermore, the carbanion can be protonated both at the α or γ position, and therefore in order to control the regioselective outcome of the reaction, a systematic study on the influence of the *N* substituents is required.

Table 1. Transition-metal-free borylation of electronic deficient variants of allenamides[a]



Entry	Substrate	T (ºC)	%NMRYield[b] (A/B)	[%IY][c]**A**	[%IY][c]**B**
1		70	16%	np	np
		90	53%(2/1)	**1A**[34%]	**1B**[22%]
		110	82%(2/1)	**1A**[53%]	**1B**[28%][d]
2		110	86%(2/1)	**2A**[48%]	**2B**[9%][d]
3		110	84%(2/1)	**3A**[47%][d]	**3B**[28%][d]
4		110	60%(2/1)	**4A**[20%][d]	**4B**[11%][d]
5		110	75%(2/1)	**5A**[41%]	**5B**[12%][d]
6		110	90%(2/1)	**6A**[51%]	**6B**[25%][d]
7		70	**98%(1/-)**	**7A**[71%]	**7B**----

[a]Conditions: allenamide (0.2 mmol), KO^{t}Bu (30 mol%), B_2pin_2 (1.2 equiv), MeOH (0.4 M), 70-110ºC, 16h. [b]NMR Yields calculated in ^{1}H NMR spectra with naphthalene as internal standard from consumption of substrate. [c]%IY= isolated yield. [d]% enriched purified product



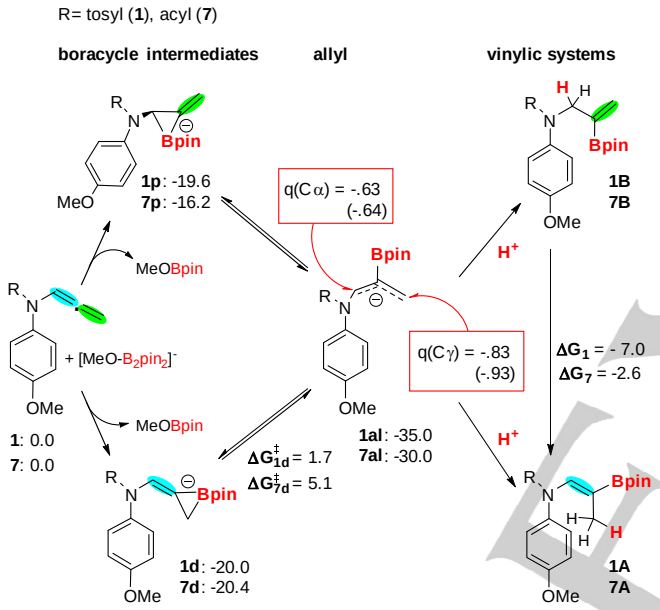
Scheme 3. Umpolung reactivity of allenamides via electrophilic or nucleophilic activation

10.1002/chem.201803004

WILEY-VCH

COMMUNICATION

Previous DFT studies had characterized the mechanisms for transition-metal-free diboration and borylation of alkenes by diboron reagents activated with Lewis bases.[10,18] Those studies proposed that the nucleophilic attack of the adduct [MeO-Bpin-Bpin]$^-$ to double bond yields an anionic, 3-membered boracycle intermediate (see Scheme 4, top) an the release of Bpin-OMe. Subsequent protonation leads to the hydroborated product. For allenamides, we propose that the formation of this anionic intermediate is favoured because conjugation with the exocyclic C=C bond stabilizes the negative charge. However, in these allenamides, the boracycle intermediate can open to form a more stable allylic anion that can be then protonated to give the final product. To evaluate this mechanistic proposal and to rationalize the observed stereoselective, we have performed DFT calculations[19] on the key intermediates, using substrates **1** and **7** as representative examples.



Scheme 4. Proposed mechanism for the hydroboration of allenamides**1** and **7**. Relative Gibbs free-energies and barriers ($\Delta G^{\ddagger}$) in kcal·mol^{-1}. Electrostatic-based atomic charges for the α and γ carbons of allyl species in a.u.

Scheme 4 summarizes the results of our computational study for allenamides **1** and **7**. Initially, we characterized the formation of the two boracycle intermediates corresponding to the borylation of the proximal (**1p** and **7p**) and distal (**1d** and **7d**) double bonds. The functionalization of the distal C=C bond is thermodynamically preferred, although in the case of the tosyl substituent (**1**), both regioisomers are almost isoenergetic. Nevertheless, for both substituents the open allylic species **1al** and **7al** with the Bpin moiety attached to central carbon are thermodynamically favoured, the overall process for boryl addition to allene being highly exergonic, -35.0 and -30.0 kcal·mol^{-1} for **1al** and **7al**, respectively. In addition, the formation of the allylic intermediate from boracycle has a low free-energy barrier (1.7 and 5.1 kcal·mol^{-1}, respectively, from the lowest energy distal isomers **1d** and **7d**), indicating that the process is a very fast *transformation* at the high reaction temperature. Thus, it is likely that protonation to yield the hydroborated product occurs at the allylic intermediate and that this irreversible reaction step determines the selectivity of the process. Moreover, in the structures of the more stable allylic anion, the amine substituent has an *anti*-configuration (see Scheme 4) that should yield a *trans* configuration between the amine and the Bpin substitutens in the major alkene product **A**.

To understand the difference in reactivity between the Cα and Cγ, we performed an analysis of charge distribution in the allylic intermediates **1al** and **7al** (Scheme 4). Our calculations show that the Cγ is more negatively charged than the Cα, and consequently, more reactive towards electrophiles in full agreement with experimental selectivity. The protonation at the Cγ results in products (**1A** and **7A**) which are more stable than that resulting from protonation at Cα (**1B** and **7B**) by 7.0 and 2.6 kcal·mol^{-1}, respectively. Nevertheless, we assume that the selectivity is not thermodynamically but kinetically controlled in the irreversible protonation step. Accordantly, in the allylic intermediate **7al**, the difference in atomic charges is larger than that computed for **1al**, which could explain the higher selectivity observed in the hydroboration of allenamide **7**.

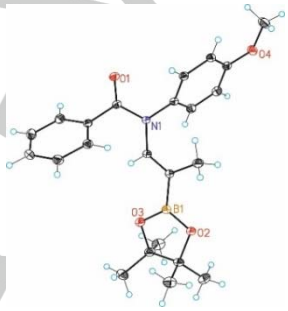


Figure 1. X-ray diffraction structure of stereocontrolled borylated product **14A**

Taking advantage of the exclusive regioselectivity observed by the acyl substituted allenamide **7**, we conducted a series of reactivity to stablish the substrate scope but also the limitations in the methodology. Changing the electron properties of the *para*-substituents of the aryl group in the allenamide substrates, it was proved that electron releasing *para*-substituents contributed to quantitative conversions with complete stereoselectivity towards the formation of the *Z*-isomer (Table 2, entries 1-3). However, a trend that diminished conversions was observed when electron withdrawing *para*-substituents on the aryl group were involved, (Table 1, entries 4 and 5), but fortunately without effecting the exclusive regioselective product formation. Replacement of the Me group by *t*-Bu group at the acyl moiety, did not influenced in the reaction outcome, since product **12A** was obtained in quantitatively yield as a single *Z*-isomer from *N*-(4-methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)pivalamide (**12**), (Table 2, entry 6).The reaction was also generalized for *N*-(4-methoxyphenyl)-*N*-(propa-1,2-dien-1-yl)benzamide (**14**) demonstrating that the nature of the aryl substituents in the acyl group contributed similarly to the borylation reaction (Table 2, entry 8). The exclusive product (**14A**) formed from the transition-metal-free borylation of **14**, could be fully characterized with the X-ray diffraction structure. Figure 1 illustrates the *trans*-stereoselectivity of the amine and boryl moieties along the trisubstituted alkene. Moreover, the electron releasing substituents in the phenyl group favoured the reaction in contrast to the electron withdrawing substituents (Table 2, entries 8 and 9

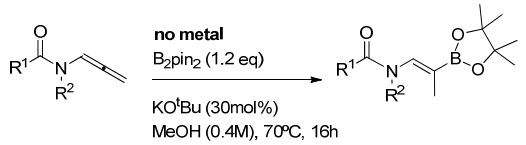
10.1002/chem.201803004

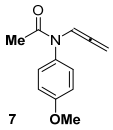
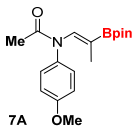
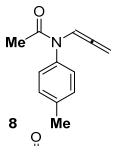
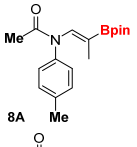
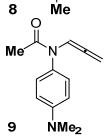
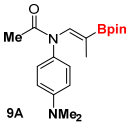
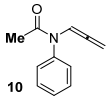
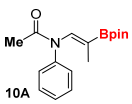
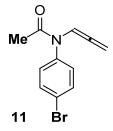
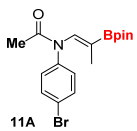
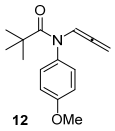
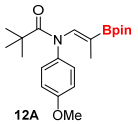
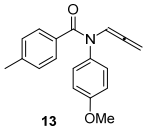
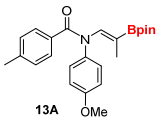
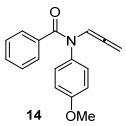
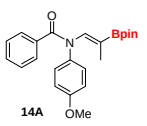
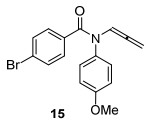
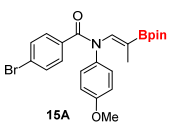
WILEY-VCH

COMMUNICATION

for comparison). The reaction, however, showed a limitation for the alpha and gamma substituted allenamides (*N*-(buta-2,3-dien-2-yl)-*N*-(4-methoxyphenyl)benzamide and *N*-(4-methoxyphenyl)-*N*-(penta-1,2-dien-1-yl)benzamide respectively) probably due to the steric hindrance offered by the substrates to the nucleophilic attack of the Bpin moiety.

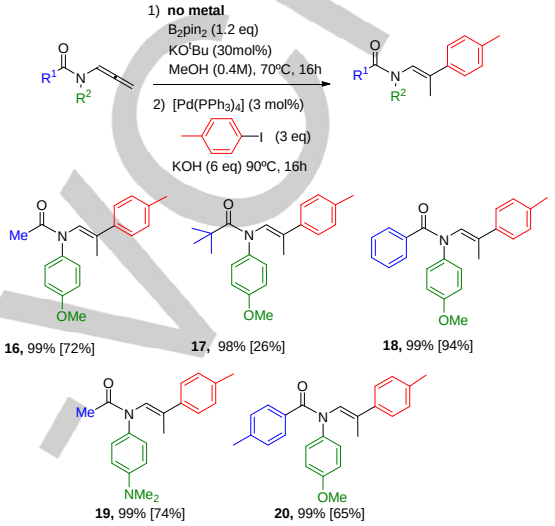
Table 2. Transition-metal-free borylation of acyl substituted allenamides[a]



Entry	Substrate	Product	%NMR Yield[b]	[%IY][c]
1			98%	71%
2			96%	62%
3			99%	78%
4			52%	24%
5			25%	--
6			94%	65%
7			99%	74%
8			90%	72%
9			16%	--

[a]Conditions: allenamide(0.2 mmol), KO^{t}Bu (30 mol%), B_2pin_2 (1.2 equiv), MeOH (0.4 M), 70ºC, 16h. [b]NMR Yields calculated in ^{1}H NMR spectra with naphthalene as internal standard. [c]%IY= isolated yield

Next, we explored the "in situ" functionalization of the 2-pinacolboryl prope-1-en-1-amine intermediates, through a one-pot metal-free borylation of the allenamide followed by a Pd-catalyzed Suzuki-Miyaura cross-coupling reaction with 1-iodo-4-methylbenzene. The consecutive reaction allowed the straightforward formation of the tri-substituted olefin, with total control on the stereoselectivity, (Scheme 5). The methodology seems to be general since it is tolerant to alkyl and aryl substituents on the acyl moiety.



Scheme 5. Sequential transition-metal-free borylation of acyl substituted allenamides with concomitant Pd-catalyzed Suzuki-Miyaura cross-coupling.

To conclude, we have described a transition metal-free borylation of electronic deficient variants of allenamides, with high yields and complete stereocontrol on the hydroboration of the distal double bond, providing exclusively the *Z*-isomers. The acyl groups on the amine moiety are crucial to obtain the complete stereoselective as a consequence of the formation of a stable allylic anion intermediate that is further regioselectively protonated to give the final product. The transition-metal freee borylation can be followed by Pd-catalyzed cross coupling with aryl iodides generating stereoselective trisubstitutd olefins.

Acknowledgements

The present research was supported by the Spanish Ministerio de Economia y competitividad (MINECO) through projects FEDER-CTQ2016-80328-P and FEDER-CTQ2017-83633-P and by the Basque Government (Project IT908-16). L. G. and N. M. also acknowledges Spanish MINECO for a FPI fellowship. We thank AllyChem for the gift of diboranes.

Keywords:allenamines • borylation • transition-metal-free • DFT calculations • stereoselectivity

[1] K. Semba, N. Bessho, T. Fujihara, J. Terao, Y. Tsuji, *Angew. Chem. Int. Ed.*, **2014**, *53*, 9007.
[2] Y. Yamamoto, R. Fujikawa, A. Yamada, N. Miyaura,*Chem. Lett.* **1999**, *28*, 1069.
[3] W. Yuan, S. Ma, *Adv. Synth. Catal.*, **2012**, *354*, 1867.

10.1002/chem.201803004

[4] a) F. Meng, B. Jung, F. Haeffner, A. H. Hoveyda, *Org. Lett*., **2013**, *15*, 1414; b) H. Jang, B. Jung, A. H. Hoveyda, *Org. Lett*., **2014**, *16*, 4658.

[5] K. Semba, M. Shinomiya, T. Fujihara, J. Terao, Y. Tsuji, *Chem. Eur. J*., **2013**, *19*, 7125.

[6] S. B. Thorpe, X. Guo, W. Santos, *Chem. Commun*., **2011**, *47*, 424.

[7] W. Yuan, X. Zhang, Y. Yu, S. Ma, *Chem. Eur. J*., **2013**, *19*, 7193.

[8] C. Zhu, B. Yang, Y. Qiu, J.-E- Bäckvall, *Chem. Eur. J.***2016**, *22*, 2939.

[9] a) A. B. Cuenca, R. Shishido, H. Ito, E. Fernández, *Chem. Soc. Rev.* **2017**, *46*, 415; b) E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev*., **2016**, *16*, 9091; b) J. Cid, H. Gulyás, J. J. Carbó, E. Fernández, *Chem. Soc. Rev.***2012**, *41*, 3558.

[10] A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed*.,**2011**, *50*, 7158.

[11] C. Solé, H. Gulyás, E. Fernández, *Chem. Commun.*, **2012**, *48*, 3769.

[12] A. Bonet, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed*., **2010**, *49*, 5130.

[13] N. Miralles, R. Alam, K. Szabó, E. Fernández, *Angew. Chem. Int. Ed*., **2016**, *55*, 4303.

[14] L.-L. Wei, J. A. Mulder, H. Xiong, C. A. Zificsak, Ch. J. Douglas, R. P. Hsung, *Tetrahedron*, **2001**, *57*, 459.

[15] For the synthesis of **1** see (a) Y. Yang, F. D. Toste, *Chem. Sci.* 2016, 7, 2653. See also (b) Villar, L.; Uria, U.; Martinez, J. I., Prieto, L.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 10535.

[16] T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang, R. P. Hsung, *Chem Rev*., **2013**, *113*, 4862.

[17] a) C. Romano, M. Jia, M. Monari, E. Manori, M. Bandini, *Angew. Chem. Int. Ed*., **2014**, *53*, 13854; b) X. Yang, F. D. Toste, *Chem. Sci*., **2016**, *7*, 2653; c) R.-R. Liu, J.-P- Hu, J.-J. Hong, Ch.-J. Lu, J.-R. Gao, Y.-X. Jia, *Chem. Sci*., **2017**, *8*, 2811.

[18] N. Miralles, J. Cid, A. B. Cuenca, J. J. Carbó, E. Fernández, *Chem. Commun.*, **2015**, *51*, 1693.

[19] Calculations were performed using Gaussian09 (M06-2X functional) and the 6-311g(d,p) basis set. Energies include free energy corrections and the solvent effect of methanol (ε = 32.613) by SMD continuum solvent model.See ESI for details.

10.1002/chem.201803004

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

L. García, J. Sendra, N. Miralles, E. Reyes, J. J. Carbó, J. L. Vicario,* E. Fernández**

Page No. – Page No.

Title

Complete stereocontrol on the transition-metal-free hydroboration of the distal double bond of allenamides can be achieved when allenamides contain acyl substituents, providing exclusively the *Z*-isomer. The consecutive Pd-catalyzed cross coupling reaction allowed the straightforward formation of tri-substituted enamides, with total control on the stereoselectivity.