Synergistic Stereoselective Organocatalysis with Indium(III) Salts

Andrea Gualandi,[a] Luca Mengozzi,[a] Claire Margaret Wilson,[b] Pier Giorgio Cozzi*[a]

[a] Dipartimento di Chimica 'G. Ciamician', ALMA MATER STUDIORUM – Università di Bologna, Via Selmi 2, 40126 Bologna, Italy
Fax +39(051)2099456; E-mail: piergiorgio.cozzi@unibo.it

[b] Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Dublin, Ireland

Received: 14.01.2014; Accepted after revision: 25.02.2014

Abstract: The compatibility of indium(III) Lewis acids with water and amines allows their employment in synergistic and cooperative catalysis. Stereoselective organocatalytic S_N1-type reactions, in which carbenium ions are generated, are promoted by the presence of indium salts. The peculiar properties of indium salts can be exploited in organocatalysis for the design of water-compatible, benign, green processes. The development of such indium(III)-promoted organocatalytic procedures is the focus of our recent research, a summary of which is presented in this article.

Key words: organocatalysis, stereoselective, amine catalysis, enamine-mediated catalysis, indium(III)

Synergistic catalysis was recently defined as the synthetic strategy wherein both the nucleophile and the electrophile are activated simultaneously by two separate and distinct catalysts to afford a single transformation.[1] This new tool has emerged as a powerful strategy for the development of reaction methodologies. Synergistic interaction of two catalytic cycles can be advantageously used to induce new reactivity, improve existing reactions, and introduce stereocontrol in existing transformations.

Due to their unusual properties, indium reagents and salts have shown potential for use in synergistic systems. The use of indium in organometallic chemistry has attracted considerable attention since the discovery of indium-mediated reactions in aqueous media.[2] This remarkable discovery was highlighted by several authors, who have shown the compatibility of organometallic indium reagents with water and air.[3] Moreover indium(III) Lewis acids have shown similar properties, inspiring attempts to use such Lewis acids in catalytic processes where water is present.[4] In addition to water compatibility, indium(III) salts do not favorably form strong or irreversible complexes with tertiary amines. This characteristic allows indium(III) to act as a Lewis acid in the presence of strong amines, as shown by the catalytic indium(III)–tertiary amine reaction of alkynes with aldehydes.[5] In the presence of indium(III) bromide ($InBr_3$) (10 mol%) and *N*,*N*-diisopropylethylamine (DIPEA) (20 mol%), aromatic aldehydes reacted smoothly with terminal alkynes. Spectroscopic studies showed dual activation of the terminal alkyne and of the carbonyl group.

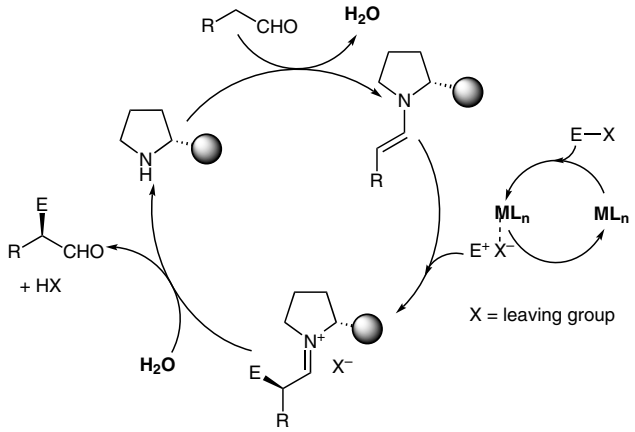
SYNTHESIS 2014, 46, 1321–1328
Advanced online publication: 25.03.2014
DOI: 10.1055/s-0033-1341022; Art ID: SS-2014-C0033-OP

The indium(III) chloride catalyzed Mukaiyama aldol reaction has been investigated in detail by Juaristi, with attempts made to achieve good reactivity in water-containing solvents.[6] In addition, enantioselective variants of the reaction have been developed.[7] The Lewis acid properties of indium salts in the presence of water (produced as a reaction by-product) makes it possible to use indium(III) in such multicomponent reactions.[8] The Lewis acidity of indium(III) salts can also be modulated by combination with silylating agents.[9] The remarkable enhancement of the Lewis acidity of indium(III) chloride by chlorosilanes can be seen in various reactions such as the aza-Michael addition of carbamates to enones,[10] Friedel–Crafts alkylation, hydrosilylation, and reductive allylation.[11] In these processes the alcohol (secondary, benzylic and tertiary) reactivity is quite remarkable, with smooth generation of transient carbenium ions, catalyzed by indium(III) chloride. From these processes a key lesson can be learnt; the Lewis acidity of indium salts is compatible with water and with the generation of carbenium ions. As previously mentioned, amines are also compatible with indium salts. Amines and water are key components in enamine catalysis, indicating the potential use of indium salts in enamine-mediated organocatalytic processes.

Stereoselective enamine-mediated catalysis has reached a significant level of sophistication and can even be employed in the total synthesis of natural products.[12] After the publication of seminal works by MacMillan[13] and List,[14] many researchers have entered the field, generating more and more useful chemistry. However, the range of electrophiles that can be used in enamine-mediated catalysis is relatively limited. In fact, electrophiles are generally Michael acceptors or electrophilic sources of heteroatoms.[15] Simple alkylating agents are still particularly difficult substrates for enamine-mediated catalysis, due to side reactions and deactivation of the amine catalyst.[16]

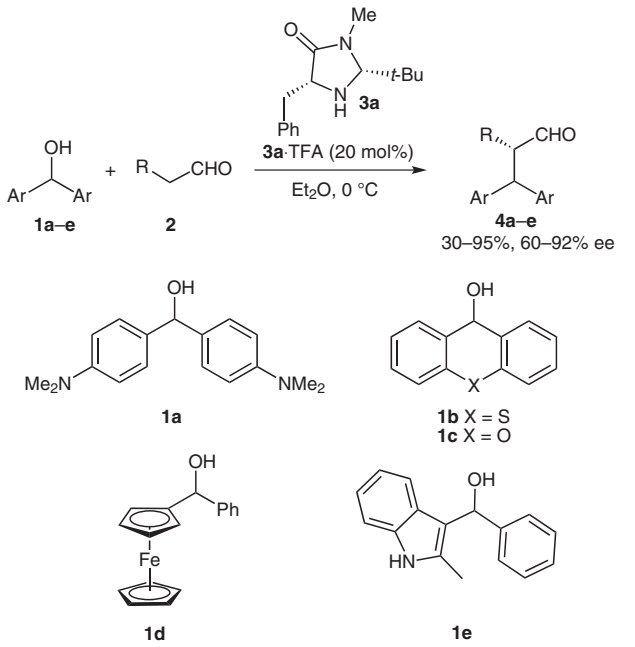
It was thought that the scope of enamine-mediated catalysis could be enhanced if an additive could be found that was capable of forming the desired electrophile in situ, thus avoiding unwanted side reactions and deactivation of the catalyst (Scheme 1). In particular, the use of a metal in synergistic cooperative catalysis could extend the range of usable electrophiles.[1] The synergistic use of metals could also make the development of new, previously inaccessible chemical reactions possible. The use of transition metals, pioneered by Córdova in a Tsuji–Trost variant of

enamine-mediated catalysis,[17] has been explored by many researchers who have developed new methods for the alkylation of aldehydes [singly-occupied molecular orbital (SOMO) catalysis][18] using copper,[19] gold,[20] and other metals.[21] We have considered indium(III) salts as potential Lewis acids for the promotion of enamine-mediated alkylation. In such S_N1-type reactions, an electrophilic carbenium ion is generated in the presence of an organocatalyst, using a Lewis acid.[22]



Scheme 1 Synergistic cooperation between an organocatalyst and a metal complex (Lewis acid) in an alkylation reaction

Our small contribution to this field was inspired by the limiting practical problems we encountered during our research. In 2009, we described an organocatalytic stereoselective S_N1-type reaction using alcohols as alkylating agents (Scheme 2).[23]

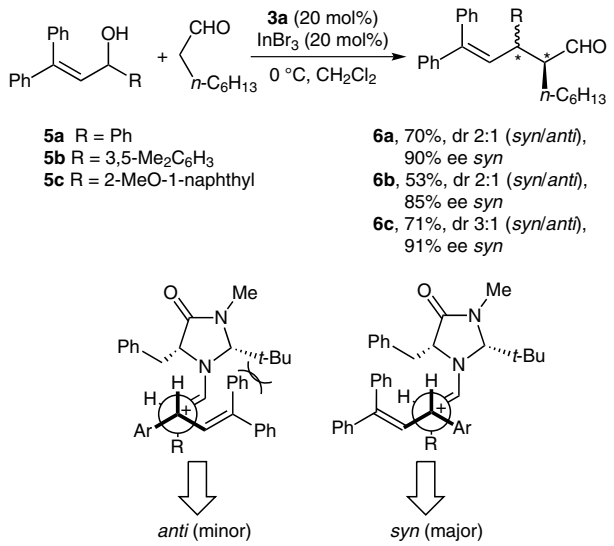


Scheme 2 Reaction of alcohols **1a**–**e** with aliphatic aldehydes in the presence of the MacMillan catalyst **3a**

Essentially, most organocatalytic reactions can be simply described as the reaction of electrophiles with nucleophiles. Mayr has introduced the linear free-energy relationship, $\log k(20\ °C) = s_N(E + N)$,[24] where electrophiles are characterized by one parameter (E), and nucleophiles are characterized by the solvent-dependent nucleophilicity (N) and sensitivity (s_N) parameters. The Mayr equation allows for simple prediction of organocatalytic reactions.[25a] A simple rule introduced by Mayr states that a reaction will proceed at 20 °C if $(E+N) > -5$.[25b] The solvent-dependent nucleophilicity parameters of the enamines derived from aldehydes and various organocatalysts were determined by Mayr.[25a] For example, considering the enamines derived from phenylacetaldehyde and MacMillan's imidazolidinones, it is possible to predict that only strong electrophiles such as stabilized carbenium ions ($-8 < E < -2$) would be suitable reaction partners. We have successfully combined the Mayr scale[26] with organocatalysis, using compatible carbenium ions that can easily be generated during enamine-mediated catalysis (Scheme 2). These carbenium ions are located precisely on the Mayr scale between –1.5 and –7, and react rapidly with the powerful enamine-nucleophile in the reaction mixture. However, the scope of the reaction was limited as many carbenium ions could not be generated under such conditions. For example, when we investigated allylic alcohols[27] as substrates for our methodology, only starting materials and by-products (derived from the auto condensation of the aldehyde) were isolated.

Clearly this limitation was a consequence of the enhanced electrophilicity of the carbenium ion, resulting in difficulties in its generation under the reaction conditions. In an effort to overcome this limitation, we drew inspiration from simple chemistry; alcohols are known to react with many electrophiles in S_N1-type reactions carried out in the presence of Lewis and Brønsted acids.[28] We therefore studied an organocatalytic alkylation reaction (with 1,3-diphenylprop-2-en-1-ol and propanal in the presence of a MacMillan catalyst) with many Lewis and Brønsted acids. However, the peculiar properties of indium(III) salts attracted our attention immediately. We discovered that the allylation of aldehydes, with the allylic carbenium ions generated in situ, occurred with good yield and stereoselectivity in the presence of these salts.[29] In order to enhance the stereoselectivity we selected compound **5a** as an allylic alcohol model substrate (Scheme 3). It should be noted that this substrate is completely unreactive in the absence of indium(III) bromide.

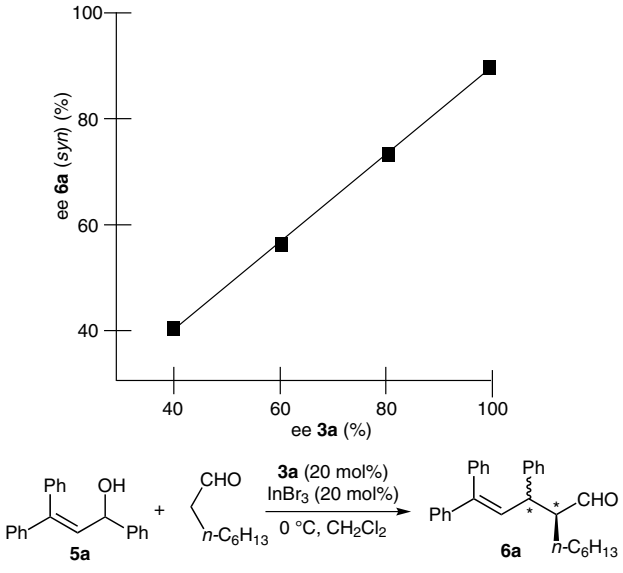
The scope of the reaction was large, and included variously substituted allylic alcohols that were easily prepared. Unfortunately, with R = alkyl, we were unable to detect the desired product, even in the presence of indium salts. Again the stability of the carbenium ion dictates the reaction outcome. Due to the presence of water and the high electrophilicity of the generated carbenium ion, the reaction was not successful. The products obtained in the effective indium(III)-mediated reactions were a mixture of diastereoisomers, with a slight preference for the *syn* con-



Scheme 3 Reaction of allylic alcohols promoted by the presence of $InBr_3$ in the reaction mixture

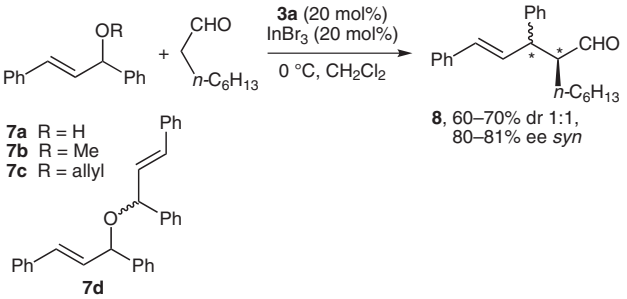
figured product. A steric model (Scheme 3) suggested a possible explanation for the selectivity observed. The model has some flaws, such as not taking into account the role of the indium in this chemistry. The generated carbenium ion is not thought to be free in solution, with the alcohol activated by indium, as suggested in many cases reported in the literature.[8–10] In addition, NMR experiments clearly demonstrated the complexation of the MacMillan amine catalyst with indium. To shed light on the process and to understand the role of indium, simple experiments were carried out.

A study of the 'nonlinear effect'[30] (Scheme 4) clearly supported the hypothesis that only one MacMillan catalyst was involved in the transmission of stereochemical information. This observation precluded the possible roles played by indium aggregates or complexes in determining the stereochemical outcome of the reaction.



Scheme 4 Absence of a nonlinear effect in the indium-mediated alkylation reaction

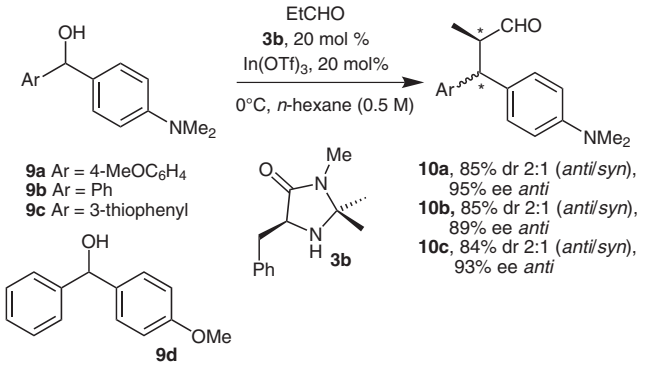
The major role of indium(III) is determined by its Lewis acidity, as shown by other simple experiments that were carried out. When the reaction was performed with allylic ethers **7a**–**c** (Scheme 5), the results were all similar in terms of the yield and stereoselectivity.



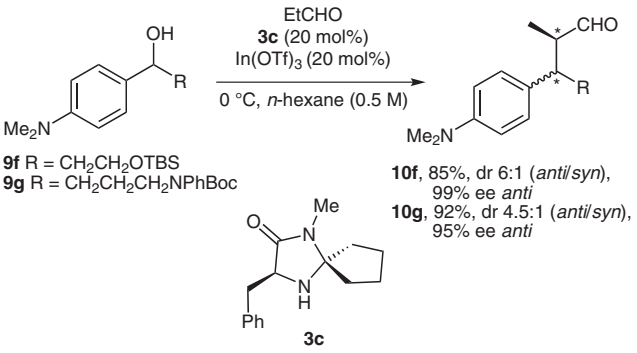
Scheme 5 Reactions of allylic ethers **7a**–**c** with octanal and the organocatalyst **3a** (20 mol%)

In addition, when allylic alcohol **7a** was reacted in the presence of catalytic quantities of an indium(III) salt, we immediately observed the formation of the corresponding ether **7d** as a mixture of stereoisomers. We can conclude that the role of indium in this methodology is to aid the slow and reversible formation of the allylic carbenium ion, which is able to react with the chiral enamine obtained in situ. The Lewis acidity of indium(III) precludes the use of the more nucleophilic chiral enamines derived from the Hayashi–Jørgensen catalyst,[31,32] as this catalyst is not stable in the presence of indium salts.

We have also explored the possibility of increasing the range of the benzhydrylic and benzylic alcohols that can be employed in the S_N1-type reaction with synergistic use of indium(III) salts. A limited number of examples of benzhydrylic alcohols were examined in our first paper.[33] In this study, we found that as the carbenium ions generated from the alcohols were above or near zero on the Mayr scale, no reactivity was observed without the use of indium(III) salts (Scheme 6). The presence of a dimethylamino group on the aromatic ring was necessary to achieve the desired reactivity. Although a methoxy group at the *para*-position of one aryl group is sufficient to activate the substrate **9d**, with this and other benzhydrylic alcohols, the reaction was quite sluggish and gave moderate to low yields. For alcohols **9a**–**c**, the presence of indium(III) was required to produce the desired reactivity. With this type of alcohol, the combination of indium(III) triflate [$In(OTf)_3$] with *n*-hexane as the reaction solvent gave excellent results in terms of the enantiomeric excess. A further advantage of the dimethylamino group was the possibility of further functionalization by various cross-coupling reactions.[34]

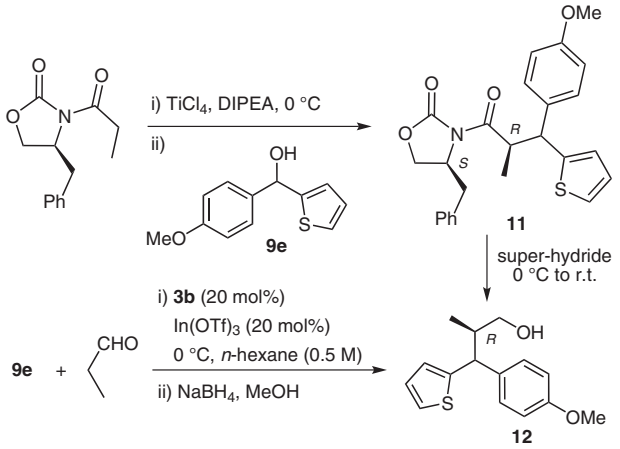


Scheme 6 Organocatalytic alkylation of propanal with benzhydrylic alcohols promoted by indium



Scheme 8 Organocatalytic indium-mediated reactions of functionalized benzylic alcohols

We were also able to establish the absolute configuration of the products by employing an S_N1-type reaction as described by Evans et al. (Scheme 7).[35] Based on the finding from this and previous studies, the model for the stereoselective induction considered the approach of the carbenium ion from the less hindered face of the enamine. Using this model, starting with the (*S*)-MacMillan catalyst, we expected to form the (*R*)-configured stereocenter at the α-position of the aldehyde (Scheme 7).



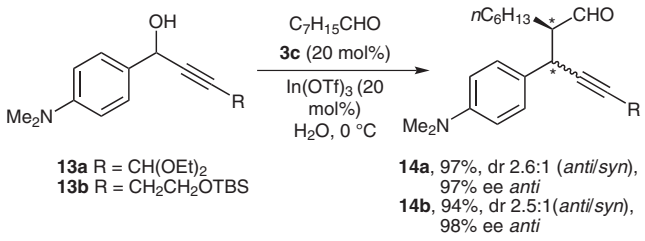
Scheme 7 Determination of absolute configuration using Evans' auxiliary chemistry

Benzylic carbenium ions were not previously studied in our S_N1-type reaction, due to their high electrophilicity. Again, in order to consider the corresponding alcohol as a substrate, we introduced a dimethylamino group on the aromatic moiety to improve the stability of the carbenium ion. Various substituents at the benzylic position showed tolerance to the reaction conditions employed (Scheme 8). Other benzylic substrates bearing different aromatic groups were also applicable and successful in this reaction.

As previously mentioned, the dimethylamino group is not only an activating group capable of stabilizing the carbenium ion, it can also be advantageous for further synthetic transformations using nickel- or palladium-catalyzed cross-coupling reactions.[34a,b] After reduction and protection of the primary alcohol group with *tert*-butyldimethylsilyl chloride, the key transformation involves preparation of the corresponding ammonium triflate by treatment with methyl triflate. The ammonium salts are good starting materials for cross-coupling reactions and their formation proceeds without racemization.

In continuation of our efforts to expand the repertoire of organocatalytic S_N1-type reactions, we have also considered propargylic alcohols as substrates. The direct use of propargylic alcohols in organocatalytic S_N1-type reactions did not provide the desired results. Again, this is due to the stability of the resulting carbenium ion, which could not be generated under our reaction conditions. While we were publishing the synergistic use of indium with allylic alcohols, Nishibayashi reported two complementary methods for the enantioselective α-propargylation of aldehydes. This methodology combines enamine-mediated catalysis and transition-metal catalysis, with propargylic alcohols[36a,b] and propargylic benzoates[36c] as substrates. Interestingly, the stabilization of the cationic propargylic intermediates was possible through the formation of the corresponding metal–allenylidene complexes with copper and ruthenium. However, the reaction was limited to terminal alkynes, as the key metal–allenylidene intermediates could not be formed with internal alkynes. We considered using indium(III) salts with this type of substrate and embarked on the optimization of this process. Preliminary results were obtained in 2010, and considerable efforts and studies were devoted to improving the stereoselectivity and enantiomeric excess. We found that when the reaction was performed using water as the solvent, the formation of the ether (generated by attack of the propargylic alcohol on the incipient propargylic cation) was minimized. The scope of the reaction was investigated, and naturally the stabilization of the propargylic cation was required for the reaction to proceed. Although generally the 4-methoxyphenyl group was sufficient to stabilize

the carbenium ion, the use of water as the reaction solvent limited the possible use of such substitution (Scheme 9).[37]



Scheme 9 Addition of aldehydes under synergistic cooperative catalysis using indium(III) salts, with water as the reaction medium

Quite remarkably, the reaction tolerated a range of functional groups including thio, amides, silyl ether, and even acetals on the alkyne moiety. Different functionalized aldehydes were also used, and the corresponding products were isolated in good yield as mixtures of two diastereoisomers, each with high stereoselectivity. The relative and absolute configurations of the products were determined for this class of substrate, and the selective functionalization of the obtained products was also described. Moreover, the absolute and relative configurations of the reaction products were in agreement with the proposed model, which seems capable of predicting the stereochemical outcome of these reactions (Figure 1).

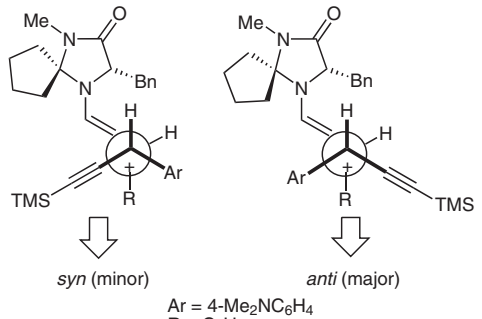


Figure 1 Stereochemical model for the indium(III)-mediated alkylation of propargylic alcohols

The possibility of performing the synergistic S_N1-type reaction in water with a suitable Lewis acid is quite interesting. We have investigated if the formation of the propargylic ether is determined by the presence of the Lewis acid, and if the propargylic carbenium ion is formed reversibly under the reaction conditions. When the reaction was performed in an organic solvent, ether formation occurred as a side reaction affecting the yield of the desired product. It seems that in the case of propargylic substrates, when the ether is formed, the carbenium ion is not easily regenerated, even in the presence of indium(III) salts. When the reaction is performed in water, formation of the by-product propargylic ether is minimized.

In conclusion, indium(III) salts can be used in synergistic processes in which carbenium ions are generated. Allylic, benzylic, benzhydrylic and propargylic alcohols are suitable substrates for this chemistry. The Hayashi–Jørgensen catalyst (normally a good catalyst for the α-functionalization of aldehydes) could not be employed in these processes.[31a,b] Studies on this topic are ongoing in our research group, using indium(III) salts in order to generate carbenium ions in the presence of various organocatalysts. We will disclose more general and efficient S_N1-type organocatalytic reactions in the near future.

Chromatographic purification was performed with Merck KGaA SiO_2 (240–400 mesh). Determination of diastereomeric ratios (dr) and enantiomeric excesses (ee) was accomplished with an Agilent Technologies 1200 instrument equipped with a variable wavelength UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm ID × 25 cm) and HPLC grade *i*-PrOH and *n*-hexane as eluting solvents. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm relative to TMS, with the residual solvent resonance as the internal standard [$\delta = 7.27$ (^1H), $\delta = 77.0$ (^{13}C) ppm]. ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, tt = triplet of triplets, br s = broad singlet, m = multiplet), coupling constant(s) (Hz). GC–MS spectra were recorded by EI ionization at 70 eV on a Hewlett-Packard 5971 instrument with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained using an Agilent Technologies MSD1100 single-quadrupole mass spectrometer.

Organocatalytic Enantioselective α-Allylation of Aldehydes; General Procedure A

To a solution of compound **5** or **7** (0.1 mmol, 1 equiv) in CH_2Cl_2 (1 mL), MacMillan catalyst **3a** (0.02 mmol, 20 mol%) and an aldehyde (0.3 mmol, 3 equiv) were added at 0 °C. The mixture was stirred for 5 min at the same temperature and then $InBr_3$ solution (20 mol%, 0.33 M in MeCN) was slowly added. The mixture was stirred at the same temperature until no further conversion took place (monitored by TLC). The reaction was then quenched with H_2O (3 mL). The organic layer was separated and the aq layer extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with H_2O (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography.

Enantioselective α-Alkylation of an Aldehyde with Benzylic and Benzhydrylic Alcohols; General Procedure B

Alcohol **9a–g** (0.1 mmol, 1 equiv), catalyst **3b** or **3c** (20 mol%, 0.02 mmol), and an aldehyde (0.3 mmol, 3 equiv) were placed in a vial containing anhydrous *n*-hexane (0.5 M) at 0 °C. The mixture was stirred and a solution of $In(OTf)_3$ (20 mol%, 0.33 M in MeCN) was added. The solution was stirred for 8 h at 0 °C. The reaction was quenched with H_2O (5 mL). The organic layer was separated and the aq layer extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography.

Enantioselective α-Alkylation of Aldehydes with Propargylic Alcohols; General Procedure C

The catalyst **3c** (0.02 mmol, 20 mol%), propargylic alcohol **13a**,**b** (0.1 mmol, 1 equiv) and H_2O (0.5 mL) were added to a vial. The suspension was cooled to 0 °C, and then octanal (0.3 mmol, 3 equiv) and a solution of $In(OTf)_3$ (20 mol%, 0.33 M in MeCN) were added. The mixture was stirred for 24 h and then diluted with Et_2O (3 mL). The organic phase was separated and the aq layer extracted with Et_2O (3 × 10 mL). The organic phases were combined, washed with brine (5 mL), dried over Na_2SO_4 and evaporated in vacuo. The crude product was reduced with $NaBH_4$ (0.4 mmol, 4 equiv) in

MeOH (1 mL) a 0 °C. After 1 h, the reaction was quenched with H_2O (2 mL) and diluted with Et_2O (10 mL). The organic layer was separated and the aq layer extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with H_2O (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography.

(*S*)-2-[(*R*/*S*)-1,3,3-Triphenylallyl]octanal (6a)

The title product was prepared according to the general procedure A. The residue was purified by flash chromatography (cyclohexane–Et_2O, 7:3).

Yield: 0.036 g (90%); yellow oil; dr = 2:1 (*syn*/*anti*) (determined by integration of the RCHO ^{1}H NMR signals); ee (*syn*) = 90%, ee (*anti*) = 75% [ees were determined by chiral HPLC after reduction of the product with $NaBH_4$ in MeOH (Daicel Chiralcel column IC: *n*-hexane–*i*-PrOH, 99:1, flow rate = 0.50 mL/min, 30 °C, λ = 210, 254 nm)]; t_R (*syn*) = 23.6 min (major), 19.2 min (minor), t_R (*anti*) = 17.2 min (major), 20.6 min (minor).

^{1}H NMR (200 MHz, $CDCl_3$): δ (*syn*) = 0.89 (t, *J* = 6.2 Hz, 3 H), 1.13–1.26 (m, 8 H), 1.62–1.65 (m, 2 H), 2.73–2.75 (m, 1 H), 3.75 (t, *J* = 9.6 Hz, 1 H), 6.14 (d, *J* = 10.6 Hz, 1 H), 7.16–7.46 (m, 15 H), 9.34 (d, *J* = 4.0 Hz, 1 H).

^{1}H NMR (200 MHz, $CDCl_3$): δ (*anti*) = 0.89 (t, *J* = 6.2 Hz, 3 H), 1.13–1.26 (m, 8 H), 1.62–1.65 (m, 2 H), 2.73–2.75 (m, 1 H), 3.64 (t, *J* = 9.6 Hz, 1 H), 6.26 (d, *J* = 11.2 Hz, 1 H), 7.16–7.46 (m, 15 H), 9.43 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (*syn*/*anti*) = 14.0, 22.5, 26.9, 27.1, 27.4, 27.5, 28.9, 29.3, 31.4, 31.6, 45.9 (*syn*), 46.1 (*anti*), 57.8 (*syn*), 58.5 (*anti*), 126.7 (2 C), 127.2 (3 C), 127.4 (5 C), 127.8 (2 C), 127.9 (2 C), 128.1, 128.2 (3 C), 128.3 (4 C), 128.8 (4 C), 129.0, 129.3, 129.7 (4 C), 139.5 (2 C), 141.8 (4 C), 141.9 (2 C), 204.2 (*syn*), 204.5 (*anti*).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{29}H_{32}O$: 396.24531; found: 396.24588.

(2*R*/*S*,3*S*)-3-[4-(Dimethylamino)phenyl]-2-methyl-3-(thiophen-3-yl)propanal (10c)

The title product was prepared according to the general procedure B. The residue was purified by flash chromatography (cyclohexane–Et_2O, 7:3).

Yield: 0.023 g (84%); colorless oil; dr = 2:1 (*anti*/*syn*) (determined by integration of the RCHO ^{1}H NMR signals); ee (*anti*) = 93%, ee (*syn*) = 90% [ees were determined by chiral HPLC (Daicel Chiralcel column IA: *n*-hexane–*i*-PrOH, 99:1 to 90:10 over 30 min, flow rate = 0.50 mL/min, 30 °C, λ = 210, 254 nm)]; t_R (*anti*) = 21.7 min (major), 24.3 min (minor), t_R (*syn*) = 23.1 min (minor), 28.7 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*) = 1.02 (d, *J* = 6.8 Hz, 3 H), 2.94 (s, 6 H), 3.08–3.19 (m, 1 H), 4.32 (d, *J* = 10.2 Hz, 1 H), 6.66–6.70 (m, 2 H), 6.89–6.96 (m, 2 H), 7.13 (d, *J* = 8.3 Hz, 1 H), 7.00–7.18 (m, 2 H), 9.67 (d, *J* = 3.0 Hz, 1 H).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*) = 1.12 (d, *J* = 6.8 Hz, 3 H), 2.92 (s, 6 H), 3.08–3.19 (m, 1 H), 4.31 (d, *J* = 9.9 Hz, 1 H), 6.66–6.70 (m, 2 H), 6.92–6.89 (m, 2 H), 7.06–7.18 (m, 3 H), 9.57 (d, *J* = 2.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*/*anti*) = 13.4 (*anti*), 13.5 (*syn*), 40.4 (2 C), 40.5 (2 C), 47.2, 48.0, 51.9 (*syn*), 52.0 (*anti*), 112.4, 112.6 (2 C), 112.7, 124.0 (2 C), 124.2, 126.5, 126.6, 128.6, 128.7 (2 C), 129.2 (*anti*), 129.3, 129.4 (*syn*), 132.7 (*syn*), 146.8 (*syn*), 147.1 (*anti*), 149.2 (*syn*), 149.5 (*anti*), 204.0 (*syn*), 204.1 (*anti*).

ESI-MS: *m*/*z* (%) = 274.2 (100) [M + H]$^+$.

***tert*-Butyl {(4*S*/*R*,5*R*)-4-[4-(Dimethylamino)phenyl]-5-methyl-6-oxohexyl}(phenyl)carbamate (10g)**

The title product was prepared according to the general procedure B. The residue was purified by flash chromatography (cyclohexane–Et_2O, 8:2).

Yield: 0.041 g (92%); orange oil; dr 4.5:1 (*anti*/*syn*) (determined by integration of the RCHO ^{1}H NMR signals); ee (*anti*) = 95%, ee (*syn*) = 97% [ees were determined by chiral HPLC (Daicel Chiralcel OD-H column: *n*-hexane–*i*-PrOH, 99:1 to 90:10 over 30 min, flow rate = 0.50 mL/min, 30 °C, λ = 214, 254 nm)]; t_R (*anti*) = 21.3 min (minor), 22.1 min (minor), t_R (*syn*) = 25.0 min (major), 27.8 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*) = 0.86 (d, *J* = 7.1 Hz, 3 H), 1.39 (s, 9 H), 1.54–1.77 (m, 4 H), 2.27–2.38 (m, 1 H), 2.73–2.81 (m, 1 H), 2.93 (s, 6 H), 3.58–3.70 (m, 2 H), 6.67 (d, *J* = 8.7 Hz, 2 H), 6.95 (d, *J* = 9.1 Hz, 2 H), 7.08 (br d, *J* = 7.5 Hz, 2 H), 7.17 (tt, *J* = 5.9 Hz, *J* = 7.1 Hz, *J* = 8.3 Hz, 1 H), 7.30 (d, *J* = 4.5 Hz, 2 H), 9.61 (d, *J* = 3.5 Hz, 1 H).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*) = 0.88 (d, *J* = 7.1 Hz, 3 H), 1.39 (s, 9 H), 1.54–1.77 (m, 4 H), 2.44–2.56 (m, 1 H), 2.73–2.81 (m, 1 H), 2.93 (s, 6 H), 3.58–3.70 (m, 2 H), 6.67 (d, *J* = 8.7 Hz, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 7.08 (d, *J* = 7.5 Hz, 2 H), 7.17 (tt, *J* = 5.9 Hz, *J* = 7.1 Hz, *J* = 8.3 Hz, 1 H), 7.30 (d, *J* = 4.5 Hz, 2 H), 9.51 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*anti*) = 12.1, 14.1, 22.7, 28.3 (3 C), 31.2, 40.7 (2 C), 45.1, 52.4, 77.2, 80.0, 112.7 (2 C), 125.9 (2 C), 128.6 (2 C), 128.8, 129.0 (2 C), 142.4, 149.4, 154.7, 205.4.

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*) = 12.1, 14.1, 22.7, 28.3 (3 C), 31.2, 40.7 (2 C), 45.1, 52.4, 77.2, 80.0, 112.7 (2 C), 125.9 (2 C), 128.6 (2 C), 128.8, 129.0 (2 C), 142.4, 149.4, 154.7, 205.4.

ESI-MS: *m*/*z* (%) = 447.2 (100) [M + Na]$^+$, 871.4 (18) [2 M + Na]$^+$.

(*R*)-2-{(*R*/*S*)-1-[4-(Dimethylamino)phenyl]-4,4-diethoxybut-2-yn-1-yl}octanal (14a)

The title product was prepared according to the general procedure C. The product was isolated as the corresponding alcohol after reduction with $NaBH_4$ (see Supporting Information for details). The residue was purified by flash chromatography (cyclohexane–Et_2O, 8:2).

Yield: 0.038 g (97%); yellow oil; dr = 2.6:1 (*anti*/*syn*) (determined by integration of the RCHO ^{1}H NMR signals); ee (*anti*) = 97%, ee (*syn*) = 94% [ees were determined by chiral HPLC (Daicel Chiralcel column IC: hexane–*i*-PrOH, 95:5, flow rate = 0.50 mL/min, 40 °C, λ = 210, 254 nm)]; t_R (*anti*) = 29.2 min (major), 23.9 min (minor), t_R (*syn*) = 30.5 min (major), 56.8 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*) = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.21–1.34 (m, 16 H), 1.83 (m, 1 H), 2.94 (s, 6 H), 3.57–3.66 (m, 3 H), 3.69–3.79 (m, 3 H), 3.82 (d, *J* = 5.7 Hz, 1 H), 5.33 (d, *J* = 1.6 Hz, 1 H), 6.69–6.71 (m, 2 H), 7.20–7.23 (m, 2 H), 9.69 (d, *J* = 3.4 Hz, 1 H).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*) = 0.85 (t, *J* = 7.0 Hz, 3 H), 1.21–1.34 (m, 16 H), 1.83 (m, 1 H), 2.94 (s, 6 H), 3.57–3.66 (m, 3 H), 3.69–3.79 (m, 3 H), 3.93 (d, *J* = 6.3 Hz, 1 H), 5.34 (d, *J* = 1.6 Hz, 1 H), 6.69–6.71 (m, 2 H), 7.20–7.23 (m, 2 H), 9.65 (d, *J* = 3.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ (*anti*) = 14.1, 15.1 (2 C), 22.6, 27.2, 29.2, 29.5, 31.8, 38.4, 40.6 (2 C), 47.1, 60.7 (2 C), 63.3 (2 C), 86.7, 91.5, 112.6 (2 C), 127.2, 128.7 (2 C), 149.6.

^{13}C NMR (50 MHz, $CDCl_3$): δ (*syn*) = 14.1, 15.1 (2 C), 22.6, 27.2, 29.2, 29.5, 31.8, 38.4, 40.6 (2 C), 47.1, 60.8 (2 C), 63.3 (2 C), 86.7, 91.5, 112.6 (2 C), 127.2, 128.7 (2 C), 149.6.

ESI-MS: *m*/*z* (%) = 390.2 (100) [M + H]$^+$, 412.3 (21) [M + Na]$^+$.

(*R*)-2-{(*R*/*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-[4-(dimethylamino)phenyl]pent-2-yn-1-yl}octanal (14b)

The title product was prepared according to the general procedure C. The residue was purified by flash chromatography (cyclohexane–Et_2O, 8:2).

Yield: 0.042 g (94%); yellow oil; dr = 2.5:1 (*anti*/*syn*) (determined by integration of the RCHO ^{1}H NMR signals); ee (*anti*) = 98%, ee

(*syn*) = 92% [ees were determined by chiral HPLC (Daicel Chiralcel column IA: *n*-hexane–*i*-PrOH, 99.5:0.5, flow rate = 0.50 mL/min, 30 °C, λ = 210, 254 nm)]; t_R (*anti*) = 12.3 min (major), 15.1 min (minor), t_R (*syn*) = 14.1 min (major), 11.8 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*) = 0.07 (s, 6 H), 0.84–0.86 (m, 3 H), 0.89 (s, 9 H), 1.24–1.35 (m, 8 H), 1.60–1.89 (m, 2 H), 2.34 (t, *J* = 7.3 Hz, 2 H), 2.43–2.46 (m, 1 H), 2.93 (s, 6 H), 3.71 (t, *J* = 7.1 Hz, 2 H), 3.95 (d, *J* = 5.4 Hz, 1 H), 6.70 (d, *J* = 8.9 Hz, 2 H), 7.19 (d, *J* = 8.9 Hz, 2 H), 9.68 (d, *J* = 3.5 Hz, 1 H).

^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*) = 0.08 (s, 6 H), 0.84–0.86 (m, 3 H), 0.91 (s, 9 H), 1.24–1.35 (m, 8 H), 1.60–1.89 (m, 2 H), 2.34 (t, *J* = 7.3 Hz, 2 H), 2.48–2.51 (m, 1 H), 2.92 (s, 6 H), 3.73 (t, *J* = 7.3 Hz, 2 H), 3.95 (dt, *J* = 2.1 Hz, *J* = 6.4 Hz, 1 H), 6.69 (d, *J* = 8.9 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 9.66 (d, *J* = 3.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*anti*) = –5.3 (2 C), 14.1, 18.3, 22.6, 23.8, 25.9 (3 C), 27.0, 28.9, 29.0, 31.6, 34.0, 37.9, 40.7 (2 C), 62.1, 80.1, 82.1, 112.8 (2 C), 126.9, 128.6 (2 C), 149.7, 204.8.

^{13}C NMR (100 MHz, $CDCl_3$): δ (*syn*) = –5.3 (2 C), 14.0, 18.3, 22.5, 23.9, 25.9 (3 C), 26.9, 29.2, 29.3, 34.4, 37.2, 40.7 (2 C), 62.2, 81.7, 85.8, 112.7 (2 C), 126.8, 129.7 (2 C), 149.7, 204.9.

ESI-MS: *m*/*z* (%) = 444.3 (100) $[M + H]^+$, 466.2 (24) $[M + Na]^+$.

Acknowledgment

Financial support for A. Gualandi and L. Mengozzi came from Bologna University, PRIN (Rome) and from the European Projects: IBAAC, LigBANK, BioHEMLig, MolarNet, and in particular, the organocatalytic CATAFLUO.OR project. Issue number 7 of ChemCatChem, **2012**, is dedicated to this project and has special contributions from many outstanding scientists. Special gratitude for financial support is due to STMicroelectronics. C. M. Wilson is grateful for the award of an Irish Research Council (IRC) Enterprise Partnership Scheme Postgraduate Scholarship in collaboration with Eli Lilly.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633.
(2) Li, C.-J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.
(3) (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (b) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (d) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. T.; Williamson, T. C., Eds.; Oxford University Press: Oxford, **1998**, 250. (e) Lubineau, A.; Augé, J. *Top. Curr. Chem.* **1999**, *206*, 1.
(4) Loh, T.-P.; Chua, G.-L. *Chem. Commun.* **2006**, 2739.
(5) (a) Takita, R.; Fukuta, Y.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363. (b) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760.
(6) Munoz-Muniz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622.
(7) Fu, F.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 4267.
(8) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
(9) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1990**, 2239.
(10) Yang, L.; Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2007**, *48*, 1599.
(11) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227.
(12) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183.
(13) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(14) List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395.
(15) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.
(16) For a recent breakthrough in α-alkylation, see: List, B.; Corić, I.; Grygorenko, O. O.; Kaib, P. S. J.; Komarov, I.; Lee, A.; Leutzsch, M.; Pan, S. C.; Tymtsunik, A. V.; van Gemmeren, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 282.
(17) (a) Ibrahem, I.; Córdova, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952. (b) Afewerki, S.; Ibrahem, I.; Rydfjord, J.; Breistein, P.; Córdova, A. *Chem. Eur. J.* **2012**, *18*, 2972.
(18) For reviews on enantioselective organo-SOMO catalysis, see: (a) MacMillan, D. W. C.; Rendler, S. *In Asymmetric Synthesis II*; Christmann, M.; Bräse, S., Eds.; Wiley-VCH: Weinheim, **2012**, 8. (b) MacMillan, D. W. C. In *Science of Synthesis: Asymmetric Organocatalysis*; Vol. 1; List, B.; Maruoka, K., Eds.; Thieme: Stuttgart, **2012**, 271.
(19) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260.
(20) Chiarucci, M.; di Lillo, M.; Romaniello, A.; Cozzi, P. G.; Cera, G.; Bandini, M. *Chem. Sci.* **2012**, *3*, 2859.
(21) For a recent review of methodology combining transition-metal catalysis with organocatalysis, see: Du, Z.; Shao, Z. *Chem. Soc. Rev.* **2013**, *42*, 1337.
(22) (a) Gualandi, A.; Cozzi, P. G. *Synlett* **2013**, 281. (b) Gualandi, A.; Petruzziello, D.; Emer, E.; Cozzi, P. G. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Dalko, P. I., Ed.; Wiley–VCH: Weinheim, **2013**, 729. (c) Tak-Tak, L.; Dhimane, H.; Dalko, P. I. *Angew. Chem. Int. Ed.* **2011**, *50*, 12146.
(23) (a) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 1313. (b) Benfatti, F.; Benedetto, E.; Cozzi, P. G. *Chem. Asian J.* **2010**, *5*, 2047.
(24) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.
(25) (a) Mayr, H.; Lakhdar, S.; Maji, B.; Ofial, A. R. *Beilstein J. Org. Chem.* **2012**, *8*, 1458. (b) Mayr, H.; Kuhn, O.; Gotta, M. F.; Patz, M. *J. Phys. Org. Chem.* **1998**, *11*, 642.
(26) (a) Kanzian, T.; Lakhdar, S.; Mayr, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9526. (b) Duan, X.-H.; Mayr, H. *Org. Lett.* **2010**, *12*, 2238. (c) Richter, D.; Tan, Y.; Antipova, A.; Zhu, X.-Q.; Mayr, H. *Chem. Asian J.* **2009**, *4*, 1824. (d) Baidya, M.; Horn, M.; Zipse, H.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 7157. (e) Lakhdar, S.; Ammer, J.; Mayr, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 9953.
(27) For a recent study measuring the electrophilicity of allylic alcohols, see: Troshin, K.; Schindele, C.; Mayr, H. *J. Org. Chem.* **2011**, *76*, 9391.
(28) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647.
(29) Capdevila, M. G.; Benfatti, F.; Zoli, L.; Stenta, M.; Cozzi, P. G. *Chem. Eur. J.* **2010**, *16*, 11237.
(30) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 456.
(31) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

(32) For the use of $CuCl_2$ and $IrCl_3$ as Lewis acids with the Hayashi–Jørgensen catalyst, see: Xiao, J. *Org. Lett.* **2012**, *14*, 1716.
(33) Capdevila, M. G.; Emer, E.; Benfatti, F.; Gualandi, A.; Wilson, C. M.; Cozzi, P. G. *Asian J. Org. Chem.* **2012**, *1*, 38.
(34) (a) Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Lee, H.; Jee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 4388. (b) Paras, N.; Simmons, B.; MacMillan, D. W. C. *Tetrahedron* **2009**, *65*, 3232.
(35) Evans, D. A.; Reger, D.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
(36) (a) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 7289. (b) For γ-propargylation, see: Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2012**, *31*, 3810. (c) Yoshida, A.; Ikeda, M.; Hattori, G.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2011**, *13*, 592.
(37) (a) Sinisi, R.; Victoria Vita, M.; Gualandi, A.; Emer, E.; Cozzi, P. G. *Chem. Eur. J.* **2011**, *17*, 7404. (b) For similar studies with CH_2Cl_2 as the reaction solvent, see: Motoyama, K.; Ikeda, M.; Myake, Y.; Nishibayashi, Y. *Eur. J. Org. Chem.* **2011**, 2239.

