A new manifold for the Morita reaction: diene synthesis from simple aldehydes and acrylates/acrylonitrile mediated by phosphines†

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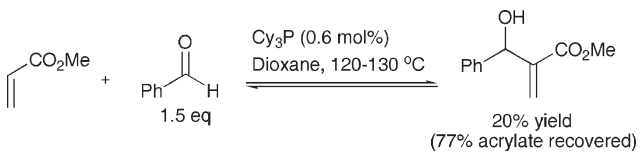
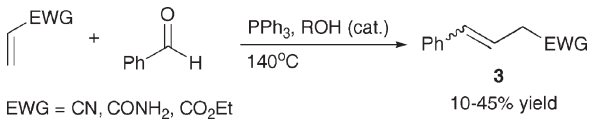
Dienes have been formed with good stereoselectivity and in good yield from simple aldehydes and acrylates/acrylonitrile in the presence of a phosphine and a Lewis acid through a modification of the Morita reaction.

The Morita–Baylis–Hillman (MBH) reaction (the phosphine or amine catalysed hydroxyalkylation of activated alkenes) is an important tool in organic synthesis as it converts cheap, readily available substrates into densely functionalised products in an atom economic process. Reminiscent of earlier work by Rauhut and Currier[1] (the phosphine catalysed dimerisation of acrylates), the reaction was introduced by Morita in the form of an (inefficient) intermolecular phosphine catalysed transformation (Scheme 1).[2] Shortly afterwards, Baylis and Hillman filed a patent describing the more efficient amine catalysed variant that is now commonly employed.[3] Since then there has been substantial development with regard to enhancement of rates,[4] production of enantiomerically enriched products,[5] and expansion of substrate scope.[4a,6]



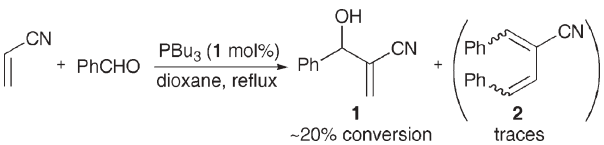
Scheme 1 Example from Morita's original work.

The mechanism of the amine catalysed reaction is well understood and the importance of the requisite proton transfer event (1,3-proton transfer), established as the RDS, has been highlighted in our laboratory and that of McQuade.[7] Recently, DFT calculations on the phosphine catalysed variant support the same RDS and a fully and more rapidly reversible reaction (compared to amines).[8] However, it is observed that, whilst amines are the catalyst of choice for most intermolecular transformations, phosphines have often been found to be superior in intramolecular variants.[9] In particular, the inefficiency of the seminal work (Scheme 1) was intriguing. Although the low yield may reflect a K_{eq} value of less than unity of a fully reversible[9c] and dilute reaction at high temperature,[10] we were mindful of potentially important differences between amines and phosphines, such as the latter's greater nucleophilicity, inferior leaving group ability[11] and much increased propensity to form ylidic intermediates, particularly in the basic environment of the MBH as described by Oda *et al.* (Scheme 2).[12] We therefore undertook a re-examination of the Morita reaction.



Scheme 2 Results by Oda and co-workers.

Using Morita's conditions and PBu_3 as catalyst, we confirmed the low conversion to MBH adduct **1**. However, in addition, tributylphosphine oxide and traces of dienes **2** were also observed, indicative of ylidic intermediates and Wittig-type transformations. Such processes would remove the catalytic amounts of phosphine, thus slowing down the reaction (Scheme 3). Altering the conditions to promote diene formation [acrylonitrile (1.0 eq.), PBu_3 (1.0 eq.) and benzaldehyde (2 eq.), 1,4-dioxane, RT, 24 h] resulted in the formation of all 4 possible stereoisomers of diene **2** in 17% yield.



Scheme 3 Repeating Morita's original work.

A solvent screen suggested that toluene or dichloromethane were optimum. The phosphine was also varied: PBu_3 gave good conversion, PCy_3 resulted in a sluggish reaction and P^tBu_3 or PPh_3 gave no conversion.[13] Using 2 equivalents of PBu_3 and PhCHO and 1.6 equivalents of acrylonitrile resulted in an improved yield (45%). In addition, three side-products were formed and identified as the Oda-product **3** (EWG = CN, 5%), 4-oxo-4-phenylbutanenitrile (10%), and 2-hydroxy-1,2-diphenylethanone (21%), the latter two formed by Stetter reaction and benzoin condensation respectively. To inhibit these processes, Lewis acids were added to the reaction mixture. The addition of 2 equivalents of $Ti(O^iPr)_4$ improved the yield to 66% and furthermore only two of the four possible stereoisomers were now formed in a 4 : 1 ratio. With these optimised conditions in hand the substrate scope with respect to the aldehyde was evaluated (Table 1).

Aliphatic aldehydes worked well (entries 1–3), although sterically demanding aldehydes resulted in somewhat reduced yields but higher stereoselectivity (compare entries 1 and 3). Aromatic aldehydes with electron donating/neutral groups worked well (entries 4–7) but increasing electron withdrawing groups resulted in reduced yields (entries 8 and 9). Employing

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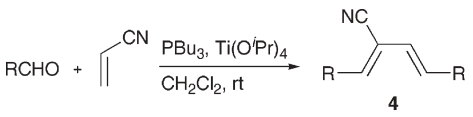
ortho-substituted aromatic and aliphatic dialdehydes gave cyclic dienes (entries 10 and 11).

Table 1 Substrate scope with acrylonitrile[a]

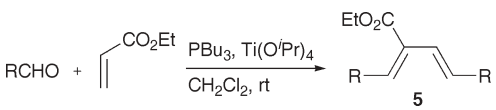


Entry	R	Yield[b]	Ratio[c]	Major product
1	Et	86%	3 : 1	**4a**
2	Cy	96%	4 : 1	**4b**
3	^{t}Bu	59%	6 : 1	**4c**
4	Ph–C=C	80%	[d]	**4d**[c]
5	Ph	66%	4 : 1	**4e**
6	*p*-MeO–Ph	71%	4 : 1	**4f**
7	*o*-Me–Ph	61%	5 : 1	**4g**
8	*p*-Br–Ph	43%	3 : 1	**4h**
9	*p*-CN–Ph	0%	—	—
10	*o*-CHO–Ph[e]	76%	—	**4i**
11	OHC–$(CH_2)_3$	41%[f]	—	**4j**

[a] Reaction conditions: PBu_3 (1.0 mmol) added to acrylonitrile (0.8 mmol), aldehyde (1.0 mmol) and $Ti(O^iPr)_4$ (1.0 mmol) in CH_2Cl_2 (2 ml) under N_2 and stirred for 15 h. [b] Based on aldehyde. [c] *Z* : *E* ratio of trisubstituted olefin. Disubstituted olefin is always *E*. [d] A mixture of several of the possible 8 isomers was isolated. [e] 0.5 mmol of dialdehyde used. [f] 5 mmol glutaraldehyde used, yield based on acrylonitrile.

The reaction was also performed on ethyl acrylate as the activated olefin (Table 2). Similar results were obtained, although in this case the sterically encumbered pivaldehyde failed to react (entry 3).

Table 2 Substrate scope with ethyl acrylate[a]

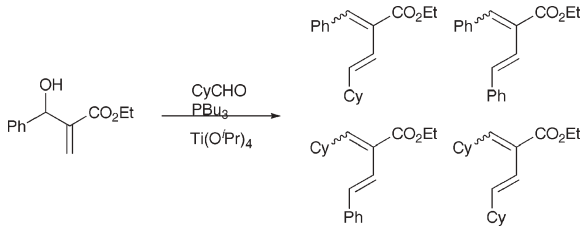


Entry	R	Yield[b]	Ratio[c]	Major product
1	Et	89%	3 : 1	**5a**
2	Cy	74%	4 : 1	**5b**
3	^{t}Bu	Trace	—	—
4	Ph	84%	5 : 1	**5e**
5	*p*-MeO–Ph	83%	4 : 1	**5f**
6	*o*-Me–Ph	63%	5 : 1	**5g**
7	*p*-Br–Ph	30%	3 : 1	**5h**
8	*p*-CN–Ph	0%	—	—
9	*o*-CHO–Ph[d]	20%	—	**5i**
10	OHC–$(CH_2)_3$	43%[e]	—	**5j**

[a] Reaction conditions: PBu_3 (1.0 mmol) added to ethyl acrylate (0.8 mmol), aldehyde (1.0 mmol) and $Ti(O^iPr)_4$ (1.0 mmol) in CH_2Cl_2 (2 ml) under N_2 and stirred for 15 h. [b] Based on aldehyde. [c] *Z* : *E* ratio of trisubstituted olefin. Disubstituted olefin is always *E*. [d] 0.5 mmol of the dialdehyde used. [e] 5 mmol glutaraldehyde used, yield based on ethyl acrylate.

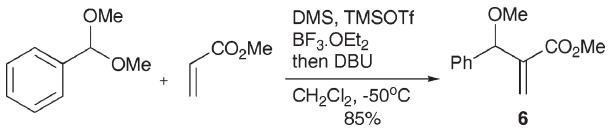
Diene stereochemistry was determined by a combination of NMR spectroscopy and computational methods and is detailed in the ESI.†

The products described incorporate two identical aldehyde molecules. In order to obtain substrates with non-identical groups we attempted the reaction between a preformed MBH adduct and a second (different) aldehyde under the same reaction conditions [PBu_3 (1.0 eq.) and $Ti(O^iPr)_4$ (1.0 eq.)]. However, this gave a mixture of all four possible dienes indicating a relatively rapid retro-MBHR (Scheme 4).[9c]



Scheme 4 Initial attempts to form unsymmetrical dienes.

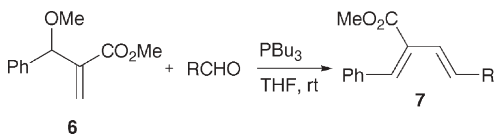
In order to inhibit the retro-MBHR, the hydroxyl group was exchanged for a methoxy ether. Although this compound can be obtained by alkylation of the MBH adduct, we and others have found that such compounds can be obtained directly through a vinylogous Sakurai reaction of acetals (Scheme 5).[14,15]



Scheme 5

Adduct **6** was treated with tributylphosphine in the presence of different aldehydes (Table 3). The reaction worked well with both aliphatic (entries 1–2) and aromatic (entries 3–5) aldehydes and the stereoselectivity observed in the one-pot procedure was retained.[16]

Table 3 Preparation of unsymmetrical dienes[a]

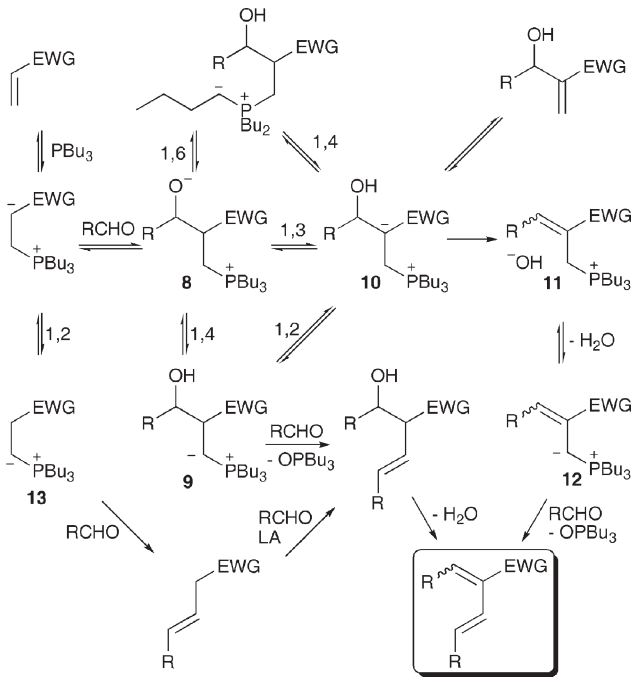


Entry	R	Yield	Ratio[b]	Major product
1	Et	57%	5 : 1	**7a**
2	Cy	75%	7 : 1	**7b**
3	*p*-MeO–Ph	75%	5 : 1	**7c**
4	*o*-Me–Ph	68%	4 : 1	**7d**
5	*p*-CF_3–Ph	95%	4 : 1	**7e**

[a] Reaction conditions: PBu_3 (0.6 mmol) added to **6** (0.5 mmol) and aldehyde (0.5 mmol) in THF (2 ml) under N_2 and the mixture stirred for 15 h. [b] *Z* : *E* ratio of trisubstituted olefin. Disubstituted olefin is always *E*.

Possible pathways for the formation of dienes are depicted in Scheme 6. Conjugate addition of the phosphine to the activated olefin followed by addition to the aldehyde furnishes alkoxide **8**. At this point, three different proton transfers can be envisioned. A 1,4-proton transfer gives the ylide **9**, which undergoes a Wittig reaction followed by elimination of water to give the diene. An alternative pathway is a 1,3-proton transfer (mediated by RCHO or traces of water)[7] to enolate **10**, followed by elimination of hydroxide to give **11**. Deprotonation then furnishes the ylide **12**, which undergoes the Wittig reaction leading to the diene. The intermediate enolate **10** could also be obtained from **8** through sequential 1,6- and 1,4-proton transfer events—processes that are unique to alkyl phosphines. The zwitterions obtained *via* 1,3- and

1,4-proton transfer (**10** and **9** respectively) may be interconvertible *via* 1,2-proton transfer. It is also possible that the Oda ylide **13**, formed *via* 1,2-proton transfer of the initially formed phosphonium enolate, could also lead to diene *via* a Wittig reaction followed by a Lewis acid-catalysed aldol condensation.



Scheme 6 Proposed pathways for diene formation.

The transformation to dienes using the methylated MBH adducts supports the relevance of dehydration–Wittig sequence (**10** → **11** → **12**) but the alternative pathways may also be in operation, particularly in those reactions without Lewis acid. The alternative proton transfer events presented here, which are specific to alkyl phosphonium intermediates, may be more relevant in intramolecular MBH catalysis where amines but not phosphines require protic additives.[17]

This analysis may shed some light on the origin of the low yields in the original Morita reaction involving alkyl phosphines[2] and why in the presence of phenols high yields can be achieved.[9d,e] In the original Morita reaction the high temperature will result in $K_{eq} < 1$ and some of the myriad intermediates may also follow alternative pathways; both factors contributing to low yields. In contrast, at RT, ($K_{eq} \sim 1$) and in the presence of phenol rapid alcohol-assisted 1,3-proton transfer (**8** → **10**)[7a,7c] followed by elimination (**10** → **1**) occurs and many of the alternative pathways (presumably now much slower) are not followed. Amine catalysed reactions (Baylis–Hillman) are much less rapidly reversible,[9c] K_{eq} may be greater than unity under standard reaction conditions (high concentration, RT) and ylide-type intermediates are not accessible, thus leading to generally higher yields.

In conclusion, through careful analysis of the original Morita reaction we have discovered a new efficient synthesis of dienes with moderate to good control of the double bond geometry from simple aldehydes and Michael acceptors using PBu_3. Since dienes are not only useful synthetic intermediates but also ubiquitous in nature, we believe this method could find wide application.

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Notes and references

1 M. Rauhut and H. Currier, *US Patent*, 3,074,999, 1963.
2 K. Morita, Z. Suzuki and H. Hirose, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2815.
3 (*a*) A. B. Baylis and M. E. D. Hillman, *Offenlegungsschrift*, 2155113, 1972 (*US Patent*, 3,743,669, 1972); (*b*) A. B. Baylis and M. E. D. Hillman, *Chem. Abs.*, 1972, **77**, 34174q. For reviews see: (*c*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811; (*d*) S. E. Drewes and G. H. P. Roos, *Tetrahedron*, 1988, **44**, 4653; (*e*) E. Ciganek, *Org. React. (N. Y.)*, 1997, **51**, 201; (*f*) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001.
4 (*a*) V. K. Aggarwal, I. Emme and S. Y. Fulford, *J. Org. Chem.*, 2003, **68**, 692; (*b*) K.-S. Park, J. Kim, H. Choo and Y. Chong, *Synlett*, 2007, 395; (*c*) J. Cai, Z. Zhou and C. Tang, *Org. Lett.*, 2002, **4**, 4723; (*d*) V. K. Aggarwal, D. K. Fean, A. Mereu and R. Williams, *J. Org. Chem.*, 2002, **67**, 510; (*e*) S. Luo, B. Zhang, J. He, A. Janczuk, P. G. Wang and J.-P. Cheng, *Tetrahedron Lett.*, 2002, **43**, 7369; (*f*) C. Yu, B. Liu and L. Hu, *J. Org. Chem.*, 2001, **66**, 5413; (*g*) J. Auge, N. Lubin and A. Lubineau, *Tetrahedron Lett.*, 1994, **35**, 7947; (*h*) F. Ameer, S. E. Drewes, S. Freese and P. T. Kaye, *Synth. Commun.*, 1988, **18**, 495.
5 (*a*) Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatekeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219. For reviews on asymmetric MBH reactions, see: (*b*) P. Langer, *Angew. Chem., Int. Ed.*, 2000, **39**, 3049; (*c*) G. Masson, C. Housseman and J. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 4614.
6 (*a*) C. Faltin, E. M. Fleming and S. J. Connon, *J. Org. Chem.*, 2004, **69**, 6496; (*b*) C. Yu and L. Hu, *J. Org. Chem.*, 2002, **67**, 219.
7 (*a*) V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2005, **44**, 1706; (*b*) K. E. Price, S. J. Broadwater, B. J. Walker and D. T. McQuade, *J. Org. Chem.*, 2005, **70**, 3980. (*c*) Insight into the mechanisms for 1,3-proton transfer have been established through DFT calculations. See: R. Robiette, V. K. Aggarwal and J. N. Harvey, *J. Am. Chem. Soc.*, 2007, DOI: 10.1021/ja717865.
8 J. Xu, *J. Mol. Struct.: THEOCHEM*, 2006, **767**, 61.
9 (*a*) M. E. Kraft, T. F. N. Haxell, K. A. Seibert and K. A. Abboud, *J. Am. Chem. Soc.*, 2006, **128**, 4174; (*b*) W.-D. Teng, R. Huang, C. K.-W. Kwong, M. Shi and P. H. Toy, *J. Org. Chem.*, 2006, **71**, 368; (*c*) F. Roth, P. Gynax and G. Fráter, *Tetrahedron Lett.*, 1992, **33**, 1045. In the presence of phenols, the intermolecular reaction can also give moderate–high yields, see: (*d*) M. Shi and W. Zhang, *Tetrahedron*, 2005, **61**, 11887; (*e*) Y. M. A. Yamada and S. Ikegami, *Tetrahedron Lett.*, 2000, **41**, 2165.
10 From DFT calculations it has been found that the BHR is slightly exothermic (~5 kcal mol^{-1}) at RT. However, it is entropically unfavourable so should have ΔG at RT ~ 0 kcal mol^{-1}. See ref. 7*c*.
11 V. K. Aggarwal, J. N. Harvey and R. Robiette, *Angew. Chem., Int. Ed.*, 2005, **44**, 5468.
12 R. Oda, T. Kawabata and S. Tanimoto, *Tetrahedron Lett.*, 1964, 1653.
13 A recent communication has highlighted that while triarylphosphonium enolates exhibit substantial oxaphosphatane character, trialkylphosphonium enolates do not: X.-F. Zhu, C. E. Henry and O. Kwon, *J. Am. Chem. Soc.*, 2007, **129**, 6722. Considering this, the lack of catalysis using PPh_3 under our conditions (without Lewis acid or protic additive) may be due to the formation of a stable oxaphosphatane of poor nucleophilicity.
14 (*a*) S. Kim, J. H. Park, Y. G. Kim and J. M. Lee, *J. Chem. Soc., Chem. Commun.*, 1993, 1188; (*b*) J. S. Rao, J.-F. Brière, P. Metzner and D. Basavaiah, *Tetrahedron Lett.*, 2006, 3553.
15 (*a*) E. L. Myers, C. P. Butts and V. K. Aggarwal, *Chem. Commun.*, 2006, 4434; (*b*) E. L. Myers, J. G. de Vries and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2007, **46**, 1893.
16 The acetate analogue of **6** was also tested in the same reaction but gave reduced yields compared to **6** itself (*cf*. entry 3: OAc analogue of **6** gave 28% yield of dienes whereas **6** gave 75% yield of the same dienes).
17 G. E. Keck and D. S. Welch, *Org. Lett.*, 2002, **4**, 3687.

