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Stereo-controlled *anti*-hydromagnesiation of aryl alkynes by magnesium hydrides†

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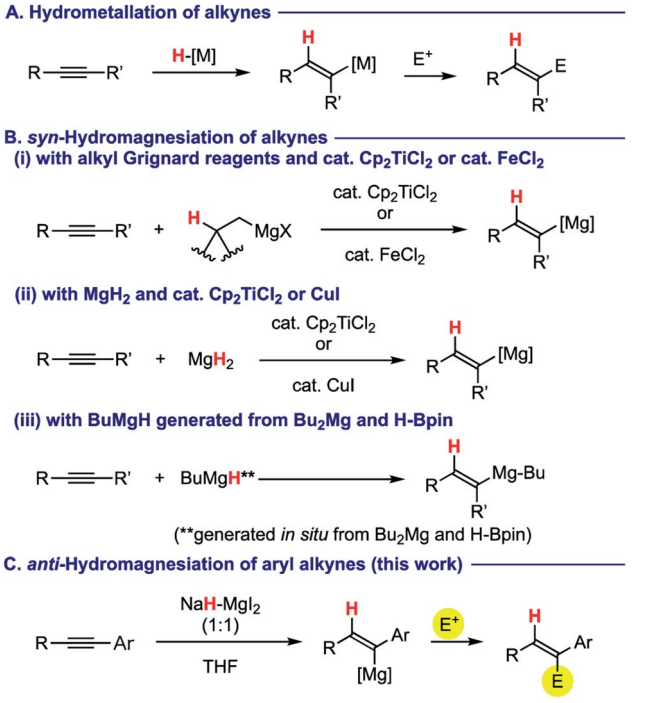
A concise protocol for *anti*-hydromagnesiation of aryl alkynes was established using 1 : 1 molar combination of sodium hydride (NaH) and magnesium iodide (MgI_2) without the aid of any transition metal catalysts. The resulting alkenylmagnesium intermediates could be trapped with a series of electrophiles, thus providing facile accesses to stereochemically well-defined functionalized alkenes. Mechanistic studies by experimental and theoretical approaches imply that polar hydride addition from magnesium hydride (MgH_2) is responsible for the process.

Introduction

Stereo-controlled construction of substituted alkenes is one of the most fundamental yet important processes in synthetic chemistry.[1] For this purpose, hydrometallation of readily available alkynes[2] has been investigated as a powerful and promising tactic of choice (Scheme 1A). Among various metals involved, use of a magnesium element for hydrometallation of alkynes (*i.e.* hydromagnesiation) allows for direct preparation of alkenylmagnesium species, which is very useful for a sequential bond-forming process with various electrophiles,[3] thus providing facile access to multi-substituted alkenes. For this purpose, alkyl Grignard reagents having β-hydrogen atom(s) have been used as a hydrogen source in the presence of a catalytic amount of titanocene dichloride (Cp_2TiCl_2)[4] or iron(II) chloride ($FeCl_2$),[5] in which metal hydride species (H–M: M = Ti or Fe), generated *via* β-hydride elimination from the corresponding alkylmetal intermediates, undergo *syn*-hydrometallation onto alkynes (Scheme 1B-i). Ashby demonstrated *syn*-hydromagnesiation of alkynes using magnesium hydride (MgH_2) in the presence of Cp_2TiCl_2 (ref. 6) or CuI[7] as a catalyst (Scheme 1B-ii). Very recently, Cavallo and Rueping revealed in their magnesium-catalysed hydroboration of alkynes that butylmagnesium hydride generated *in situ* from dibutylmagnesium and pinacolborane induces *syn*-hydromagnesiation (Scheme 1B-iii).[8] Moreover, Mahon and Hill showed that structurally well-defined dimeric β-diketoiminato magnesium hydrides undergo *syn*-hydromagnesiation onto diphenylacetylene.[9] As such, the stereochemical mode taking place in all the cases above is *syn*-hydromagnesiation. Herein, we report *anti*-hydromagnesiation of aryl alkynes using 1 : 1 molar combination of sodium hydride (NaH) and magnesium iodide (MgI_2), which does not need the aid of any transition metal catalyst (Scheme 1C). The resulting alkenylmagnesium species could be functionalized with a series of electrophiles, to



Scheme 1 Hydrometallation of alkynes.

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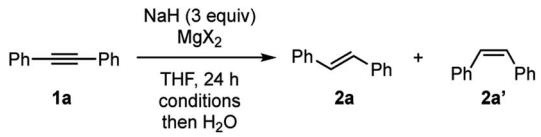
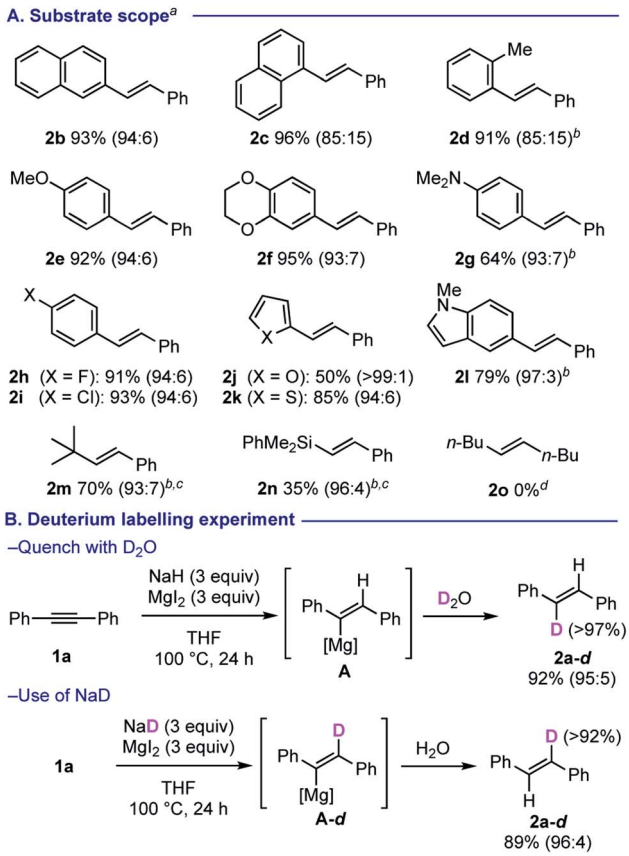
Table 1 Optimization of reaction conditions[a]



Entry	MgX_2 (equiv.)	Temp [°C]	Conv.[b] [%]	Yield[b] [%] 2a	2a′
1	MgI_2 (1.5)	80	60	38	1
2	MgI_2 (2)	80	62	40	2
3	MgI_2 (3)	80	73	68	4
4	MgI_2 (3)	100	>99	93[c]	6
5	$MgBr_2$ (3)	100	99	93[d]	5
6	$MgCl_2$ (3)	100	94	89	4

[a] All the reactions were conducted using 0.5 mmol of **1a** in THF (2.5 mL). [b] GC yields with *n*-dodecane as an internal standard. [c] Isolated yield was 96% as a 94 : 6 *trans*/*cis*-mixture. [d] Isolated yield was 93% as a 94 : 6 *trans*/*cis*-mixture.

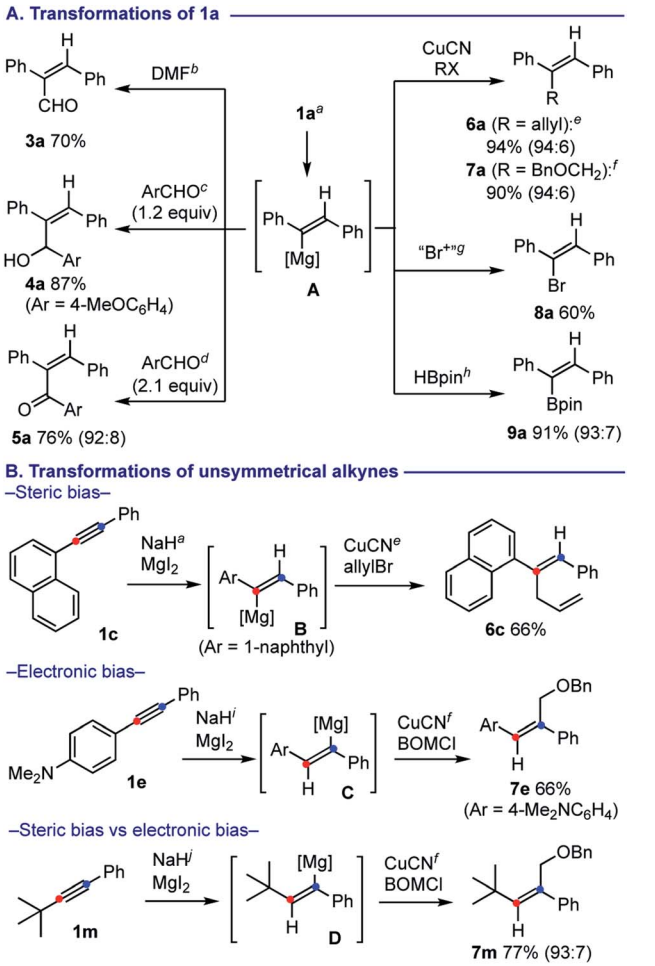


Scheme 2 *Trans*-selective reduction of aryl alkynes **1**. [a] Unless otherwise stated, the reactions were conducted using 0.5 mmol of alkynes **1** with NaH (3 equiv.) and MgI_2 (3 equiv.) THF (2.5 mL) at 100 °C. The *trans*/*cis* ratio was indicated in the parentheses. [b] The reactions were performed using NaH (5 equiv.) and MgI_2 (5 equiv.). [c] The reaction was performed at 120 °C. [d] Recovery of 5-decyne (**1o**) in >90% yield.

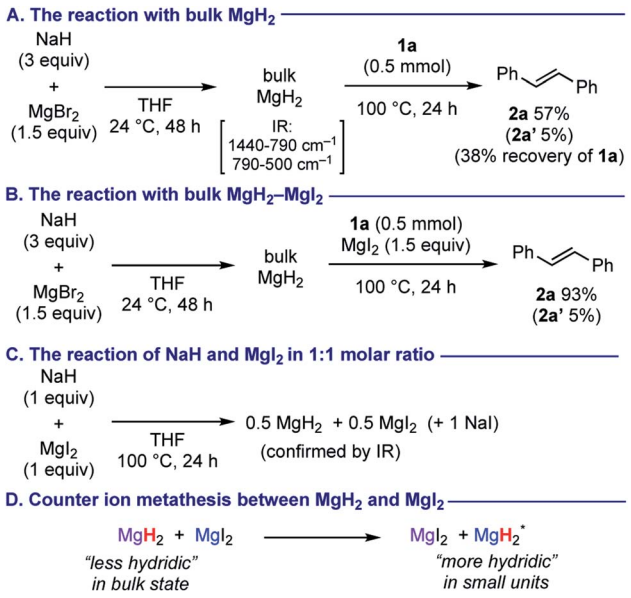
provide stereochemically well-defined substituted alkenes. Discovery, optimization, and substrate scope as well as preliminary mechanistic proposals are described.

Results and discussion

Our group has recently uncovered unprecedented hydride reduction of polar π-electrophiles such as nitriles and amides by NaH in the presence of dissolving iodide salts such as sodium iodide (NaI),[10] where counter ion metathesis between bulk NaH and NaI is supposed to be a key to activate NaH.[11,12] We also found NaH could be used as a hydride source for facile generation of main group metal hydrides. For example, we



Scheme 3 Functionalization with various electrophiles. [a] The reactions were conducted using 0.5 mmol of **1** with NaH (3 equiv.) and MgI_2 (3 equiv.) in THF (2.5 mL) at 100 °C. [b] DMF (4 equiv.), 0–24 °C, 6 h. Minor isomer **3a′** was isolated in 9% yield. [c] 4-$MeOC_6H_4CHO$ (1.2 equiv.), 0 °C, 3.5 h. Minor isomer **4a′** was isolated in 7% yield. [d] 4-$MeOC_6H_4CHO$ (2.1 equiv.), 0–24 °C, 15 h. [e] CuCN·2LiCl (10 mol%), allylbromide (4 equiv.), 0 °C, 3 h. [f] CuCN·2LiCl (10 mol%), BOMCl (1.2 equiv.), 0 °C, 2 h. [g] $BrCl_2CCCl_2Br$ (2.2 equiv.), 0 °C, 30 min. [h] HBpin (1.1 equiv.), 0–24 °C, 2.5 h. [i] The reaction was conducted using 0.5 mmol of **1e** with NaH (5 equiv.) and MgI_2 (5 equiv.) in THF (2.5 mL) at 100 °C. [j] The reaction was conducted using 0.5 mmol of **1m** with NaH (5 equiv.) and MgI_2 (5 equiv.) in THF (2.5 mL) at 120 °C. BOM = benzyloxymethyl.



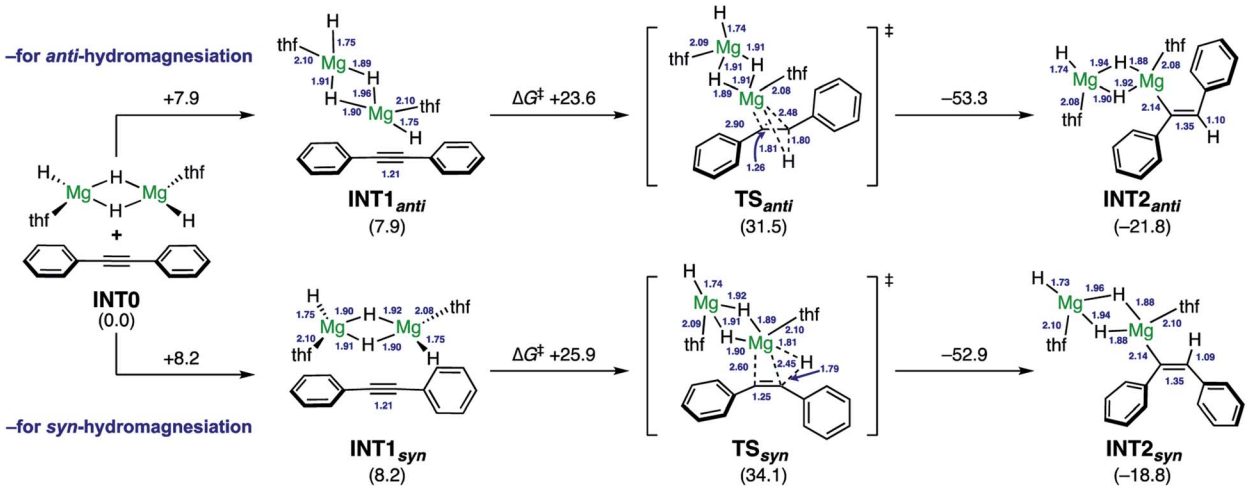
Scheme 4 Elucidation of active hydride species.

demonstrated controlled reduction of carboxamides into alcohols or amines by a combination of NaH with ZnI_2 or $ZnCl_2$.[13,14] Based on these findings, our current attention is directed to seek for reductive molecular transformations of non-polar π-systems such as alkynes by main group metal hydrides.

We embarked on our investigation of chemical reactivity of various main group metal hydrides, derived from NaH and the corresponding metal halides, toward reduction diphenylacetylene (**1a**). Among main group metal iodides examined for the optimization (see the ESI† for details), we found that a combination of NaH and MgI_2 shows a promising reactivity toward semi-hydrogenation of **1a** to *trans*-stilbene (**2a**) (Table 1).[15] Use of NaH and MgI_2 in 1 : 1 molar ratio resulted in the best outcome for the formation of **2a** (entries 1–3). Full conversion of **1a** was attained at 100 °C as the reaction temperature, providing stilbene **2a** in 96% yield with high *trans*-selectivity (*trans* : *cis* = 94 : 6) (entry 4). Interestingly, the reactions with $MgBr_2$ and $MgCl_2$ gave comparable results (entries 5 and 6),[16] implying that a common reactive magnesium hydride species is generated and responsible for the present reduction of **1a** (*vide infra*). It should be noted that the reactions with other alkaline earth metal iodides based on Ca, Sr, and Ba were not optimal for this transformation.

Having optimized the reaction conditions in hands (Table 1, entry 4), we next investigated the substrate scope of alkynes for their *trans*-semi-reduction (Scheme 2A). Various diarylalkynes **1b–1g** could be converted selectively into the corresponding *trans*-alkenes **2b–2g** in good yields in general. Stereoselectivity was slightly dropped when a sterically bulky aryl group is installed onto the substrates (for **2c** and **2d**), while the electronic nature of the aryl substituents does not affect much onto the stereoselectivity (**2e–2g** *vs.* **2h–2i**). Alkynes having heteroaryl motifs such as furan, thiophene, and indole could also be reduced in efficient manners (for **2j–2l**). Reduction of 1-phenyl-2-*t*-butylacetylene (**1m**) afforded the corresponding *trans*-alkene **2m** in good yield, while that of 1-phenyl-2-phenyldimethylsilylacetylene (**1n**) resulted in formation of alkenyl silane **2n** in only moderate yield. However, this method was found not applicable for reduction of dialkyl alkynes such as 5-decyne (**1o**). Deuterium labeling experiments using D_2O (for quenching) and NaD unambiguously suggested the presence of alkenylmagnesium species **A** as an intermediate, that is formed *via anti*-hydromagnesiation (Scheme 2B).

The alkenylmagnesium **A** could be further functionalized by subsequent treatment with various electrophiles (Scheme 3A).[17] Formylation with *N*,*N*-dimethylformamide (DMF) proceeded smoothly to form 2,3-diphenylacrylaldehyde (**3a**) in 70% yield. Addition of 1.2 equiv. of 4-anisaldehyde afforded allylalcohol **4a** in 87% yield, whereas use of 2.1 equiv. of 4-anisaldehyde resulted in Oppenauer-type oxidation[18] to form α,β-unsaturated ketone **5a** in 76% yield. Allylation with allylbromide was



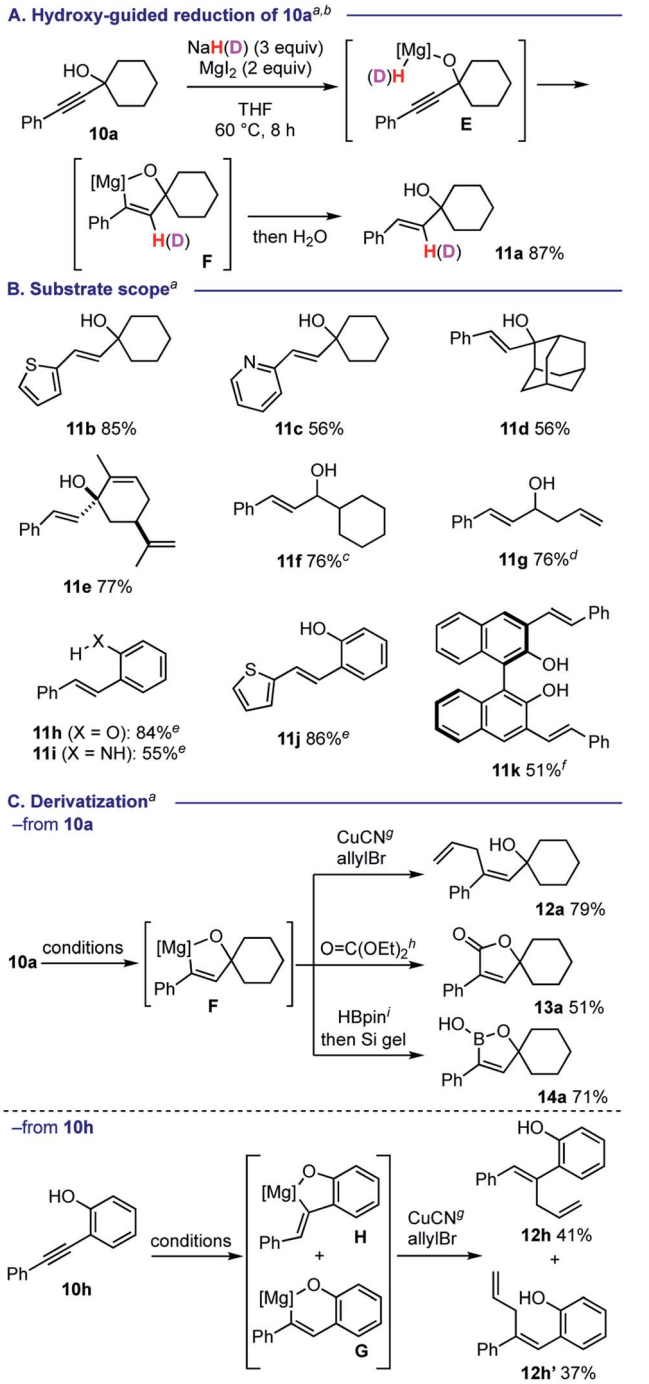
Scheme 5 DFT calculations for model reactions of diphenylacetylene with MgH_2·thf dimeric species. Energy changes and bond lengths at the ωB97XD/6-311++G**/SMD(THF)//ωB97XD/6-31++G** level of theory are shown in kcal mol^{-1} and Å, respectively. thf = tetrahydrofuran.

facilitated by a catalytic amount (10 mol%) of CuCN·2LiCl[19] to afford skipped diene **6a** in 94% yield. Similarly, installation of a benzyloxymethyl (BOM) unit was achieved for synthesis of **7a** using BOMCl. Use of 1,2-dibromo-1,1,2,2-tetrachloroethane allowed for smooth bromination of **A** to form alkenyl bromide **8a**. Borylation of **A** could be achieved with pinacolborane by following the Singaram's protocol,[20] affording alkenylboronic ester **9a** in 91% yield.

We next questioned how the steric and electronic bias could affect the regioselectivity on the hydromagnesiation of unsymmetrical aryl alkynes (Scheme 3B). The reaction of **1c** having a sterically bulkier 1-naphthyl group underwent selective hydromagnesiation to form alkenylmagnesium **B** with installation of a hydride at the less hindered distal carbon (marked in blue) as a major form, that could be trapped by subsequent allylation to provide **6c** in 66% yield.[21] On the other hand, hydromagnesiation of **1e** having an electron-rich 4-dimethylaminophenyl group resulted in installation of hydride on the proximal carbon (marked in red) to generate alkenylmagnesium **C**, that was functionalized with BOMCl to provide **7e** in 66% yield. Hydromagnesiation of 1-phenyl-2-*t*-butylacetylene (**1m**) occurred in regioselective manner, where hydride attack was observed at the β-carbon (marked in red) to the phenyl group, while the side was sterically shielded by the *t*-Bu group. The resulting alkenylmagnesium **D** could be further transformed into BOM adduct **7m** in 77% yield.

To elucidate the active hydride species responsible for the present *anti*-hydromagnesiation of alkynes, we conducted several control experiments (Scheme 4 and see the ESI†). Ashby reported preparation of magnesium hydride MgH_2 in bulk state by treatment of $MgBr_2$ with 2 equiv. of NaH in THF at room temperature (in quantitative yield together with the formation of inert sodium bromide).[22,23] We observed that the reaction of alkyne **1a** with bulk MgH_2, prepared from 3 equiv. of NaH and 1.5 equiv. of $MgBr_2$ by following the Ashby's protocol, resulted in selective formation of *trans*-stilbene (**2a**) despite poor conversion of **1a** (Scheme 4A). On the other hand, treatment of **1a** with bulk MgH_2 in the presence of MgI_2 (1.5 equiv.) greatly enhanced the conversion of **1a**, providing almost the same outcome with that in the optimized reaction conditions (Scheme 4B). The IR spectrum of the mixture obtained from the reaction of NaH and MgI_2 in 1 : 1 molar ratio showed the presence of only MgH_2 and MgI_2 (NaI is transparent in the IR window) (Scheme 4C). We reasoned that while bulk MgH_2 itself is less hydridic due to its polymerized structure with high lattice energy,[24] synergistic cooperation between bulk MgH_2 and MgI_2 through counter ion metathesis allows for freshly generating more hydridic MgH_2 probably of smaller units (Scheme 4D), that is the key for the success in use of NaH and MgI_2 in 1 : 1 molar ratio for the efficient *anti*-hydromagnesiation.

The DFT calculations for the reactions of diphenylacetylene (**1a**) with a MgH_2 dimer as the model of activated $(MgH_2)_n$ species were thus carried out at the ωB97XD/6-311++G**/SMD(THF)//ωB97XD/6-31++G** level of theory (Scheme 5). From **INT1**$_{anti}$, the reduction of diphenylacetylene smoothly proceeded *via* **TS**$_{anti}$ ($\Delta G^{\ddagger}$ +23.6 kcal mol^{-1}), in the manner of *anti*-hydromagnesiation to afford alkenylmagnesium species **INT2**$_{anti}$. In this event, the hydride in the same plane as one of the benzene rings attacks on the proximal alkyne carbon center and, the magnesium cation successively shifts to the distal



Scheme 6 Guided reduction. [a] The reactions were conducted using 0.5 mmol of **10** with NaH (3 equiv.) and MgI_2 (2 equiv.) THF (2.5 mL) at 60 °C. [b] The reaction with NaD installed a deuterium on the β-styryl moiety in 93% incorporation rate (see the ESI† for details). [c] *Trans* : *cis* = 99 : 1. [d] **11g** was isolated as its TBS ether. See the ESI† for details. [e] The alkyne reduction was conducted at 80 °C. [f] The alkyne reduction was conducted using NaH (6 equiv.) and MgI_2 (4 equiv.) at 100 °C. [g] CuCN·2LiCl (10 mol%), allylbromide (4 equiv.), 0 °C, 2 h. [h] Diethyl carbonate (4 equiv.), 40 °C, 15 h. [i] HBpin (1.1 equiv.), 0–24 °C, 0.5 h then treatment with Si gel.

alkyne carbon, indicating the polar hydride transfer mechanism. Thus, the steric and electronic bias of the aromatic ring should result in profound effects on the regioselectivity (*i.e.* Scheme 3B). Further investigations led to find the *syn*-reduction pathway. In $\mathbf{TS}_{syn}$, diphenylacetylene is distorted, where two phenyl rings are almost perpendicular (the dihedral angle is *ca.* 84°). Accordingly, $\mathbf{TS}_{syn}$ was located 2.6 kcal mol^{-1} higher than $\mathbf{TS}_{anti}$. These computed results well corroborated the reducing ability of the NaH–MgI_2 system for the *anti*-selective hydromagnesiation.[25]

We observed that the reaction of propargyl alcohol **10a** with 3 equiv. of NaH[26] and 2 equiv. of MgI_2 proceeded smoothly at 60 °C, affording *trans*-alkene **11a** as a single isomer in 87% yield (Scheme 6A). Based on the deuterium labelling experiments using NaD and D_2O (Scheme 6A for use of NaD in the reduction of **10a**. See the ESI† for details), we proposed that the process is triggered by the formation of alkoxymagnesium hydride **E**, that mediates hydromagnesiation to afford 5-membered magnesiocycle **F**. This hydroxy-guided approach[27] allowed for *trans*-semi-reduction of various propargylic alcohols **10b–10g** into the corresponding allylic alcohols **11b–11g** (Scheme 6B). Heteroaromatic motifs such as 2-thienyl and 2-pyridyl groups were compatible with the process (for **11b** and **11c**). Sterically more hindered substrates based on adamantane (for **10d**) and derived from (*R*)-carvone (for **10e**) generated homoallylic alcohols **11d** and **11e** in 56% and 77% yields, respectively. Secondary propargylic alcohols **10f** and **10g** could also be smoothly reduced. Formation of **11e** and **11g** kept alkenyl moieties intact, suggesting that the present protocol is selective in the hydromagnesiation of alkynes. Phenol and aniline moieties were also capable in guiding *trans*-semi-reduction of alkynes for providing the corresponding **11h–11k** in good to moderate yields.

The 5-membered magnesiocycle intermediate **F** could be further functionalized by CuCN-catalyzed allylation to form skipped diene **12a** in good yield (Scheme 6C). Treatment of **F** with diethyl carbonate allowed for construction of lactone **13a**. Furthermore, the reaction with pinacolborane followed by workup with Si gel resulted in formation of 1,5-dihydro-1,2-oxaborole **14a**. On the other hand, we found that the reaction of 2-(phenylethynyl)phenol (**10h**) likely involves a mixture of 6-membered magnesiocycle **G** and 5-membered one **H**, which could be trapped under CuCN-catalyzed allylation reaction conditions to afford skipped dienes **12h** (41% yield) and **12h′** (37% yield), respectively.

Conclusions

In conclusion, we have developed a concise protocol for *anti*-hydromagnesiation of aryl alkynes that operates with the magnesium hydride species derived from NaH and MgI_2 under transition-metal free conditions. Subsequent treatment of the resulting alkenylmagnesium intermediates with various electrophiles allowed for the synthesis of stereochemically defined tri-substituted alkenes. Efforts are currently underway to apply the NaH–MgI_2 system for reductive functionalization of other π-conjugate systems.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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