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Diastereodivergent Behavior of Alkyl versus Cyano Allenylcuprates toward Aldehydes: A Key Role for Lithium

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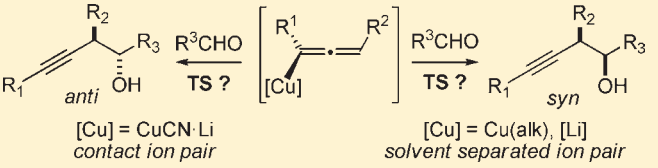
Supporting Information

ABSTRACT: The stereodivergent behavior of allenyl(*cyano*)- and allenyl(*alkyl*)cuprates toward aldehydes, providing a selective preparation of both *syn*- and *anti*-homopropargylic alcohols, is described. This study, which combines both experimental and theoretical support, shows that the copper nontransferred "dummy ligand" controls the localization of the lithium cation with respect to the allenylcuprate moiety. As a consequence, Li^+ acts as a Lewis acid activator but also controls the diastereoselectivity during the addition of allenylcuprates onto aldehydes. The combined high selectivity, efficiency, and versatility of these cuprate compounds opens the way to new one-pot synthetic procedures, as illustrated by the combined Klein rearrangement/transmetalation methodology described herein.



INTRODUCTION

The development of versatile methodologies allowing the specific control of the chemo-, regio-, and/or diastereoselectivity of a reaction starting from a single reactant is challenging. Due to their high versatility, organometallics derived from propargylic compounds are, for this purpose, attractive reagents. Indeed, the metalation of a propargylic compound may lead to a mixture of two distinct organometallic species: a propargylic one and an allenic one. Depending on the nature of the substituents (R^1 and R^2) and of the metal center [M], these two forms can exchange via a metallotropic equilibrium (Scheme 1). Thus, upon addition onto aldehydes, four different products (two diastereomeric allenic alcohols and two diastereomeric homopropargylic alcohols) can be formed according to not only the nature of R^1, R^2, and [M] but also the reaction conditions (Scheme 1).[1]

Whereas general and efficient access to *anti*-homopropargylic alcohols is well described,[1,2] the preparation of the *syn* isomers is less documented and requires the preparation and isolation of delicate allenyltin or -silicon reagents.[3] With a more practical one-pot access to these products in mind, our group developed an original approach based on the utilization of electron-rich allenyl(di-*tert*-butyl)zincate reagents. The process revealed *syn* selectivity, but its moderate scores (ranging from 75/25 *syn*/*anti* ratio using PhCHO to 85/15 with *t*-BuCHO) leave space for further improvement.[4] Aiming at increasing this diastereoselectivity, we recently screened allenyl (A)(cyano)cuprates ([A-Cu-CN]Li) whose addition onto aldehydes yields, regioselectively, the corresponding homopropargylic alcohol as a main diastereomer. However, an unexpected *anti* selectivity was returned this time, regardless of the nature of the allenic substituents (Scheme 2).[5]

This behavior is somehow unexpected as it contradicts the usual *ad hoc* models. Actually, the versatile stereochemistry of the addition of allenic organometallic (A-[M]) reagents onto aldehydes is generally assigned to the existence of two different transition states (TSs). A cyclic TS, mainly providing the *anti* adduct, is proposed when the allenic metal center [M] exhibits Lewis acidic properties and exerts a direct activation of the aldehyde (Scheme 3, eq 1). When a non-Lewis acidic allenic metal (a category in which the Cu in cyanocuprates mentioned above is usually classified[6]) is employed, an external Lewis acid (LA) is needed, and the reaction is expected to proceed via an open TS leading to the *syn* adduct (Scheme 3, eq 2).[1]

The *anti* selectivity observed with allenyl(cyano)cuprates (the structure of these compounds will be discussed later) does not fit these usual models. Indeed, since in the case of $[R_2Cu]^-$ the copper center lacks electrophilicity,[6] a classical six-membered TS can be ruled out. Previous experimental and theoretical studies, in particular by Nakamura and colleagues, have highlighted the crucial role played by the Li^+ counterion associated to the cuprate reagents in the activation and organization of the TS.[5c,7,8] Hence, the structure and nature of the ion pairs formed by the cuprate

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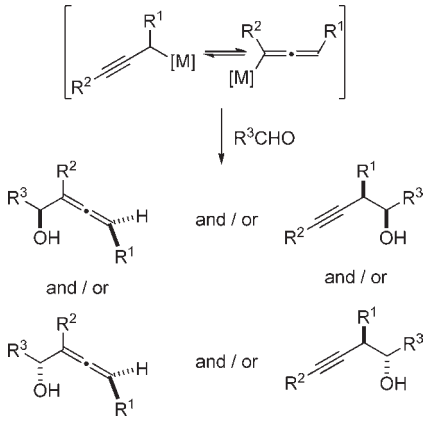
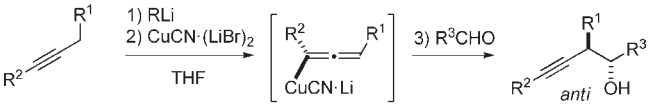
Scheme 1. Possible Products from the Addition of Metalated Propargylic Reagents onto Aldehydes

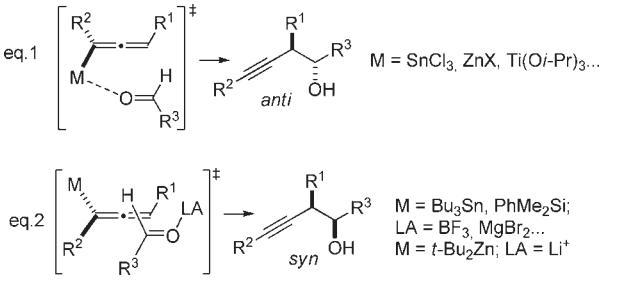


Scheme 2. Addition of Allenyl(cyano)cuprates onto Aldehydes

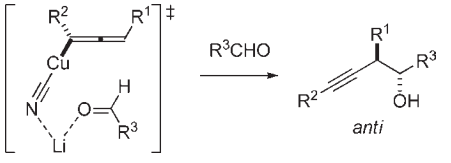


R^1 = OR, NR_2, alkyl; R^2 = TMS, Ph, alkyl

Scheme 3. Classical Six-Membered Cyclic vs Open Transition State



Scheme 4. Proposed Nine-Membered Transition State Leading to the *Anti* Product



and its cationic counterpart are likely to be essential also here. Previous X-ray diffraction studies[9] exhibited contact ion pairs between Li^+ and the cyano group of cyanocuprate species. We thus envisioned that a nine-membered ring TS, resulting from the activation of the aldehyde by a lithium cation still in close contact with the cyano ligand (Scheme 4), could explain the observed *anti* selectivity.

As a consequence, we assumed that any change in the nature of the copper's "dummy ligand"[10,11] (R_d, CN in Scheme 4) was likely to alter the interaction with the lithium and exert a dramatic effect on the reaction with aldehydes[12] and its diastereochemical outcome. To test this hypothesis, we turned our attention to allenyl(alkyl)cuprate species such as those derived from $[CuMe_2]Li$, for which contact ion pair (CIPs) and solvent-separated ion-pair (SSIP) forms are known to be in equilibrium in solution (see Scheme 5). In solvents with a high affinity for Li^+, such as THF, this equilibrium is in favor of SSIP.[8,13,14] Nakamura et al.[8g] have proposed that this equilibration may occur through a continuum of species. Scheme 5, in which a continuum of CIP^n species forms upon progressive fragmentations and solvations, gives a good example of this concept. Therein, a cyclic dicuprate (dimeric) CIP^1 opens up into a linear (but still dimeric) CIP^2 and then decays into two (monomeric) lithium cuprates CIP^3, the latest being in equilibrium after solvation and dissociation with the SSIP formed by a solvated Li^+ associated to a cuprate anion.

With cyanocuprates, this "dissociative equilibrium cascade" is displaced to the left, most probably because the Li^+ cation has a larger affinity for the cynano copper ligand than for the methyl one. We thus imagined that resorting to an allenyl(methyl)cuprate instead of an allenyl(cyano)cuprate would result, in THF, in the de-coordination of Li^+ from the diorganocuprate moiety.[15] This could disfavor the hypothetical cyclic TS and lead to the desired *syn* selectivity through an open TS (Scheme 6). However, all this remained highly speculative since the behavior of allenylcuprates can hardly be predicted: these reagents have been poorly studied and have never been the subject of thorough physicochemical studies. We thus began a combined theoretical (B3LYP/6-31++G** level, see Computational Procedure for details) and experimental study of various copper species ($[A\text{-}Cu\text{-}R_d]Li$) such as allenyl(cyano) (R_d = CN) and allenyl(alkyl) (R_d = alk) cuprates. As a heteroatomic substituent on the allenyl group could interfere with the lithium cation,[9e,16] alkyl propargylic precursors (R^1 = alkyl in Scheme 6) were selected as model substrates.

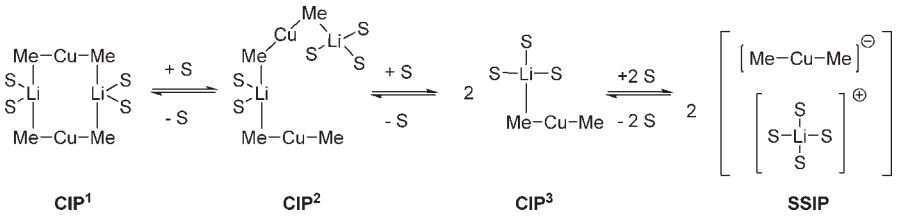
RESULTS AND DISCUSSION

Original Procedure. The reactions were first performed in THF as solvent to favor the formation of SSIP forms.[13] The alkyne derivative **1a** or **1a′** (SM in Table 1) was subjected to metalation using *t*-BuLi in THF. Deuteration experiments showed complete deprotonation after 1 h at 0 °C.[17] The lithiated intermediate was then transmetalated by dropwise addition to a THF solution of the desired copper reagent (1.5 equiv) $CuI\cdot(LiBr)_2$ or $(CuR_d)\cdot(LiBr)_2$ (R_d = CN, Me, *t*-Bu) at −90 °C, affording in all cases a clear solution. It is far more advantageous to start from the soluble $CuI\cdot(LiBr)_2$ or $CuCN\cdot(LiBr)_2$ complexes to allow transmetalation at low temperature.[18] This is essential for the generation of the allenyl(*t*-Bu)cuprate due to the very short lifetime of *t*-BuCu[19] in solution at −80 °C, which makes impossible its formation in heterogeneous conditions where the transmetalation usually occurs above −40 °C.

Scope of the Reaction. The reaction of the copper species with aldehydes was then studied. A THF solution of the desired aldehyde was added to the allenylcopper reactants over 1 h via a syringe pump at −90 °C,[20] and the mixture was stirred at this temperature for an additional hour before hydrolysis. Results obtained are summarized in Table 1.

As anticipated, the nature of the copper reagent was found to dramatically influence the stereochemical outcome of the reaction. In strong contrast with the *anti* selectivity observed with

Scheme 5. Example of SSIP−CIP Equilibrium



Scheme 6. Lithium Cuprates Ion Pair Structures as a Key To Control Diastereoselectivity

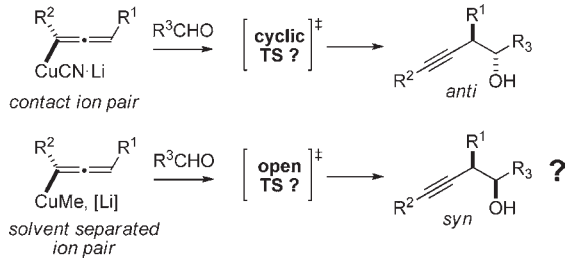
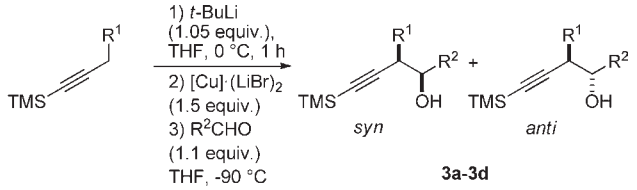


Table 1. Influence of the Nature of the Copper Reagent on Diastereoselectivity



$R^1 = C_7H_{15}$ (**1a**) R^2 = *i*-Pr (**2a**)
$R^1 = CH_3$ (**1a'**) R^2 = *t*-Bu (**2b**)
R^2 = *n*-Pr (**2c**)
R^2 = Ph (**2d**)

entry	[Cu]	R^1	R^2CHO	product	*syn*/*anti*[a]	yield (%)[b]
1	CuCN	C_7H_{15}	**2a**	**3a**	8/92	65
2	CuMe[c]	C_7H_{15}	**2a**	**3a**	90/10	76
3 ($R^1 = CH_3$)	CuMe[c]	CH_3	**2a**	**3a'**	90/10	75
4	CuMe[c]	C_7H_{15}	**2b**	**3b**	>95/5	80
5	CuMe[c]	C_7H_{15}	**2c**	**3c**	80/20	78
6	CuMe[c]	C_7H_{15}	**2d**	**3d**	80/20	77
7	Cu*t*-Bu[d]	C_7H_{15}	**2c**	**3c**	79/21	81
8	CuI[e]	C_7H_{15}	**2a**	**3a**	70/30	53

[a] Determined by ^{1}H NMR of the crude product based on integration value of the homopropargylic protons. [b] Isolated yield (*syn* + *anti*). [c] Obtained by addition of 1 equiv of MeLi to 1 equiv of $(CuI)\cdot(LiBr)_2$ reagent. [d] Obtained by addition of 1 equiv of *t*-BuLi to 1 equiv of $(CuI)\cdot(LiBr)_2$ reagent. [e] 1.2 equiv.

allenyl(cyano)cuprates, allenyl(methyl)cuprates derived from **1a** or **1a'** react with **2a** to give mainly *syn* **3a** or **3a'** (90/10 *syn*/*anti* ratio, entries 2 and 3, as compared to the 8/92 ratio observed with the allenyl(cyano)cuprate analogue, entry 1). An alternative protocol to provide the allenyl(methyl)cuprate, based on the lithiation of **1a** followed by a sequential addition of a THF solution of a $(CuI)\cdot(LiBr)_2$ reagent, and of MeLi to generate the allenyl(methyl)cuprate, gave similar results.

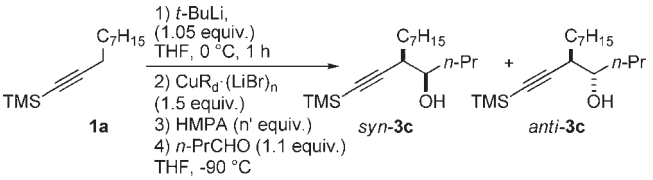
The influence of the structure of the aldehydes reacted with allenyl(methyl)cuprate derivatives was then investigated. We observed that good levels of selectivity are generally reached and are enhanced by steric factors: the *syn*/*anti* ratio increases with the bulk of the aldehyde (primary to secondary and tertiary alkyl R^2). The best selectivity is observed with pivaldehyde (**2b**) (*syn*/*anti* > 95/5, entry 4), whereas butyraldehyde (**2c**) and the conjugated benzaldehyde (**2d**) give a lower 80/20 *syn*/*anti* ratio (entries 5 and 6).

The influence of the nature of the alkyl group R_d in allenyl(alkyl)cuprates ($[A\text{-}Cu\text{-}R_d]^-$) was then addressed using **2c** as a model aldehyde. The increase in bulk of the alkyl copper substituent R_d, from Me to *t*-Bu, had little impact on the selectivity (entry 7), in contrast to what was noted above for the aldehydes. This suggests a geometrical arrangement for the TS where the reacting center is now relatively remote from the copper ligand R_d, a situation hardly met in a cyclic TS. This hypothesis will be confirmed below. The *syn* selectivity observed with alkylcuprates was also obtained with the allenylcopper reagent (A-Cu). Addition of isobutyraldehyde (**2a**) at −90 °C to this latter reagent, obtained by metalation of **1a** with *t*-BuLi in THF and transmetalation with the soluble $(CuI)\cdot(LiBr)_2$ complex (1.2 equiv), resulted in the formation of the homopropargylic alcohol **3a** in a 70/30 *syn*/*anti* ratio. By comparison, the *anti* isomer is mainly obtained using CuCN instead of CuI as transmetallating agent (Table 1, entries 1 and 8).

Nature of the Reactive Species. Whereas the structure and the reactivity of numerous metalated propargylic species have been extensively explored, allenylcopper reagents are virtually unknown. Hence, little is known about their reactivity,[21] and, to the best of our knowledge, no data are available regarding their structure in solution. Due to the particular nature of the allene moiety, the structures in solution of alkyl or aryl organocuprate reagents known to date[8] cannot be easily transposed to the allenylcuprate reagents employed here. In addition, the relationship between reactivity and structure is, as always, ambiguous: the thermodynamically most stable species is not necessarily the kinetically most active one. This deterred us from determining the nature of the major species in solution but rather prompted us to undertake a systematic study on the effect of the reaction conditions on kinetics and diastereoselectivity, in an effort to build a working model and better understand the behavior of the allenylcuprate reagents. A set of complementary experiments were thus undertaken with alkyne **1a** and butyraldehyde **2c** to fuel up the theoretical study with useful data (Table 2). The allenyl(alkyl)cuprate was first considered. The problem of the possible competition between SSIP and CIP forms was tackled by adjusting three parameters: the presence of salt (LiBr), the presence of a chelating additive (HMPA), and the nature of the solvent (THF vs Et_2O).

(i) The effect of LiBr was probed by a transmetalation experiment in which the allenyllithium intermediate was added dropwise to a LiBr-free suspension of CuI (1.5 equiv) in THF

Table 2. Influence of Experimental Conditions on the Diastereoselectivity



entry	CuR_d (1.5 equiv)	LiBr (*n* equiv)[a]	HMPA (*n'* equiv)[b]	*n*-PrCHO (equiv)[c]	*syn*/*anti*[d]	yield (%)[e]
1	CuMe[f]	0	0	1.1	81/19	73
2	CuMe[f]	0	2	1.1	75/25	49
3	Cu*t*-Bu[g]	2	2	1.1	77/23	52

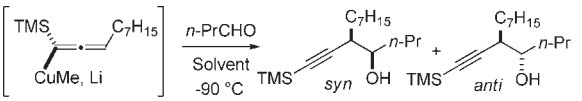
[a] Based on the amount of copper. [b] Based on the total amount of Li^+ in the reaction mixture. [c] Based on the amount of alkyne. [d] Determined by ^1H NMR of the crude product based on integration value of the homopropargylic protons. [e] Isolated yield (*syn* + *anti*). [f] Obtained by addition of 1 equiv of MeLi to 1 equiv of CuI reagent. [g] Obtained by addition of 1 equiv of *t*-BuLi to 1 equiv of $(CuI)\cdot(LiBr)_2$ reagent.

at −90 °C and the mixture was allowed to reach −20 °C, where a clear solution was formed. The addition of a solution of butyraldehyde atop this mixture in THF at −90 °C gave **3c**, with yield (73%) and selectivity (81/19 *syn*/*anti* ratio) similar to those obtained in the presence of 2 equiv of LiBr (compare Table 1, entry 5, and Table 2, entry 1). Extra LiBr has thus no influence on yield and selectivity; it was nevertheless employed in the rest of this study for solubility issues (see above). The negligible influence of LiBr on the yield (78% yield with LiBr, Table 1, entry 5, vs 73% yield without LiBr, Table 2, entry 1) is worth noting since previous theoretical calculations and NMR studies have pointed out the effect of lithium halides on the aggregation state of diorganocuprates in solution.[8i,22] If oligomeric CIP forms are the reactive species, then their structure should be altered by an extra 2 equiv of LiBr, and their selectivity should be modified.

(ii) Similarly, a strong Li^+ chelating agent such as HMPA should alter the structure of the CIP forms and displace the possible equilibria in favor of the corresponding SSIP forms.[23] Our previous studies on the addition of allenyl(cyano)cuprate reagents on aldehydes showed that the rate of the reactions is dramatically lowered or even stopped in the presence of HMPA.[5c,d] In our case, in standard condition (2 h at −90 °C), the presence of HMPA in the reaction mixture resulted in a significant decrease of the yield (compare Table 1, entries 5 and 7, and Table 2, entries 2 and 3), while diastereoselectivity remained unaltered.[7b,22d,24] This is fully consistent with a Li^+ activation step.

(iii) Changing the solvent from THF to Et_2O should shift the equilibrium described in Scheme 5 toward the left by favoring more aggregated forms.[13d] As anticipated, metalation in this medium is trickier but was successfully achieved by the use of *s*-BuLi at 0 °C for 2 h. The resulting clear ethereal solution was added to a suspension[25] of CuMe in ether at −80 °C, warmed to −20 °C, and stirred for 30 min at this temperature to give a highly heterogeneous mixture,[26] in contrast to the clear solution obtained in THF. This suggests the formation of polycuprate CIP aggregates (structures of $(ACuMeLi)_n$ composition, with $n > 1$, the exact composition of which is unknown). A dilute solution of butyraldehyde in Et_2O was then added in 1 h at −90 °C, the mixture was stirred an additional 1 h at this temperature before hydrolysis, and the conversion was determined by ^1H NMR of the crude mixture using 1,3,5-triphenylbenzene as internal standard. In these conditions, the use of

Scheme 7. Comparison of the Diastereoselectivity (Determined by ^1H NMR of the Crude Product Based on Integration Value of the Homopropargylic Protons) of the Addition of Allenyl(methyl)cuprate to Butyraldehyde in THF and in Et_2O



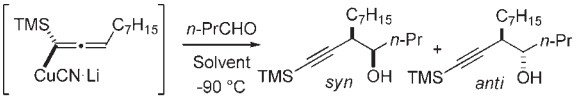
Solvent = THF: 80 / 20 (Table 1, entry 5)
= Et_2O: 45 / 55 (44% conversion)

allenyl(methyl)cuprate gives a 45/55 *syn*/*anti* mixture (44% conversion along with the starting material), in strong contrast with results obtained in THF (80/20 *syn*/*anti* ratio, Scheme 7). We thus conclude that when the formation of CIPs is favored, an inversion of stereoselectivity is observed.

In summary, the addition of HMPA and LiBr has little influence on the diastereochemical outcome of the addition of allenyl(methyl)cuprate onto butyraldehyde. In contrast, running the reaction in Et_2O rather than THF has a significant effect. These observations suggest that in THF the reactive species tend to deaggregate into monocopper CIP[3] or a SSIP (see Scheme 5),[13] the reactivity of which is little influenced by the presence of Li^+ salts. We believe that the addition of HMPA, which slows the reaction but does not alter its selectivity, changes marginally the structure of the TS but renders coordination of the aldehyde to Li^+ difficult. In contrast, the structure of the TS would be completely different in diethyl ether, resulting in a deep alteration of the aggregation state of the reagent, which would explain the changes observed in the stereochemical outcome of the reaction.

The case of allenyl(cyano)cuprate was then addressed. The competition between CIP and SSIP is probably not a key issue here, as the CIP structure is favored by the coordination of the lithium to the cyano entity,[9b] even though the formation of polycuprate aggregates remains possible.[23b,27] Previous studies conducted in our group have shown that allenyl(cyano)cuprates, like allenyl(methyl)cuprate, afford an unchanged diastereoselectivity when the extra 2 equiv of LiBr is omitted.[5d] In the same way, we observed that the presence of HMPA in the reaction mixture had little influence on the diastereoselectivity but induced a drastic lowering of the reaction rate.[5d,24] Similarly to

Scheme 8. Comparison of the Diastereoselectivity (Determined by ^{1}H NMR of the Crude Product Based on Integration Value of the Homopropargylic Protons) of the Addition of Allenyl(cyano)cuprate to Butyraldehyde in THF and in Et_2O



Solvent	= THF:	10	/	90	(ref. 5d)
	= Et_2O:	27	/	73	(37% conversion)

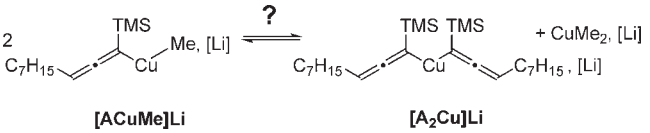
allenyl(methyl)cuprate, these results are in good accordance with a Li^+ activation model and suggest that oligomeric CIP species cannot be the reactive species. Next, the allenyl(cyano)cuprate stemming from **1a** was generated in Et_2O as described above but using CuCN as the transmetallating agent. As for the methyl cuprate analogue, a highly heterogeneous mixture was obtained, which may be the consequence of the formation of oligomeric CIP forms. The addition of a dilute solution of butyraldehyde in ether gave the desired product in a 27/73 *syn*/*anti* ratio and 37% conversion (as a mixture with the starting material). Notably, a slight variation of *anti* selectivity in Et_2O is observed along with a dramatic decrease in reactivity. The observation of a highly heterogeneous mixture in Et_2O suggests, in accordance with the literature,[13,14] that poly (di-, tri-, etc.) copper CIP forms are involved. The slight decrease of the *anti*/*syn* ratio from 90/10 in THF to 73/27 in Et_2O (Scheme 8) can be connected to the shift of the equilibrium in Scheme 5 toward more aggregated (CIP) forms; as for allenyl(methyl)cuprate reagents in Et_2O, their exact structure is unknown.

For both allenyl(cyano)- or allenyl(alkyl)cuprate reagents, the presence of LiBr or the absence of HMPA has a minor effect on the diastereoselectivity, whereas the nature of the solvent (THF vs Et_2O) has an impact, stronger with allenyl(methyl)cuprates than with allenyl(cyano)cuprates. This may be coherent with a SSIP or a monocopper CIP form as reactive species for allenyl(methyl)cuprate and a monocopper CIP form for allenyl(cyano)cuprate.

Influence of Schlenk Equilibria on the Diastereoselectivity? Another important point concerns the composition of the mixed allenyl(alkyl)cuprates in solution. Indeed, heteroleptic diorganocuprates [RCuR′]Li often undergo an equilibrium with the two corresponding homoleptic species $[R_2Cu]Li$ and $[R'_2Cu]Li$.[28] In our case, such an equilibrium would involve the homoleptic $[Me_2Cu]Li$ and $[A_2Cu]Li$ on one hand and the heteroleptic [MeCuA]Li species on the other (Scheme 9).

To evaluate the possible effect of such an equilibrium, we first checked the variation of the diastereoselectivity during the reaction time. We reasoned that if homoleptic $[A_2Cu]Li$ is the reactive species, its consumption along the reaction course could exert an effect on the diastereoselectivity, which consequently could evolve within the time scale of the reaction. We thus ran the following control experiment: we carried out the typical addition of butyraldehyde onto allenyl(methyl)cuprate reagent derived from **1a** in the presence of a ^{1}H NMR internal standard. Samples were taken at 35, 60, and 100% addition of the THF solution of aldehyde (Scheme 10). The results led us to two important conclusions: (i) the reaction is almost instantaneous at −90 °C, as seen by the levels of conversion, and (ii) there is no significant variation of the

Scheme 9. Schlenk Equilibrium between Heteroleptic Allenyl(alkyl)cuprates and Homoleptic Diallenylcuprates



Scheme 10. Variation of the Diastereoselectivity during the Reaction

0.35 equiv. *n*-PrCHO: conversion[a]: 33%; *syn*/*anti*: 83/17[b]
0.60 equiv. *n*-PrCHO: conversion[a]: 55%; *syn*/*anti*: 81/19[b]
1.00 equiv. *n*-PrCHO: conversion[a]: 80%; *syn*/*anti*: 79/21[b]

[a] Determined by ^{1}H NMR of the crude product using 1,3,5-triphenylbenzene as internal standard. [b] Determined by ^{1}H NMR of the crude product.

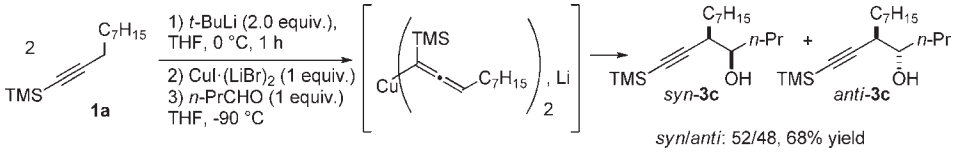
selectivity during the transformation (Scheme 10), indicating that $[A_2Cu]Li$ is probably not the major reactive species.

To confirm this assumption, the homoleptic diallenylcuprate reagent was generated by transmetalation of 2 equiv of allenyllithium by 1 equiv of $(CuI)\cdot(LiBr)_2$, followed by the addition in our standard conditions of 1 equiv of butyraldehyde. The homopropargylic alcohol **3c** was obtained as a 52/48 mixture of *syn* and *anti* products in 68% yield instead of the 80/20 *syn*/*anti* ratio observed with the corresponding allenyl(methyl)cuprate (Table 1, entry 5), clearly indicating that the contribution of $[A_2Cu]Li$ is unlikely (Scheme 11). Moreover, DFT calculations on the structure of ACuMeLi species (see below) indicate that the allenyl moiety is a better coordination site for the Li^+ cation (π coordination) than the methyl. In the case of the $[A_2Cu]Li$ reagent, the presence of two allenyl moieties may induce a stronger association with the Li^+, disfavoring the SSIP form and thus favoring the formation of the *anti* adduct through a cyclic TS, in good accordance with our initial hypothesis.

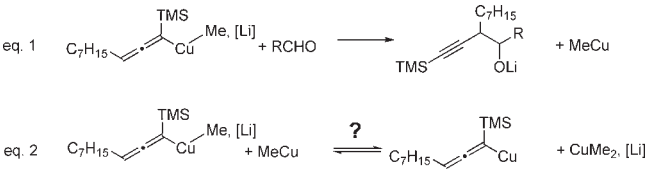
Another possible Schlenk equilibrium may be envisioned between organocopper and organocuprate species. Indeed, the two products of the reaction before hydrolysis are, at −90 °C, a lithium alloxide and CuMe (Scheme 12, eq 1).[8g,i] During the reaction, this subsidiary organocopper CuMe and the remaining organocuprate [ACuMe]Li can enter another Schlenk equilibrium with $[CuMe_2]Li$ and the allenylcopper ACu species (Scheme 12, eq 2). The organocuprate [ACuMe]Li reagent is logically the most reactive species, but the organocopper ACu is also able to yield the desired product in the reaction conditions (Table 1, entry 8). Thus, if a fast equilibrium takes place, ACu could be involved in a side reaction pathway, which may have a detrimental effect on the diastereoselectivity (see Table 1, entry 8).

Consequently, we tried to stem the pathway from an allenylcopper ACu species, and hopefully gain diastereoselectivity, by using [MeCuCN]Li instead of MeCu as transmetallating agent. This was expected to provide an organocuprate which should exist in solution as a cyanide-modified Gilman reagent, $[ACuMe]Li\cdot LiCN$.[9a,c,13b,13d,22c,22e,23a,23b,29] This would avoid the formation of MeCu species, as [MeCuCN]Li would be generated instead of MeCu during the course of the reaction (Scheme 13, eq 1). Addition of butyraldehyde to the cyano-Gilman reagent led, in our standard conditions, to **3c** in 80% yield

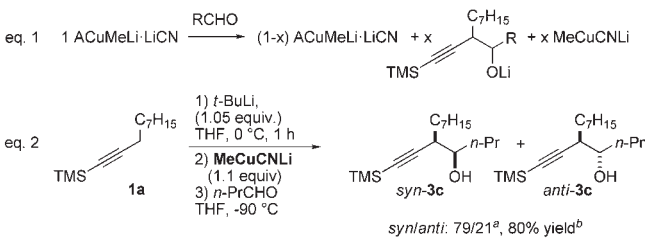
Scheme 11. Addition of $[A_2Cu]Li$ onto *n*-PrCHO



Scheme 12. Formation of CuMe during the Reaction (Eq 1) and Possible Schlenk Equilibrium between Organocopper and Organocuprate Reagents during the Reaction Time (Eq 2)



Scheme 13. Attempted Products of the Reaction Using the Cyanide-Modified Gilman Reagent $[ACuMe]Li \cdot LiCN$ (Eq 1) and Result Obtained for Its Addition to Butyraldehyde (Eq 2)



[a] Determined by ^{1}HNMR of the crude product. [b] Isolated yield (*syn* + *anti*)

with a 79/21 *syn*/*anti* ratio (Scheme 14, eq 3), a result almost identical to the one obtained with the allenyl(methyl)cuprate (80/20, see Table 1 entry 5).[30]

All these results suggest that all the various Schlenk equilibriums considered have no significant effect on the diastereoselective outcome of the reaction, and the allenyl(methyl)cuprate $[ACuMe]Li$ emerges as the major reactive species.

In summary, we have shown that alkyl- or dialkylcuprate reagents exhibit good levels of *syn* selectivity, in strong contrast with the *anti* selectivity observed with the cyanocuprate analogues. This result is in accordance with our initial hypothesis on the influence of the structure of the ion pair on the selectivity, i.e., that a fine-tuning of the spatial location of Li^+ through the judicious choice of the copper "dummy ligand" would allow an efficient control of the stereochemical outcome of the reaction. Complementary experiments suggest a monocopper CIP or a SSIP form for the allenyl(methyl)cuprate and a monocopper CIP form for the allenyl(cyano)cuprate analogue as reactive species in THF. These structures are retained for molecular modeling purposes in this solvent. All these results may be consistent with different reaction pathways: a cyclic TS in the case of allenyl(cyano)cuprates and a less compact open TS in the case of allenyl(alkyl)cuprates. A theoretical study involving allenyl(methyl)- and allenyl(cyano)cuprate species was thus initiated in order to strengthen our conclusions and to propose a working model explaining the different selectivities. As the experimental results have shown that diethyl ether modifies the structure of ion pairs and probably their aggregation degrees, these model structures are only valuable for modeling structures in THF. The study reported below is only representative of the reaction mechanism in this solvent.

DFT Description of Coordination of Lithium to $[A\text{-}Cu\text{-}R_d]^-$. First, the allenic vs propargylic nature of the organometallic reagents was examined from a theoretical point of view for various allenic substituents and copper ligands R_d. The allenic nature of the reacting moieties was confirmed in all cases (see Supporting Information for details).

Since the experimental study did not formally exclude a monocopper CIP form as the reactive species for the allenyl(methyl)cuprate reagent, the structure and the binding energies within the contact ion pair were first examined for cyano and methyl allenylcuprates. Based on the experimental observations, a minimal model[12a] was used to describe these prototypic reagents, involving only one cuprate anion in contact with a single lithium cation, whose coordination sphere is completed by explicit solvent molecules (OMe_2 being used as solvent model for THF).

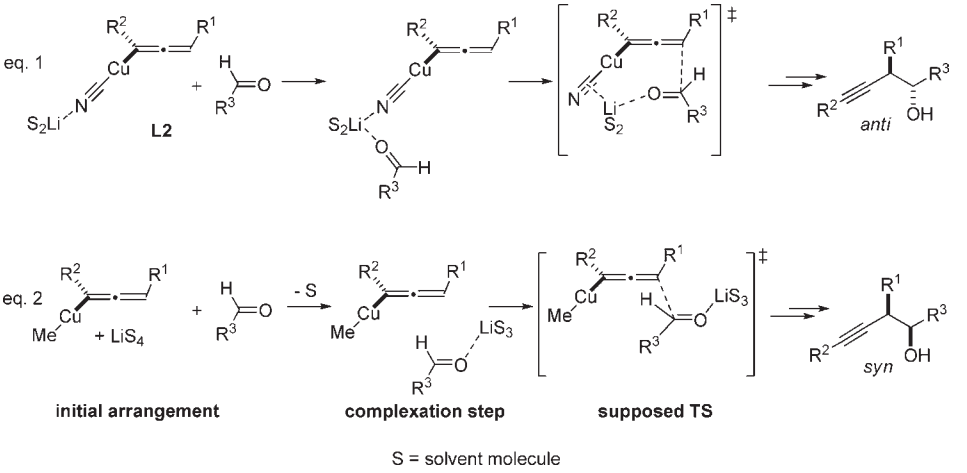
When three solvent molecules ($n = 3$, Figure 1) are coordinated to the lithium, various arrangements were optimized, depending on whether the lithium interacts with the allenyl moiety or with R_d (R_d = CN or Me) (Figure 1, top). In the former case, two faces can be envisioned for the interaction: the lithium coordinates either *cis* to the copper (**C3** structure) or *trans* (**T3** structure) with respect to the plane defined by the Me−C−H atoms. The *trans* arrangement **T3** is found to be energetically disfavored for allenyl(cyano)- and allenyl(methyl)cuprates. For R_d = CN, a fully linear arrangement (referred to as **L3** structure) is observed (Cu−CN−Li angle close to 180°), as expected when the cation interacts with the nitrogen lone pair.[31,32] In the case of allenyl(methyl)cuprate, the lithium cation interacts this time with the Cu−Me bond, as evidenced by the bent arrangement (Cu−Me−Li angle 77.8°, **B3** structure).[13d] Next, comparing ΔE (see Figure 2, SI) of **C3** with respect to **L3** or **B3** allows us to compare the relative affinity of the lithium cation for the allenyl moiety (structure **C3**) and for the R_d ligand (structure **L3** or **B3**).[33a] For both R_d = CN and Me, the $Li^+ \cdots R_d$ interaction is energetically favored over the allenyl$\cdots Li^+$ interaction, as **L3** and **B3** arrangements are found to be the most stable structures (see Supporting Information for full details about these structures). Nevertheless, the affinity of Li^+ for R_d with respect to the allenyl moiety is much larger for R_d = CN ($\Delta E_{C3/L3}$ = 12.8 kcal/mol) than for R_d = Me ($\Delta E_{C3/B3}$ = 3.2 kcal/mol).[33b,c]

Despite these geometrical differences, the interaction energy between the solvated lithium cation and the anionic cuprate moieties varies marginally with the nature of R_d, as evaluated from the energy for the ion pair separation, computed according to the reaction

$$[A\text{-}Cu\text{-}R_d]Li(OMe_2)_3 + OMe_2 \rightarrow [A\text{-}Cu\text{-}R_d]^- + [Li(OMe_2)_4]^+$$

The reaction is found to be endothermic, and its energy ΔE amounts to 69.2 kcal/mol for R_d = CN and 64.9 kcal/mol for

Scheme 14. Proposed Reaction Paths for Condensation of Allenyl(cyano)cuprate (Cyclic CIP, Eq. 1) or Allenyl(methyl)cuprate (SSIP from a *cis* Cu−RCHO Approach, Eq. 2) with Aldehydes (S Stands for One Solvent Molecule Modeled by OMe_2)



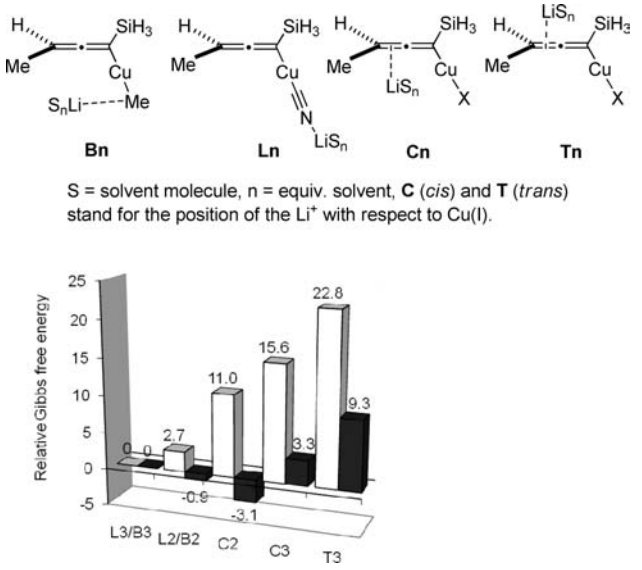


Figure 1. Relative Gibbs free energies ΔG (at 183 K, kcal/mol) computed with respect to the most stable arrangements **L3** (R_d = CN, in white) and **B3** (R_d = Me, in black).

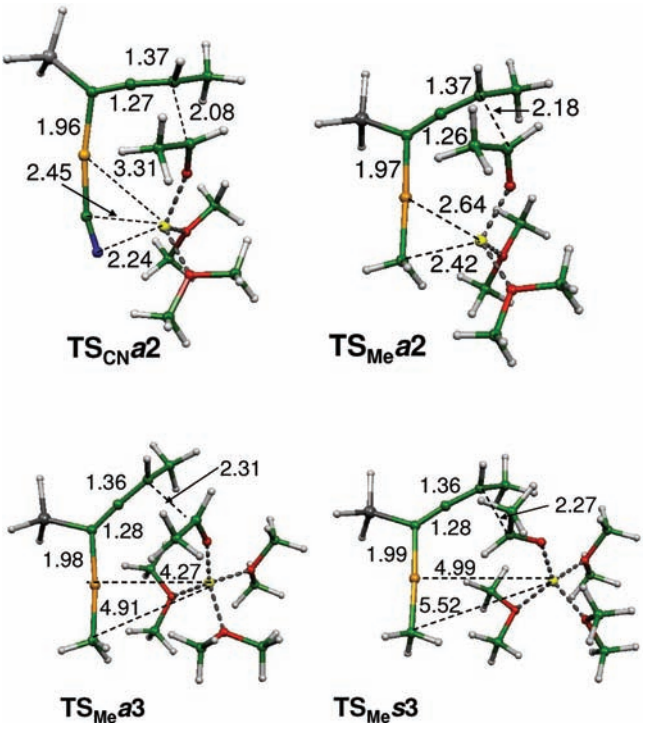


Figure 2. Optimized geometries of the TSs for the addition of acetaldehyde to the allenyl(cyano)- and allenyl(methyl)cuprate according to a nine-membered cyclic (top line) and for the allenyl(methyl)cuprate in SSIP mechanism (*cis* Cu-RCHO approach, bottom line) (see Scheme 14 for definition). Distances are given in Å. Color code: hydrogen (white), lithium (pale green), carbon (green), nitrogen (blue), oxygen (red), silicon (gray), copper (yellow).

R_d = Me. A small preference for the coordination at the allenyl(cyano)cuprate is thus found,[12b] in good accord with the reactive ion pair structures proposed above from experimental data.

Density Functional Studies of Solvent De-coordination. De-coordination of one solvent molecule from the lithium cation leads to an increase of the disorder in the system; this process is thus entropically favored. As the chemical equilibrium is governed by the Gibbs free energy (sum of energetic and entropic factors), the energetically favored tri-solvated structures compete in solution with the entropically favored di-solvated forms. Both solvation states were thus examined.

Only two arrangements could be obtained, as the di-solvated lithium (n = 2 in Figure 1) interacts either with R_d (and in a geometrical arrangement similar to that obtained for the tri-solvated structures, i.e., linear for R_d = CN (**L2**) or bent for R_d = Me (**B2**)) or with the allenyl moiety (full energetic data are given in Supporting Information). In the latter case, only the arrangement of the lithium *cis* to the copper (**C2**) can be obtained, and, compared to the **C3** structure, a strong geometry change is observed as the Li^+ cation comes closer to the copper (distance (Li···Cu) ≈ 2.6 Å in **C2** vs 3.7 Å in **C3**). Hence, the lithium is formally interacting with both the Cu−R_d bond and the allenyl ligand.

The competition between all these minima (all di- and tri-solvated ones) was then studied by computing the relative

Gibbs free energies of all arrangements at an experimental temperature of 183 K (see Figure 1, bottom).[34] For allenyl(cyano)cuprates, a linear binding to the sole CN entity is the most favored coordination mode, as all other structures are of much higher Gibbs free energy. In addition, the di- and tri-solvation (structures **L2** and **L3**) are competitive since the binding energy of the third solvent molecule is nearly exactly canceled by the entropic contribution. The de-coordination of a solvent molecule to allow the coordination of the aldehyde is thus expected to be an easy process. In the case of the allenyl(methyl)cuprate, the **B3**, **B2**, and **C2** arrangements lie within only 3.1 kcal/mol in Gibbs free energy; the hypothetical CIP in allenyl(methyl)cuprate is a much more flexible species, in which interaction with the allenyl π-system is competitive or simultaneous with that to the Cu−Me bond. The structural differences between allenyl(methyl)- and allenyl(cyano)cuprate clearly result from a lower affinity of Li^+ for the methyl than for the cyano "dummy ligand", in good accordance with our initial hypothesis. Such flexibility will not allow the lithium cation to ensure this structuring role in the TS, and such a structure is not expected to lead to good diastereoselectivity in an addition process. This will be verified below by computing the reaction mechanism starting from a CIP arrangement for both allenyl(cyano)- and allenyl(methyl)cuprates.

Density Functional Studies of CIP Mechanism. The considered reaction pathway starts from the **L3** or **B3** structures (Scheme 14, top). One solvent molecule is removed, leading to **L2** or **B2**, and allows an easy docking of the aldehyde to the lithium. Evolution through a cyclic TS then takes place with little displacement: the TS is reached by bending the Li−R_d−Cu angle, which brings the aldehyde reactant close to the nucleophilic center (via a nine-centered arrangement for R_d = CN and an eight-centered arrangement for R_d = Me). This reaction pathway was computed in arrangements yielding both the *anti* and *syn* configurations of the products. Gibbs free energies (ΔG) are gathered in Table 3, and the TS structures ($\mathbf{TS_{CN}}s2$ and $\mathbf{TS_{CN}}a2$ and $\mathbf{TS_{Me}}s2$ and $\mathbf{TS_{Me}}a2$) are given as Supporting Information. As expected for allenyl(cyano)cuprates, and in good accordance with experimental results, the cyclic TS leading to the *anti* isomer $\mathbf{TS_{CN}}a2$ is found to be the lowest in Gibbs free energy. The *anti* selectivity obtained experimentally can be fully justified by formation, under kinetic control, of the reaction product exhibiting the lowest steric interaction in a cyclic CIP TS. In contrast, in the case of the allenyl(methyl)cuprate, the two arrangements leading to *syn* and *anti* products ($\mathbf{TS_{Me}}s2$ and $\mathbf{TS_{Me}}a2$ respectively) are found to be isoergonic (Table 3). Thus, this mechanism cannot account for the experimentally observed *syn* selectivity. This difference of behavior of the same mechanism when changing R_d can be justified simply by looking at the geometry of the TS and more particularly at the length of the forming C···C bond: it is found to be significantly longer for allenyl(methyl)cuprate (2.18 Å in the *anti* arrangement, see Figure 2) than for allenyl(cyano)cuprate (2.08 Å, see Figure 2), thus yielding a smaller energy difference and an absence of selectivity between the two TS $\mathbf{TS_{Me}}s2$ and $\mathbf{TS_{Me}}a2$. As a conclusion, in the case of allenyl(cyano)cuprates, the postulated formation of a nine-membered TS from the Li−CN contact ion pair leading to an *anti* selectivity was confirmed from computational data. In addition, such a mechanism was shown to be nonselective in the case of allenyl(methyl)cuprate, as the more flexible ion-pairing leads to a less compact and less structured TS which does not impose enough steric strain to ensure selectivity.

Density Functional Studies of SSIP Mechanism. In the case of allenyl(methyl)cuprate, another mechanism has to be envisioned, as suggested from experimental data starting from a solvent separated ion pair (Scheme 14, eq 2). This structure can be proposed to be the reactive entity for two reasons: (i) it is suggested by experimental data and (ii) it is the structure obtained when computing a reaction path starting from a structure close to C3 upon coordination of the aldehyde to the lithium. Indeed, as this structure exhibits a coordination of the lithium cation to the allenyl ligand, its reactivity is lowered and no TS could be located exhibiting such an interaction.[35] Reaching a TS thus requires the full de-coordination of the lithium cation, which is triggered by coordination of an additional solvent molecule.[36] Both *cis* and *trans* arrangements of the lithium and copper (and thus of the copper and the aldehyde as activation of the aldehyde requires its coordination to lithium) around the allenyl moiety were investigated, but only mechanisms originating from the *cis* arrangement are reported, as the TSs for the *cis* arrangement are found to be over 3.5 kcal/mol lower in electronic energy than those for the *trans* arrangement. The two TSs leading to *syn* and *anti* products ($\mathbf{TS_{Me}}s3$ and $\mathbf{TS_{Me}}a3$, respectively) could be located. $\mathbf{TS_{ME}}s3$ is found to be favored by nearly 1.5 kcal/mol in Gibbs free energy (Table 3), in good accordance with the experimental results. These two TSs exhibit very different geometrical features: significantly shorter Li···Cu and Li···Me distances are obtained in $\mathbf{TS_{Me}}a3$ (Li···Cu = 4.27 Å and Li···Me = 4.91 Å, see Figure 2, bottom line) than in $\mathbf{TS_{Me}}s3$ (Li···Cu = 4.99 Å and Li···Me = 5.52 Å). The preferred TS is thus consistent with the open structure proposed in Scheme 3, eq 2. The larger Li···Me distance is associated with a larger charge separation and thus a larger dipole moment in $\mathbf{TS_{Me}}s3$. This is in line with the better selectivity observed experimentally in the more polar THF compared to Et_2O and was also confirmed computationally by including the effect of a dielectric medium: when such implicit solvation effects are added (modeling the dielectric parameters of THF), the preference for $\mathbf{TS_{Me}}s3$ increased by nearly 3 kcal/mol ($\Delta(\Delta G^{\ddagger})$ = 4.2 kcal/mol).

Table 3. Gibbs Free Energies (ΔG, kcal/mol, with Respect to the Most Stable Reacting Arrangement) of the CIP and SSIP Reaction Mechanisms (See Scheme 14)[a]

	R_d = CN CIP mechanism		R_d = Me CIP mechanism		R_d = Me SSIP mechanism	
	anti	*syn*	*anti*	*syn*	*anti*	*syn*
associated TS	$\mathbf{TS_{CN}}a2$	$\mathbf{TS_{CN}}s2$	$\mathbf{TS_{Me}}a2$	$\mathbf{TS_{Me}}s2$	$\mathbf{TS_{Me}}a3$	$\mathbf{TS_{Me}}s3$
complex	1.7	0.0	1.1	0.0	1.0	0.0
TS	11.4	12.2	4.5	4.5	2.4	1.0
end	−5.0	−4.7	−11.7	−11.7	−15.5	−10.4

[a] "End" stands for the conformation of the product immediately connected to the TS (not represented). "Complex" stands for reacting arrangement (second column of the mechanisms in Scheme 14, also referred to as a complexation step).

Substituent Effects. These working models are thus fully consistent with experimentally observed selectivities. In addition, they can help to understand the impact of steric hindrance on the outcome of the reaction. In the case of the allenyl(methyl)cuprate, the C···C bond in the TS is significantly longer than for the allenyl(cyano)cuprate (2.27 Å in $\mathbf{TS_{Me}}s3$ vs 2.08 Å in $\mathbf{TS_{CN}}a2$, respectively). The very compact arrangement found for the allenyl(cyano)cuprate is fully consistent with the good level of selectivity observed experimentally with this reactant, even with

nonhindered aldehydes. The short C···C distance results in strong steric interactions between the aldehyde and the allenyl substituent. In strong contrast, the ion pair separation responsible for the selectivity with allenyl(methyl)cuprate is increased with bulky aldehydes, resulting in a stronger effect of steric hindrance on the stereochemical outcome. Moreover, this solvent-separated ion pair structure leads to long Li···R_d distances in the TS, which could account for the small effects of the bulk of R_d (methyl vs *tert*-butyl) on diastereoselectivity.

In summary, theoretical exploration of the structural properties of allenyl(methyl)- and allenyl(cyano)cuprates as well as potential reaction pathways for condensation onto aldehydes have shed further light onto their experimentally observed stereochemical versatility when using THF as solvent. Two original plausible mechanisms have been found: a cyclic nine-membered TS for the allenyl(cyano)cuprate and an open TS for the allenyl(alkyl)cuprate.[37] Interestingly, this latter process was shown computationally to proceed through an overall *cis* arrangement of the lithium and the copper (and thus of the aldehyde since activation of the latest requires its binding to the lithium) with respect to the nucleophilic C^3 carbon plane defined by the C^2-C^3-H atoms (see Figure 3 for numbering). This is totally unexpected and unprecedented since *trans* processes of the aldehyde with respect to the metal center are systematically proposed in all known open TSs.[1,3] Even though it was not proved that conversion of the "dummy" ligand from cyano to methyl reversed the CIP vs SSIP equilibrium in solution, it was clearly shown that the reactive species are modified by this change and that the cyclic and open models can be efficiently used to predict the potential efficiency of novel experimental procedures. Such a spectacular diastereodivergent behavior between two cuprate species is, to the best of our knowledge, a unique example and provides promising perspectives. As the reaction studied above is an efficient and highly selective one-pot approach allowing preparation of both *syn*- and *anti*-homopropargylic alcohols, this methodology might be proposed as a new synthetic tool, provided it can be extended to other substituents on acetylenic and propargylic positions. We thus decided to further explore the scope of the reaction by investigating the influence of the substituents on the acetylenic starting material.

Combined Klein Rearrangement/Transmetalation Reaction. In 1970, Klein and Brenner observed for the first time an exchange reaction between allenic H and Li inside an allenyllithium species[38] (1,3-Li/H shift, see Scheme 15). Combining the versatility of allenylcopper reagents and Klein's 1,3-Li/H shift of 1-aryl-1,2-alkadienyl reagents allows us to further assess the versatility of both regioisomers of allenic cuprates obtained from a single starting material (Scheme 16). We have recently re-examined the formal 1,3-Li/H shift of 1-aryl-1,2-alkadienyl reagents and found that a catalytic amount of *i*-Pr_2NH is sufficient to promote the shift.[39] A combined experimental and theoretical study established that an exchange of protons through the *in situ* formation of a transient allene is the probable mechanism of this transformation (Scheme 15). These results were recently fully confirmed via a similar theoretical study realized by Ma and co-workers.[40] The non-rearranged structure allows evaluating the impact of replacing the TMS group by a phenyl substituent on C^1, whereas the rearranged structure will allow assessing the impact of a phenyl group at the allenic 3 position (C^3).

As allenylcuprate reagents are prepared *in situ* from the corresponding lithium analogues, it should be possible, from a unique precursor **4**, and in a straightforward one-pot procedure, to develop a selective access to *anti*- or *syn*-homopropargylic alcohol **5** or **6** (Scheme 16). From a synthetic point of view, such an approach is interesting because it gives the possibility to obtain specific control of both the regio- and diastereoselectivity of a reaction by simply changing the reaction conditions (nature of the copper reagent and presence, or not, of a catalytic amount of proton donor). For the present study, this methodology allows the preparation of four allenylcuprate analogues, starting from a unique reactant, which avoids the preparation of different starting materials. Indeed, adequate adjunction of *i*-Pr_2NH and a judicious choice of the nature of the copper species give access to all the four possible regio- and diastereoisomers **5** and **6** from **4** with a total regioselectivity and generally high diastereoselectivity (Scheme 16).

As compared to its silyl analogue **3a′**, compound *syn*-**5** is obtained with a significantly improved selectivity (95/5 *syn*/*anti* ratio for **5** and 90/10 for **3a′**, see Table 1, entry 3). The same observation can be made for the *anti* isomers,[44] showing the beneficial effect on the selectivity of a phenyl instead of a silyl substituent in position 1 of the allene (C^1). This result is in line with the increased selectivity previously observed when replacing

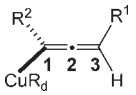
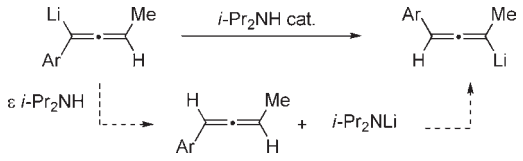
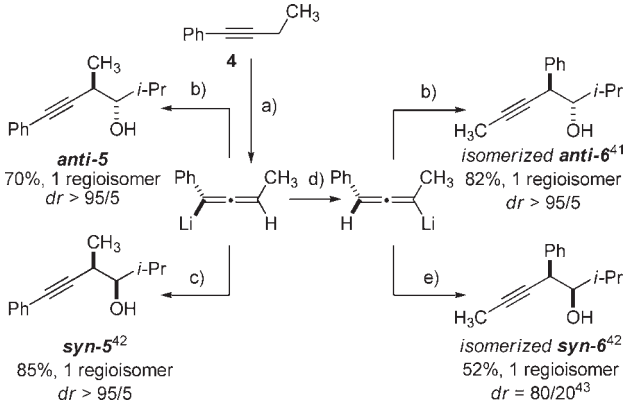


Figure 3. Carbon numbering in allenylcuprate.

Scheme 15. *i*-Pr_2NH-Catalyzed 1,3-Li/H Shift of Aryl-1,2-alkadienyl



Scheme 16. Selective Access to the Four Regio- and Diastereoisomers Resulting from the Reaction of 4 with *i*-PrCHO[a]



[a] Conditions: (a) *s*-BuLi (1.1 equiv), THF, −70 °C; (b) CuCN·2LiBr (1.5 equiv) then *i*-PrCHO (1.1 equiv); (c) CuMe·2LiBr (1.5 equiv) then *i*-PrCHO (1.1 equiv); (d) *i*-$PrNH_2$ (5 mol %), THF, −70 °C to rt; (e) *t*-BuCu·2LiBr (1.5 equiv) then *i*-PrCHO (1.1 equiv). See refs 41−43.

the TMS group by a phenyl or a methyl in the context of the addition of allenyl(cyano)cuprates derived from propargylic ethers or amines onto aldehydes.[5c] This can also be rationalized using the reactivity models described above. With a phenyl substituent instead of a silyl group, a lower inherent stabilization of the negative charge in position 1 of the allenic anion is expected and, as a result, a stronger localization of the negative charge in position 3 in the TS. As such, the forming C···C bond in the TS is expected to be shorter for phenyl substituted species **5** than for its silyl analogues, resulting in a more compact and thus more selective reaction pathway. A good selectivity is also obtained when a methyl stands in position 1 (C^1) in the case of allenyl(cyano)cuprates, as observed upon formation of *anti*-**6**, due to the compact nature of the cyclic TS. In contrast, the effect of the substituent in position 3 of the allene (phenyl group) is expected to be small with this reactant.

The effect of the phenyl group on position 3 in the case of *syn*-**6** is trickier. Acknowledging the preferred allenic form for the cuprate reagent, it is reasonable to envisage a conjugation of the phenyl group with the adjacent π system and the carbon−metal bond. This preferred conformation would dramatically decrease the steric hindrance within the carbon nucleophile environment, even with respect to the Me group used as a model in the theoretical computations, and could explain the lower selectivity for the *syn* process. The positive influence of a *t*-Bu instead of a Me group as R_d copper ligand on the selectivity (80/20 instead of 55/45 *syn*/*anti* ratio) is not fully understood. Interestingly, such a difference in behavior was not detected between Me and *t*-Bu cuprates when a TMS group was in the allenic C^1 position (Table 1, entries 5 and 7). Such a different outcome in the present case stems from the influence of the substituent at the C^1 position (Me instead of TMS group on C^1).[45]

CONCLUSION

We have shown for the first time that controlling the spatial location of the lithium through fine-tuning the nature of the copper's dummy ligands allows an efficient and specific diastereocontrol of the addition of various allenylcuprates onto aldehydes. As such, the lithium cation can be considered the key for these transformations, as it plays at the same time the roles of activator and diastereoselective inductor. The combined high selectivity, efficiency, and versatility of these cuprate reagents paves the way to new one-pot synthetic methodologies, as illustrated by the combined Klein rearrangement/transmetalation procedure described herein.

EXPERIMENTAL AND THEORETICAL DETAILS

Computational Procedure. Full geometry optimizations were systematically conducted with no symmetry restraints using the Gaussian 03 program[46] within the framework of the Density Functional Theory (DFT) using the hybrid B3LYP exchange-correlation functional[47] and the 6-31++G** basis set for all atoms as implemented in the Gaussian program. The electronic plus nuclear energy obtained from SCF and optimization procedures is referred to as "energy" and denoted *E* in the text. As such, $\Delta E_{X/Y} = E(X) - E(Y)$. Frequencies were evaluated within the harmonic approximation and used unscaled to compute Gibbs free energy (*G*) at 183 K using the standard protocol implemented in Gaussian. Solvation at the lithium cation is ensured via an explicit model by including two or three dimethyl ether molecules (as a model for THF) coordinated to the lithium (no coordination of solvent molecules to the copper could be obtained). For key structures, the importance of adding an implicit solvation was examined using single-point computations on the gas-phase optimized geometry. These results are reported only when there is a significant difference between gas-phase structures. For these computations, the PCM uses the dielectric constant implemented for THF ($\varepsilon_R = 7.58$)[48] and the default implemented in Gaussian 03, except for atomic radii, where the BONDI values are used for all atoms.

General Considerations. Experiments were carried out under a dry argon atmosphere. All glassware was dried at 120 °C and assembled while hot under a stream of argon. All moisture-sensitive reactants were handled under a nitrogen atmosphere. Low-temperature experiments were carried out by cooling a three-necked round-bottom flask with an ether/acetone (−80/−90 °C) bath, frozen with liquid nitrogen. The flask was equipped with an internal thermometer, an argon inlet, and a septum cap. Tetrahydrofuran was distilled from sodium−benzophenone ketyl. Column chromatography was pe*R*formed over silica gel Si 0.015−0.040 mesh. Melting points are uncorrected. IR data were recorded on a Perkin-Elmer Spectrum 1000 instrument. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz, both in $CDCl_3$ as solvent on a Bruker Ultra Shield 400 spectrometer. Chemical shifts are reported in ppm (reference TMS for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR). Microanalyses were pe*R*formed by ICSN-CNRS, Gif-sur-Yvette, France. Exact masses were determined by CCSM, Université Claude Bernard Lyon 1, France. Compounds **3a**,[5d] **3a′**,[49] **3c**,[5d] **3d**,[5d] and *anti*-**5**[50] have already been described.

General Procedure A for the Addition of Allenyl(methyl) cuprates Reagents to Aldehydes. Solution A: A solution of CuI (3 mmol, 571 mg) and LiBr (6 mmol, 521 mg) in THF (10 mL) cooled to −70 °C was treated dropwise with 1.6 M MeLi in Et_2O (3 mmol, 1.9 mL). The mixture was allowed to reach 0 °C over 30 min and cooled to −80 °C. **Solution B**: A solution of 1-(trimethylsilyl)dec-1-yne (2 mmol, 420 mg) or 1-(trimethylsilyl)but-1-yne (2 mmol, 252 mg) in THF (15 mL) cooled to −90 °C was treated dropwise with 1.3 M *s*-BuLi in cyclohexane/hexane (2.05 mmol, 1.6 mL), maintaining the internal temperature below −88 °C. The mixture was warmed to 0 °C, stirred 1 h at that temperature, and cooled to −80 °C. Solution B was then added dropwise via a cannula to solution A at −80 °C. The mixture was warmed to −20 °C and stirred an additional 30 min at that temperature. The resulting solution was cooled to −90 °C, and a solution of the aldehyde (2.1 mmol) in THF (10 mL) was added over 1 h via a syringe pump. After an additional 1 h at −90 °C, the reaction was quenched by the addition of an aqueous NH_4Cl/NH_4OH (2:1) solution and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and filtered off. The solvents were removed in vacuo, and the product was then subjected to flash chromatography (FC) on SiO_2 using the appropriate pentane/Et_2O eluant.

General Procedure B for the Addition of Allenyl(*tert*-butyl)cuprate Reagents to Aldehydes. Solution A: A solution of CuI (3 mmol, 571 mg) and LiBr (6 mmol, 521 mg) in THF (10 mL) cooled to −85 °C was treated dropwise with 1.6 M *t*-BuLi in pentane (3 mmol, 1.9 mL). The mixture was stirred 10 min at −80 °C to give a pale gray suspension. **Solution B**: A solution of 1-(trimethylsilyl)dec-1-yne (2 mmol, 420 mg) or 1-(trimethylsilyl)but-1-yne (2 mmol, 252 mg) in THF (15 mL) cooled to −90 °C was treated dropwise with 1.3 M *s*-BuLi in cyclohexane/hexane (2.05 mmol, 1.6 mL), maintaining the internal temperature below −88 °C. The mixture was warmed to 0 °C, stirred 1 h at that temperature, and cooled to −90 °C. Solution B was then added dropwise via a cannula to the solution A at −90 °C. The resulting suspension was stirred 30 min, maintaining the internal temperature below −80 °C. A solution of the aldehyde (2.1 mmol) in THF (10 mL) was added at −90 °C over 1 h via a syringe pump. After an additional 1 h at −90 °C, the reaction was quenched by the addition of an aqueous NH_4Cl/NH_4OH (2:1) solution and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with water and brine,

dried over magnesium sulfate, and filtered off. The solvents were removed in vacuo, and the product was then subjected to FC on SiO_2 using the appropriate pentane/Et_2O eluant.

***syn*-2-Methyl-4-phenylhept-5-yn-3-ol (3b).** This compound was prepared according to the general procedure A, using 1-(trimethylsilyl)dec-1-yne (**1a**, 2 mmol, 420 mg) and pivalaldehyde (**2b**, 2.1 mmol, 0.228 mL). The diastereoselectivity of the reaction was determined by ^{1}H NMR of the crude mixture to be >95:5 based on the chemical shifts of propargylic (δ = 3.41) and homopropargylic protons (δ = 2.57). Purification by FC (pentane/Et_2O 98:2, R_f = 0.3) gave **3b** (473 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.41 (dd, J = 4.5, 5.6 Hz, 1H); 2.57 (ddd, J = 3.8, 6.0, 9.8 Hz, 1H); 1.74 (d, J = 4.5 Hz, 1H); 1.69−1.30 (m, 12H); 1.02 (s, 9H); 0.90 (t, J = 6.6 Hz, 3H); 0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.7, 87.3, 80.5, 35.9, 35.8, 31.8, 30.3, 29.4, 29.2, 27.2, 26.9, 22.6, 14.1, 0.0. IR (neat): ν 3462 (br), 2956, 2166, 1467, 1365, 1249, 1005, 846 cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{36}OSi$ $[M + H]^+$, 297.2614; found, 297.2614.

***anti*-2,4-Dimethyl-6-phenylhex-5-yn-3-ol (*anti*-5).** A solution of 1-phenyl-1-butyne (2 mmol, 284 mL) in THF (15 mL) cooled to −90 °C was treated dropwise with 1.3 M *s*-BuLi in cyclohexane/hexane (2.05 mmol, 1.6 mL), maintaining the internal temperature below −88 °C. The mixture was warmed to −40 °C, stirred 1 h at that temperature, and cooled to −80 °C. A solution of CuCN (3 mmol, 270 mg) and LiBr (6 mmol, 521 mg) in THF (10 mL) was then added dropwise, the reaction was stirred an additional 30 min at −80 °C, and isobutyraldehyde (2.1 mmol, 0.2 mL) was added dropwise. The reaction mixture was allowed to warm to −60 °C over 1 h, stirred an additional 1 h at that temperature, quenched by the addition of aqueous NH_4Cl/NH_4OH (2/1) solution, and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and filtered off, and the solvents were removed in vacuo. The regio- and diastereoselectivity of the reaction were determined by ^{1}H NMR of the crude mixture to be >95:5 based on the chemical shifts of propargylic (δ = 3.12) and homopropargylic protons (δ = 2.93). Purification by FC (pentane/Et_2O 85:15, R_f = 0.35) gave *anti*-**5** (283 mg, 70%) as a colorless oil, the spectra of which are in good accordance with those previously reported.[50]

***syn*-2,4-Dimethyl-6-phenylhex-5-yn-3-ol (*syn*-5).** **Solution A**: A solution of CuI (3 mmol, 571 mg) and LiBr (6 mmol, 521 mg) in THF (10 mL) cooled to −70 °C was treated dropwise with 1.6 M MeLi in Et_2O (3 mmol, 1.9 mL). The mixture was allowed to reach 0 °C over 30 min and cooled to −80 °C. **Solution B**: A solution of 1-phenyl-1-butyne (2 mmol, 284 mL) in THF (15 mL) cooled to −90 °C was treated dropwise with 1.3 M *s*-BuLi in cyclohexane/hexane (2.05 mmol, 1.6 mL), maintaining the internal temperature below −88 °C. The mixture was warmed to −40 °C, stirred 1 h at that temperature, and cooled to −80 °C. Solution B was then added dropwise via a cannula to solution A at −80 °C. The mixture was warmed to −20 °C and stirred an additional 30 min at this temperature. The resulting solution was cooled to −60 °C, and a solution of isobutyraldehyde (2.1 mmol, 0.2 mL) in THF (10 mL) was added over 1 h via a syringe pump. After an additional 1 h at −40 °C, the reaction was quenched by the addition of an aqueous NH_4Cl/NH_4OH (2:1) solution and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and filtered off, and the solvent was removed in vacuo. The regio- and diastereoselectivity of the reaction were determined by ^{1}H NMR of the crude mixture to be >95:5 based on the chemical shifts of propargylic (δ = 3.44) and homopropargylic protons (δ = 2.85). Purification by FC (pentane/Et_2O 90:10, R_f = 0.30) gave ***syn*-5** (343 mg, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.28 (m, 5H); 3.44 (dd, J = 5.7, 10.6 Hz, 1H); 2.85 (p, J = 6.8 Hz, 1H); 2.10−2.02 (m, 1H); 1.77−1.75 (m, 1H); 1.32 (d, J = 6.9 Hz, 3H); 1.01 (dd, J = 6.8, 14.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.6, 128.2, 127.8, 123.5, 92.0, 82.3, 79.2, 31.0, 30.4, 19.7, 16.8, 15.7. IR (neat): ν 3339 (br), 2959, 2933, 1489, 1457, 1144, 755, 690 cm^{-1}. Elemental analysis calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97; O, 7.91. Found: C, 83.04; H, 9.06; O, 7.81.

***anti*-2-Methyl-4-phenylhept-5-yn-3-ol (*anti*-6).** A solution of 1-phenyl-1-butyne (2 mmol, 284 mL) in THF (15 mL) cooled to −90 °C was treated dropwise with 1.3 M *s*-BuLi in cyclohexane/hexane (2.05 mmol, 1.6 mL), maintaining the internal temperature below −88 °C. The mixture was warmed to −40 °C, stirred 1 h at that temperature, and cooled to −80 °C. Freshly distilled diisopropylamine (0.1 mmol, 0.014 mL) was then added, and the mixture was warmed to room temperature, stirred 30 min, and cooled to −80 °C. A solution of CuCN (3 mmol, 270 mg) and LiBr (6 mmol, 521 mg) in THF (10 mL) was then added dropwise, the reaction was stirred an additional 30 min at −80 °C, and isobutyraldehyde (2.1 mmol, 0.2 mL) was slowly added. The reaction mixture was allowed to warm to −60 °C over 1 h, stirred an additional 1 h at that temperature, quenched by the addition of aqueous NH_4Cl/NH_4OH (2/1) solution, and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and filtered off, and the solvents were removed in vacuo. The regio- and diastereoselectivity of the reaction were determined by ^{1}H NMR of the crude mixture to be >95:5 based on the chemical shifts of propargylic (δ = 3.87) and homopropargylic protons (δ = 3.36). Purification by FC (pentane/Et_2O 88:12, R_f = 0.35) gave *anti*-**6** (331 mg, 82%) as a colorless solid, mp 37−38 °C (recrystallized from pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.25 (m, 5H); 3.87 (dq, J = 2.3, 4.8 Hz, 1H); 3.36 (dd, J = 4.8, 10.5 Hz, 1H); 1.93 (d, J = 2.4 Hz, 3H); 1.81 (sextd, J = 6.8, 13.5 Hz, 1H); 1.03 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 128.6, 128.1, 127.0, 80.8, 80.5, 77.0, 42.8, 31.3, 19.8, 17.6, 3.8. IR (neat): ν 3456 (br), 2959, 2918, 1491, 1452, 1044, 698 cm^{-1}. Elemental analysis calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97; O, 7.91. Found: C, 82.91; H, 8.93; O, 8.08.[41]

***syn*-2-Methyl-4-phenylhept-5-yn-3-ol (*syn*-6).** **Solution A**: A solution of CuI (3 mmol, 571 mg) and LiBr (6 mmol, 521 mg) in THF (10 mL) cooled to −85 °C was treated dropwise with 1.6 M *t*-BuLi in pentane (3 mmol, 1.9 mL). The mixture was stirred 10 min at −80 °C to give a pale gray suspension. **Solution B**: A solution of 1-phenyl-1-butyne (2 mmol, 284 mL) in THF (15 mL) cooled to −90 °C was treated dropwise with 1.3 M *s*-BuLi in cyclohexane/hexane (2.05 mmol, 1.6 mL), maintaining the internal temperature below −88 °C. The mixture was warmed to −40 °C, stirred 1 h at that temperature, and cooled to −80 °C. Diisopropylamine (0.1 mmol, 0.014 mL) was then added, and the mixture was warmed to room temperature, stirred 30 min, and cooled to −80 °C. Solution B was then added dropwise via a cannula to solution A at −80 °C. The mixture was stirred an additional 30 min at that temperature, and a solution of the isobutyraldehyde (2.1 mmol, 0.2 mL) in THF (10 mL) was added over 1 h via a syringe pump. After an additional 1 h at −40 °C, the reaction was quenched by the addition of an aqueous NH_4Cl/NH_4OH (2:1) solution and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and filtered off, and the solvent was removed in vacuo. The regio- and diastereoselectivity of the reaction were determined by ^{1}H NMR of the crude mixture to be >95:5 for the regioselectivity and 80:20 for the diastereoselectivity based on the chemical shifts of propargylic (δ = 3.62) and homopropargylic protons (δ = 3.56). Purification by FC (pentane/Et_2O 95:5, R_f = 0.35) gave *syn*-**6** (210 mg, 52%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.26 (m, 5H); 3.64−3.60 (m, 1H); 3.58−3.54 (m, 1H); 2.15 (d sept., J = 3.7, 6.8 Hz, 1H); 1.86 (d, J = 2.3 Hz, 3H); 1.49 (d, J = 3.8 Hz, 1H); 1.01 (dd, J = 6.8, 12.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 128.7, 128.6, 127.3, 79.6, 79.5, 78.7, 43.0, 30.2, 20.4, 15.2, 3.7. IR (neat): ν 3468 (br), 2961, 2872, 1493, 1452, 1045, 996, 746, 698 cm^{-1}. Elemental analysis calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97; O, 7.91. Found: C, 82.94; H, 8.89; O, 7.75.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C spectra of **3b**, *anti*-**5**, *syn*-**5**, *anti*-**6**, and *syn*-**6**; complete ref 46; and additional computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(41) Crystallographic data for the structural analysis of *anti*-**6** have been deposited with the Cambridge Crystallographic Data Center, no. CCDC 720316.

(42) Structure assigned by comparison of spectral data with *anti*-**5** and *anti*-**6**.

(43) The use of allenyl(methyl)cuprate gave a lower 55/45 *syn*/*anti* selectivity.

(44) Addition of the allenyl(cyano)cuprate obtained from the silyl analogue of **1a** on isobutyraldehyde gives a 8/92 *syn*/*anti* ratio, see ref 5d.

(45) A possible explanation: the SiH_3 substituent used in the computational model was shown[5c] to delocalize part of the Cu−C^1 bond on the SiH_3 moiety, resulting in a larger delocalization of the negative charge of the cuprate. No such delocalization can take place in the presence of a Me substituent at C^1. The Li···cuprate interaction in $\mathbf{TS_{Me}}a\mathbf{3}$, characterized by the shorter Li···Cu distance with respect to $\mathbf{TS_{Me}}s\mathbf{3}$, is thus reinforced when changing TMS to a Me substituent on C^1, making the *syn* selectivity smaller. Moving from allenyl(methyl)cuprate to allenyl(butyl)cuprate induces steric constraint in the more compact *trans* structure, and this would contribute to re-establishing the *syn* selectivity.

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