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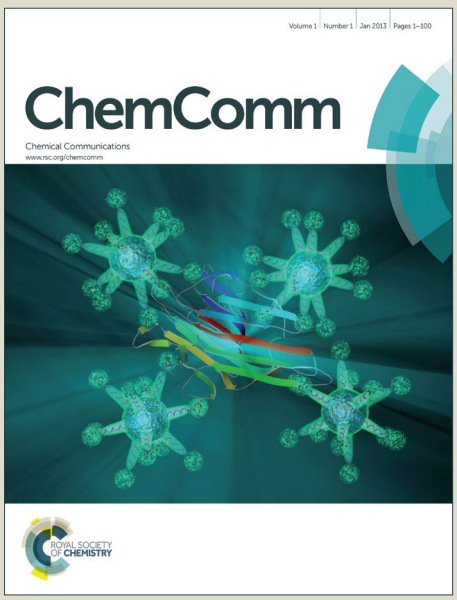

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Nickel-Catalyzed Synthesis of (*E*)-Olefins from Benzylic Alcohol Derivatives and Arylacetonitriles via C-O Activation

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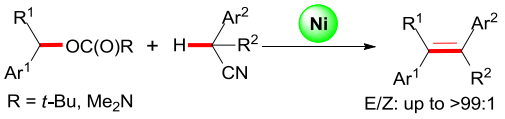
An efficient Ni-catalyzed synthesis of (*E*)-olefins using the readily available benzylic alcohol derivatives and arylacetonitriles is described. This transformation should proceed via a tandem process involving nickel-catalyzed cross coupling via C-O activation and subsequent stereoselective E2 elimination.

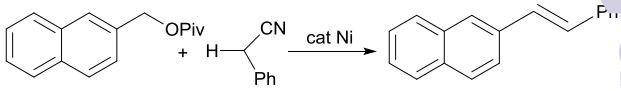
The stereoselective synthesis of olefins is of importance in organic synthesis, because many functional molecules such as materials, drugs, natural products incorporate carbon-carbon double bonds with defined (*Z*) or (*E*)-configuration.[1] Classical methods to access olefins include the popular Wittig reaction and Julia olefination, which depend on the transformation of carbonyl compounds with phosphonium salts or sulfone compounds.[2] Alternatively, many transition metal-catalyzed methodologies based on alkenes such as metathesis, Mizoroki-Heck couplings (reactions of organohalides or counterparts with terminal alkenes) and Fujiwara-Moritani couplings (reactions of electron-rich hydrocarbons with electron-deficient terminal alkenes) attracted much attention and emerged as powerful tools for the selective synthesis of olefins, but those reactions required noble metal catalysts and preparation of starting material olefins.[3]



Scheme 1 Ni-catalyzed synthesis of (*E*)-olefins from benzylic alcohol derivatives and arylacetonitriles via C-O activation.

Another efficient method to access olefins is the semihydrogenation of alkynes. However, the transformation usually suffered from over-reduction and chemo-control.[4] Thus, despite the great progress has been made in this filed, continuous efforts still deserve for developing facile and efficient methods for the preparation of olefins from simple starting materials. Herein, we report a Ni-catalyzed tandem reaction for the selective synthesis of (*E*)-olefins using the easily available benzylic alcohol derivatives and arylacetonitriles via C-O activation.[5,6] This transformation features high stereoselectivity and is applicable to prepare various (*E*)-olefins including those functional molecules (Scheme 1).[1a,7]

Table 1 Ni-catalysed synthesis of 2-styrylnaphthalene from 2-naphthylmethyl pivalate and phenylacetonitrile.[a]



1a 2a 3a

Entry	Ligand	Base (equiv)	Cat. (mmol)	Temp.	Solvent	Yield[b]
1	dcype	*t*-BuOK (2.0)	5 %	100 °C	dioxane	36%
2	PCy_3	*t*-BuOK(2.0)	5 %	100 °C	dioxane	62%
3	Ph_3P	*t*-BuOK(2.0)	5 %	100 °C	dioxane	65%
4	xantphos	*t*-BuOK(2.0)	5 %	100 °C	dioxane	53%
5	binap	*t*-BuOK(2.0)	5 %	100 °C	dioxane	60%
6	dppe	*t*-BuOK(2.0)	5 %	100 °C	dioxane	52%
7	dppp	*t*-BuOK(2.0)	5 %	100 °C	dioxane	71%
8	dppb	*t*-BuOK(2.0)	5 %	100 °C	dioxane	35%
9	**dppp**	***t*-BuOK(2.5)**	**5 %**	**100 °C**	**dioxane**	**86%**
10	dppp	*t*-BuOK(3.0)	5 %	100 °C	dioxane	86%
11	dppp	*t*-BuONa(2.5)	5%	100 °C	dioxane	30%
12	dppp	*t*-BuOLi(2.5)	5 %	100 °C	dioxane	30%
13	dppp	*t*-BuOK(2.5)	10 %	100 °C	dioxane	72 %
14	dppp	*t*-BuOK(2.5)	2.5 %	100 °C	dioxane	72%
15	dppp	*t*-BuOK(2.5)	5 %	120 °C	dioxane	86%
16	dppp	*t*-BuOK(2.5)	5 %	80 °C	dioxane	21%
17	dppp	*t*-BuOK(2.5)	5 %	100 °C	toluene	31%
18	dppp	*t*-BuOK(2.5)	5 %	100 °C	DMF	47%
19	dppp	*t*-BuOK(2.5)	5 %	100 °C	THF	74%
20[c]	dppp	*t*-BuOK(2.5)	5 %	100 °C	dioxane	trace

[a]Conditions: a mixture of **1a** (0.1 mmol), **2a** (0.15 mmol), Ni(COD)$_2$, a phosphine ligand (P/Ni = 2:1) and a base in the solvent (1.5 mL) was stirred at the temperature indicated for 24 h, *E*/*Z* > 99:1. [b] GC yield using tridecane as an internal standard. [c]In the absence of Ni catalyst.

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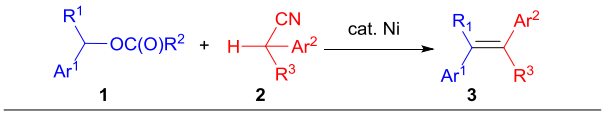
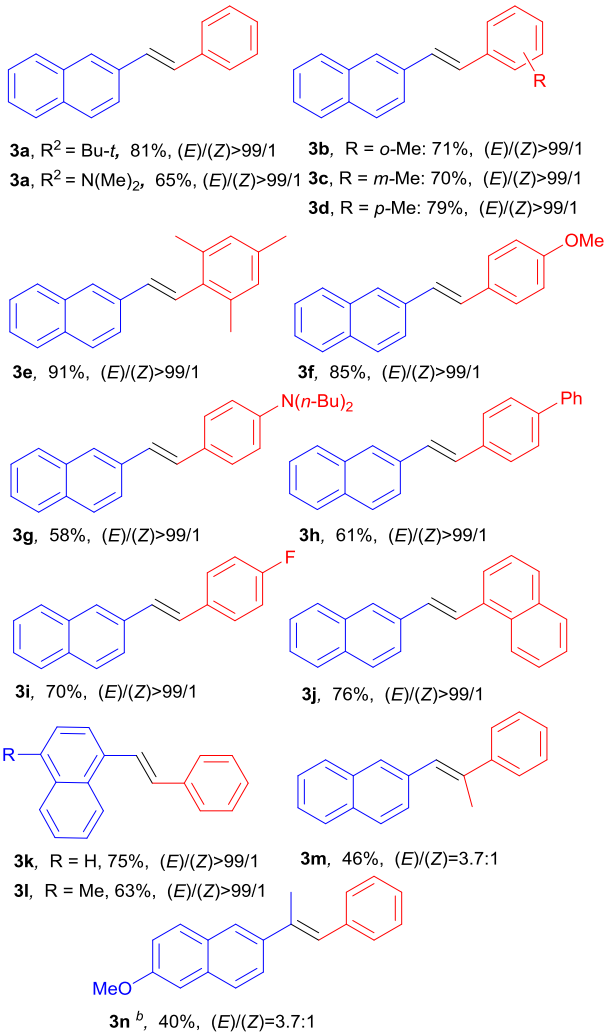
During the extensive studies on the cross coupling of C-O electrophiles with Z-H compounds,[8] we accidently found that 36% yield of 2-styrylnaphthalene **3a** with high (*E*)-selectivity was produced when naphthylmethyl pivalate **1a** was allowed to react with phenylacetonitrile **2a** in dioxane at 100 °C in the presence of 5 mol% $Ni(COD)_2$/dcype (1,2-bis(dicyclohexylphosphanyl)ethane) and 2 equiv *t*-BuOK (Table 1, entry 1). The interesting result drove us to further investigate the transformation. Other phosphine ligands selected were also effective for production of **3a** with dppp (1,3-bis(diphenylphosphanyl)propane) being the best choice (Table 1, entries 2-8). 86% yield of **3a** was produced when 2.5 equiv *t*-BuOK was employed under similar reaction conditions (Table 1, entry 9). However, further increasing the amount of base didn't improve the reaction efficiency (Table 1, entry 10). *t*-BuONa and *t*-BuOLi acted as effective base despite with relatively low yields (Table 1, entries 11 and 12). This reaction occurred well with 5 mol% nickel complex, either increasing or decreasing the loading lead to the decrease of yield (Table 1, entries 13 and 14). At an elevating temperature, the reaction also took place to give **3a** in 86% yield. However, upon lowering the temperature to 80 °C, only 21% yield of **3a** was given (Table 1, entries 15 and 16). As to the solvent, this reaction also proceeded readily in THF, but poorly in toluene and DMF (Table 1, entries 17-19). In the absence of the Ni catalyst, a trace amount of product was detected (Table 1, entry 20).

Table 2 Ni-catalyzed synthesis of (*E*)-olefins from arylacetonitriles with naphthyl-based derivatives[a]

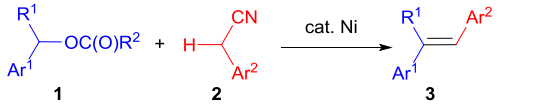


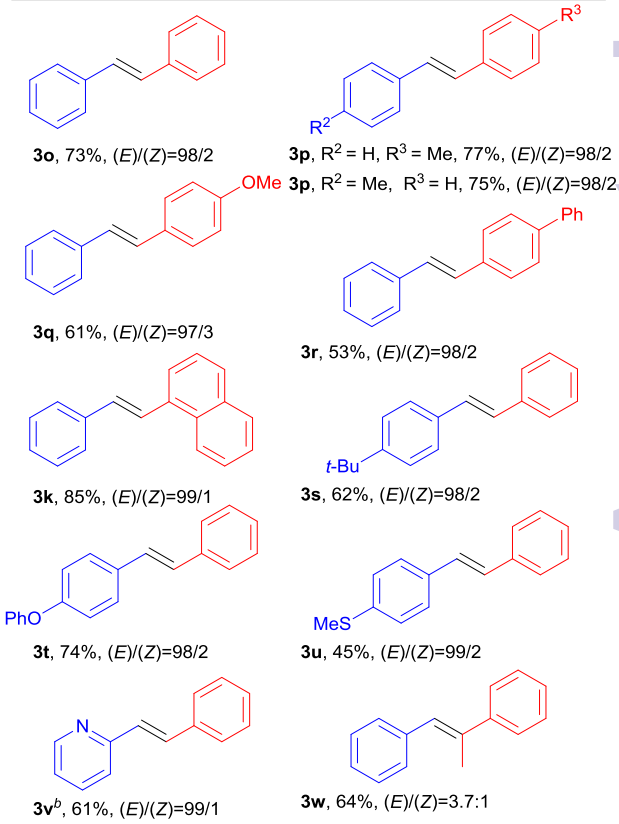


3a, R^2 = Bu-*t*, 81%, (*E*)/(*Z*)>99/1
3a, R^2 = $N(Me)_2$, 65%, (*E*)/(*Z*)>99/1
3b, R = *o*-Me: 71%, (*E*)/(*Z*)>99/1
3c, R = *m*-Me: 70%, (*E*)/(*Z*)>99/1
3d, R = *p*-Me: 79%, (*E*)/(*Z*)>99/1
3e, 91%, (*E*)/(*Z*)>99/1
3f, 85%, (*E*)/(*Z*)>99/1
3g, 58%, (*E*)/(*Z*)>99/1
3h, 61%, (*E*)/(*Z*)>99/1
3i, 70%, (*E*)/(*Z*)>99/1
3j, 76%, (*E*)/(*Z*)>99/1
3k, R = H, 75%, (*E*)/(*Z*)>99/1
3l, R = Me, 63%, (*E*)/(*Z*)>99/1
3m, 46%, (*E*)/(*Z*)=3.7:1
3n [b], 40%, (*E*)/(*Z*)=3.7:1

[a] Conditions: **1** (0.1 mmol), **2** (0.15 mmol), $Ni(COD)_2$ (5 mol%), dppp (5 mol%), *t*-BuOK (0.25 mmol), dioxane (1.5 mL), 100 °C , 24 h. Unless otherwise noted, R^2 = C(O)Bu-*t*. Isolated yield. [b] $Ni(COD)_2$ (10 mol%), dcype (10 mol%), 150 °C, 24 h.

Table 3 Ni-catalyzed synthesis of (*E*)-olefins from arylacetonitriles with benzylic alcohol derivatives.[a]





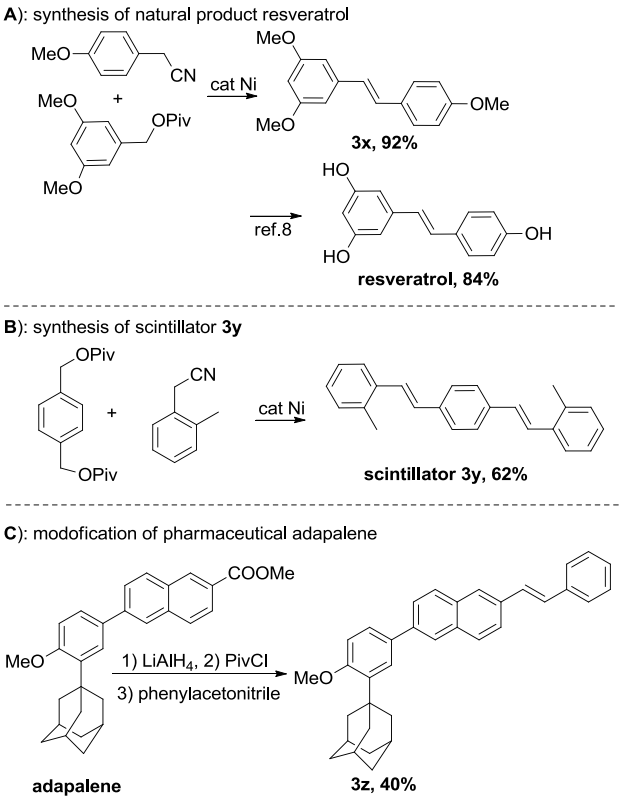
3o, 73%, (*E*)/(*Z*)=98/2
3p, R^2 = H, R^3 = Me, 77%, (*E*)/(*Z*)=98/2
3p, R^2 = Me, R^3 = H, 75%, (*E*)/(*Z*)=98/2
3q, 61%, (*E*)/(*Z*)=97/3
3r, 53%, (*E*)/(*Z*)=98/2
3k, 85%, (*E*)/(*Z*)=99/1
3s, 62%, (*E*)/(*Z*)=98/2
3t, 74%, (*E*)/(*Z*)=98/2
3u, 45%, (*E*)/(*Z*)=99/2
3v[b], 61%, (*E*)/(*Z*)=99/1
3w, 64%, (*E*)/(*Z*)=3.7:1

[a]Conditions: **1** (0.1 mmol), **2** (0.3 mmol), $Ni(COD)_2$ (10 mol%), dcype (10 mol%), *t*-BuOK (3.0 equiv), dioxane (1.5 mL), 140 °C, 24 h. Isolated yield. [b] $Ni(COD)_2$ (20 mol%), dcype (20 mol%).

This transformation is applicable to other substrates, producing the corresponding (*E*)-olefins in good to high yields. Thus, the carbamate reacted with phenylacetonitrile smoothly to afford the corresponding product **3a** in good yield under the standard reaction conditions. Phenylacetonitriles with electron donating groups such as methyl, methoxy, amine and phenyl

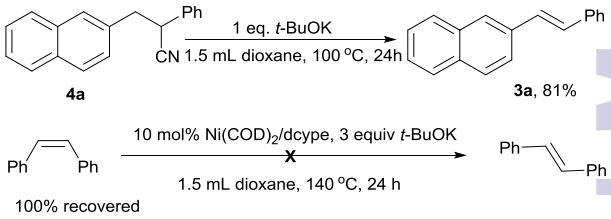
benzene ring coupled with naphthylmethyl pivalate **1a** readily, yielding the expected (*E*)-olefins in moderate to excellent yields. The fluoro group survived in the current catalytic system. However, when phenylacetonitriles with electron-withdrawing group like CF_3 was employed as the substrate, only a trace amount of product was detectable. 1-Naphthylacetonitrile also was proved to be good substrate for the reaction, and the expected product **3j** was generated in 76% yield. Worth noting is that trisubstituted alkenes **3m** and **3n** were also prepared from the expected secondary arylacetonitriles or secondary benzylic alcohol pivalates, albeit with only moderate E/Z selectivity. However, when an aliphatic nitrile like acetonitrile was subjected into the reaction, no product was detected by GC-MS.

By switching the phosphine ligand dppp to dcype, the simpler benzyl esters were also applicable to this reaction. As shown in Table 3, benzyl pivalates coupled smoothly with various phenylacetonitriles, producing the corresponding (*E*)-olefins in good yields. Other pivalate derivatives bearing functional groups on the benzene ring such as Me, *t*-Bu, OPh and SMe served well in this transformation, furnishing the coupling products in good to high yields (**3p**, **3s**-**3u**). Notably, the heterocyclic 2-(pyridin-2-yl) acetonitrile was proved to be good substrate and the expected (*E*)-olefin **3v** was produced in 61% yield with 99/1 (*E*)-stereoselectivity. Benzyl pivalate also reacted with secondary benzyl cyanide smoothly, affording the desired product **3w** in 64% yield.



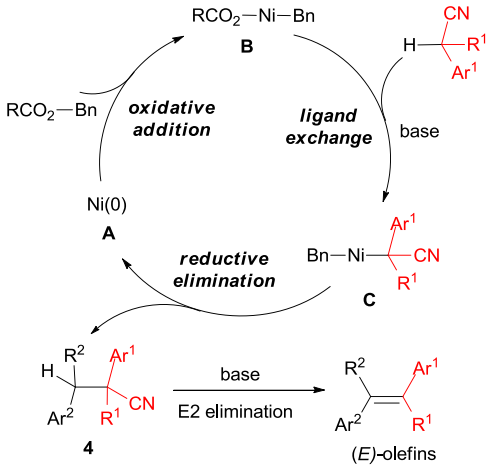
Scheme 2 Synthesis of functional molecules.

The synthetic value of the transformation was further displayed by the efficient synthesis of functional molecules. Thus, by employing the nickel catalyzed reaction, 3,5-dimethoxybenzyl pivalate coupled readily with 2-(4-methoxyphenyl)acetonitrile to produce the corresponding (*E*)-olefin **3x** in 92% yield, which could be converted easily to the natural product resveratrol following the established procedures (Scheme 2, A).[9] 1,4-Bis((*E*)-2-methylstyryl)benzene **3y** is usually used as scintillator in Scintillation Counter and scintillation spectrometer. The functional molecule was easily produced in 62% isolated yield via diolefination of 1,4-phenylenedimethanol pivalates with 2-(o-tolyl)acetonitrile under the present reaction conditions (Scheme 2, B).[10] The pharmaceutical adapalene could also be converted to the corresponding olefin **3z** by reacting with phenylacetonitrile in the current catalytic system after reduction and esterification (Scheme 2, C).



Scheme 3 Control experiments.

During the reaction of naphthylmethyl pivalate **1a** with phenylacetonitrile **2a**, α-alkylated nitriles **4a** generated from alkylation via C-O activation was detected by GC-MS. We deduced the α-alkylated nitriles would be the efficient reaction intermediate. This is indeed. The resulting **4a** could undergo elimination, producing (*E*)-olefin **3a** in high yield in the presence of 1 equiv *t*-BuOK. Under the standard reaction conditions, (*Z*)-stilbene remained intact and no trace amount of (*E*)-stilbene was detectable (Scheme 3). Those results indicated that the elimination would be a stereoselective E2 process.



Scheme 4 Proposed mechanism. Ligands are omitted for clarity.

On the basis of the results described above and literatures,[11,12] a plausible mechanism is proposed as shown in Scheme 4. Complex **B** generated from the oxidative addition of Ni(0) complex **A** with C-O electrophiles underwent ligand exchange with a nitrile by the aid of a base, producing species **C**, followed by reductive elimination to yield the α-alkylated

nitriles **4** and regenerate Ni(0) complex **A**. Stereoselective E2 elimination of the α-alkylated nitriles **4** produces the corresponding (*E*)-olefins.

In summary, we have disclosed an efficient Ni-catalyzed tandem reaction between arylacetonitriles and benzylic alcohol derivatives. This transformation coupled α-alkylation of nitriles with C-O electrophiles via C-O activation and subsequent E2 elimination, providing a simple and efficient method to access various (*E*)-olefins with high stereoselectivity from the relatively readily available starting materials.

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Notes and references

1 (a) M. Jang, L. Cai, G. O. Udeani, K. V. Slowing, C. F. Thomas, C. W. W. Beecher, H. H. S. Fong, N. R. Farnsworth, A. D. Kinghorn, R. G. Mehta, R. C. Moon and J. M. Pezzuto, *Science*, 1997, **275**, 218; (b) F. Orsini, F. Pelizzoni, L. Verotta, T. Aburjai and C. B. Rogers, *J. Nat. Prod.*, 1997, **60**, 1082; (c) P. Waffo-Teguo, D. Lee, M. Cuendet, J. M. Mérillon, J. M. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.*, 2001, **64**, 136; (d) A. Kraft, A. C. Grimsdale and A. B. Holmes, *Angew. Chem., Int. Ed.*, 1998, **37**, 402; (e) R. E. Martin and F. Diederich, *Angew. Chem., Int. Ed.*, 1999, **38**, 1350.

2 (a) J. Bautagy and R, Thomas, *Chem. Rev.*, 1974, **74**, 87; (b) M. Julia and J.-M. Paris. *Tetrahedron Lett.*, 1973, **14**, 4833.

3 (a) T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581; (b) R. F. Heck and J. P. Nolley, *J. Org. Chem*., 1972, **37**, 2320; (c) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009; (d) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res*., 2001, **34**, 633; (e) K. M. Engle, D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 14137.

4 (a) M. W. van Laren and C. J. Elsevier, *Angew. Chem., Int. Ed.*, 1999, **38**, 3715; (b) J. G. Ulan, W. F. Maier and D. A. Smith, *J. Org. Chem.*, 1987, **52**, 3132; (c) A. M. Kluwer, T. S. Koblenz, T. Jonischkeit, K. Woelk and C. J. Elsevier, *J. Am. Chem. Soc.*, 2005, **127**, 15470.

5 For reviews on the C-O functionalization catalysed by nickel, see (a) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, **48**, 886; (b) J.Yamaguchi, K. Muto and K. Itami, *Eur. J. Org. Chem.*, 2013, 19; (c) J. Cornella, C. Zarate and R. Martin, *Chem. Soc. Rev.*, 2014, **43**, 8081; (d) T. Chen and L.-B. Han, *Angew. Chem. Int. Ed.*, 2015, **54**, 8600; (e) M. Tobisu and N. Chatani, *Acc. Chem. Res.*, 2015, **48**, 1717.

6 For selected examples on nickel-catalysed C-O functionalization, see (a) J. Cornella, E. P. Jackson and R. Martin, *Angew. Chem. Int. Ed.*, 2015, **54**, 4075; (b) E. Koch, R. Takise, A. Studer, J. Yamaguchi and K. Itami, *Chem. Commun.*, 2015, **51**, 855; (c) M. R. Harris, M. O. Konev and E. R. Jarvo, *J. Am. Chem. Soc.*, 2014, **136**, 7825; (d) R. Takise, K. Muto, J. Yamaguchi and K. Itami, *Angew. Chem. Int. Ed.*, 2014, **53**, 6791; (e) K. Muto, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2012, **134**, 169; (f) A. R. Ehle, Q. Zhou and M. P. Watson, *Org. Lett.*, 2012, **14**, 1202; (g) B.-T. Guan, Yang Wang, B.-J. Li, D.-G. Yu and Z.-J. Shi, *J. Am. Chem. Soc.,* 2008, **130**, 14468; (h) K. W. Quasdorf, X. Tian and N. K. Garg, *J. Am. Chem. Soc.*, 2008, **130**, 14422; (i) A. A.-Finch, T. Blackburn and V. Snieckus, *J. Am. Chem. Soc.*, 2009, **13**, 17750; (j) Q. Zhou, H. D. Srinivas, S. Dasgupta and M. P. Watson, *J. Am. Chem. Soc.*, 2013, **135**, 3307; (k) B.-J. Li,Y.-Z. Li, X.-Y. Lu, J. Liu, B.-T. Guan and Z.-J. Shi, *Angew. Chem. Int. Ed.,* 2008, **47**, 10124; (l) M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore and E. R. Jarvo, *J. Am. Chem. Soc.* 2013, **135**, 3303; (m) A. Correa,T.León and R. Martin, *J. Am. Chem. Soc.,* 2014, **136**, 1062; (n) M. Kawatsura, K. Uchida, S. Terasaki, H. Tsuji, M. Minakawa and T. Itoh, *Org. Lett.*, 2014, **16**, 1470; (o) T. Shimasaki, M. Tobisu and N. Chatani, *Angew. Chem. Int. Ed.,* 2010, **49**, 2929; (p) A. Correa and R. Martin, *J. Am. Chem. Soc.*, **136**, 7253.

7 (a) M. C. Pinto, J. A. Garcia-Barrado and P. J. Macias, *Agric. Food Chem.*, 1999, **47**, 4842; (b) J. R. Stewart, N. E. Ward, C. G. Ioannides and C. A. O'Brian, *Biochemistry*, 1999, **38**, 13244; (c) L. Frémont, *Life Sci.*, 2000, **66**, 663.

8 J. Yang, T. Chen and L.-B. Han, *J. Am. Chem. Soc.*, 2015, **137**, 1782.

9 S. C. Söderman and A. L. Schwan, *J. Org. Chem.*, 2012, **77**, 10978.

10 Scintillator **3y** is used to be prepared from reaction of 1-(halomethyl)-2-methylbenzene with terephthalaldehyde via Wittig process, which is under protection by patent, see: V. J. Koul and B. R. Hirani, Indian 2006MU01558, patent, Sep. 19, 2008.

11 K. Muto, J. Yamaguchi, A. Lei and K. Itami, *J. Am. Chem. Soc.*, 2013, **135**, 16384.

12 (a) X. Hong, Y. Liang and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 2017; (b) H. Xu, K. Muto, J. Yamaguchi, C. Zhao, K. Itami and D. G. Musaev, *J. Am. Chem. Soc.*, 2014, **136**, 14834; (c) D. Lu, H. Yu and Y. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 8252.