ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c9cc09522e

Received 9th December 2019,
Accepted 16th December 2019

DOI: 10.1039/c9cc09522e

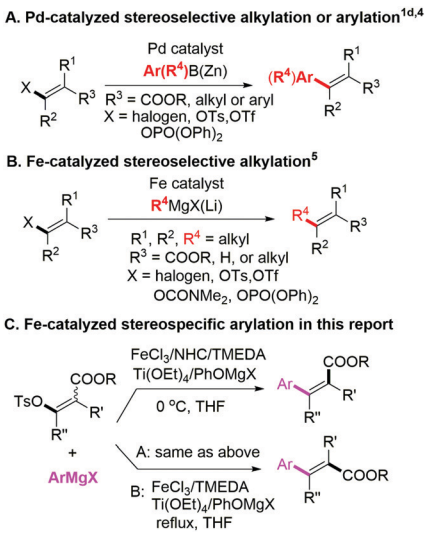
rsc.li/chemcomm

Iron-catalyzed stereospecific arylation of enol tosylates using Grignard reagents†

Yi-Ming Wei,‡ Xiao-Di Ma,‡ Lei Wang and Xin-Fang Duan *

The stereospecific Fe-catalyzed arylation of enol tosylates was reported. Various tri- or tetrasubstituted *Z* or *E*-enol tosylates of β-keto esters were arylated using common and Knochel-type Grignard reagents with complete stereofidelity. The precursors for *Z*/*E*-zimelidine, tamoxifen and other bioactive compounds were facilely prepared without precious and toxic transition metals.

The stereocontrolled synthesis of various substituted olefins is an ongoing and important task in organic synthesis because these structural motifs are ubiquitous in natural products, biologically active compounds, molecular devices and liquid crystals.[1] Transition-metal catalyzed cross couplings of alkenyl halides, tosylates (other esters) and ethers with various metal reagents (or *vice versa*, alkenyl metal reagents with alkyl or aryl (pseudo)halides) have become a very useful tool in this field.[2,3] For example, Pd-catalyzed Suzuki or Negishi couplings of configuration-defined alkenyl (pseudo)halides enabled the stereocontrolled preparations of tri- or tetrasubstituted alkenes (Scheme 1A).[1d,4] Characterized by low prices and low toxicity, Fe-catalyzed stereoselective synthesis of alkenes has attracted widespread attention. Although various Fe-catalyzed stereoselective alkylations of enol triflates, phosphates, tosylates, carbamates and alkenyl iodides with alkyl magnesium or lithium reagents have been well achieved (Scheme 1B),[5] the corresponding Fe-catalyzed arylation is very rare.[6] One important reason for this is that the iron-catalyzed C(sp^2)–C(sp^2) couplings remain challenging and are more limited than those catalyzed by palladium.[7] Besides, the arylations that generate thermodynamically less stable alkenes (*e.g.* *Z*-trisubstituted acyclic alkenes) usually require challenging reaction conditions to avoid isomerization.[8,9] To the best of our knowledge, no reports have been documented on the Fe-catalyzed stereocontrolled arylation of *Z*-substituted acyclic alkenyl (pseudo)halides with complete retention of the configuration until now.[8] In this context, Fe-catalyzed stereocontrolled arylation of *Z*- or *E*-alkenyl (pseudo)-halides, especially those that generate thermodynamically less stable *Z*-alkenes, is highly desired as an ecofriendly and sustainable alternative to reactions requiring noble or toxic metals.



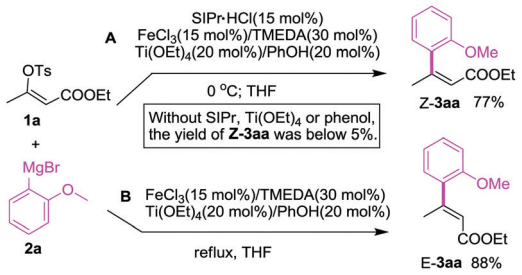
Scheme 1 Stereoselective alkylation or arylation of alkenyl (pseudo)halides.

Recently we have developed efficient protocols for Fe-catalyzed biaryl cross couplings between aryl (pseudo)halides and aryl Grignard reagents,[10] which prompted us to discover a stereoselective arylation of alkenyl (pseudo)halides. Herein, we reported two protocols for Fe-catalyzed stereospecific arylation of *Z* or *E*-enol tosylates (Scheme 1C), by which a variety of *Z*- and *E*-tri- and tetrasubstituted acrylates were facilely prepared with complete stereocontrol. Since the stereoselective preparations of various *Z*/*E*-enol tosylates have been well established by Tanabe *et al.*,[4b,c,11] and Grignard reagents are readily available, we expect this mild and general method to be a valuable alternative for the stereospecific construction of olefins without the need of precious and toxic transition metals.

College of Chemistry, Beijing Normal University, 100875, China.
E-mail: xinfangduan@vip.163.com

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9cc09522e

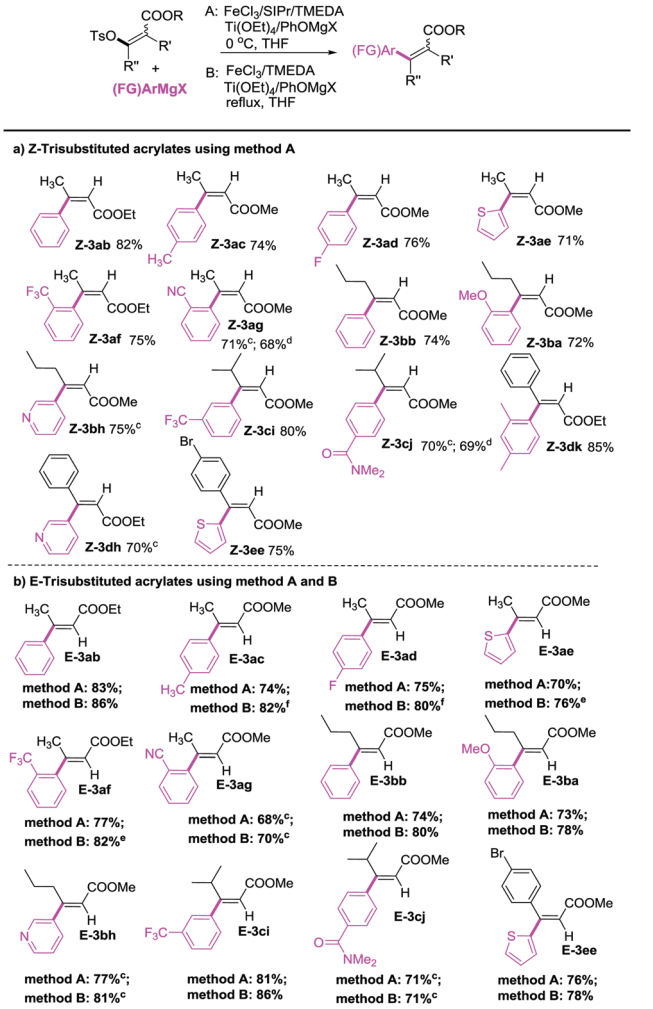
‡ These authors contributed equally.



Scheme 2 Optimized conditions for stereospecific arylation.

Our condition optimizations clearly showed that the isomerization into the thermodynamically more stable **E-3aa** was liable to occur as expected (Scheme 2). By taking advantage of this isomerisation under heated conditions, a stereospecific arylation leading to a single *E*-product was established (method B). Further optimizations indicated that temperature, ligand, $Ti(OEt)_4$ and phenolate were crucial for the stereospecific formation of **Z-3aa**, and meanwhile the reactions without either $Ti(OEt)_4$ or PhOM at 0 °C could hardly generate the arylated products, clearly indicating that the phenolate-assisted Fe/Ti synergistic effect[10a,b] was the key to the reaction (Scheme 2 and see the ESI†). Thus, the combination of $FeCl_3$/SIPr with $Ti(OEt)_4$/PhOM as a cocatalyst system enabled a facile stereospecific arylation under mild conditions (method A, Scheme 2). Although this combination has been used to promote biaryl couplings in our group,[10a,b] it has never been applied to the stereoselective arylation of enol tosylates. To our delight, it turns out to be a highly effective Fe-based catalyst system that can achieve stereospecific arylation of *Z*-enol tosylates with complete stereofidelity, leading to the thermodynamically less stable *Z*-products as a single isomer.

With the optimized conditions in hand, we investigated the scope of the Fe-catalyzed stereospecific arylation reaction. Initially, the arylations of various trisubstituted tosyloxyacrylates with different Grignard reagents was carried out, and the results are outlined in Scheme 3. A wide variety of *Z*-trisubstituted acrylates which are prone to isomerization into *E*-isomers were stereospecifically prepared using method A (Scheme 3a). In the previous reports of Pd-catalyzed stereoselective arylations of enol tosylates *via* Suzuki reaction, the reaction conditions required judicious optimizations and were often conducted under heated conditions.[1d,4c,d] By contrast, our present reactions proceeded smoothly at 0 °C, which fully showed the high activity of the Fe/Ti cocatalyst, and meanwhile reduced the possibility of the isomerization into *E*-isomers. Notably, in addition to common Grignard reagents (**Z-3ab–Z-3ad**), thiophene and hindered 2-functionalized Grignard reagents could arylate **1a** smoothly as well (**Z-3ae–Z-3ag**). We also found that in the arylations using Knochel-type Grignard reagents, the removal of the concomitant i-PrI formed during the preparation of functionalized Grignard reagents hardly improved the yields (**Z-3ag** and **Z-3cj**).[10c] Thus, omitting the procedure of removing i-PrI not only made the reaction more convenient, but also could further expand the applications of Knochel-type Grignard reagents in coupling reactions.[10] Likewise, linear and branched chain substituted



Scheme 3 *Z*- and *E*-trisubstituted acrylates by stereospecific arylations.[a,b] [a] The reaction was carried out on 5 mmol scale using method A unless indicated. [b] Only a single isomer was observed and isolated unless indicated. [c] Grignard reagent was prepared by ArI + i-PrMgCl·LiCl and used without removing i-PrI. [d] Grignard reagent was prepared by ArI + i-PrMgCl·LiCl and used after removing i-PrI. [e] Using *Z*-substrate. [f] Using a mixture of *Z*- and *E*-substrates.

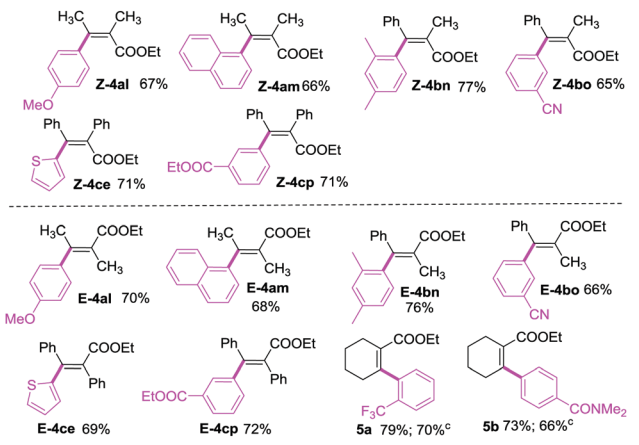
tosyloxyacrylates could also be arylated stereospecifically (**Z-3bb–Z-3cj**), where 2-substituted (**Z-3ba**), pyridyl (**Z-3bh**) and functionalized (**Z-3ci** and **Z-3cj**) Grignard reagents performed equally well. The stereospecific arylation by method A also proved facile for 3-aryl-3-(tosyloxy)acrylates (**Z-3dk–Z-3ee**). It should be mentioned that a selective arylation of OTs over Br could also be achieved with stereospecificity (**Z-3ee**).

As outlined in Scheme 3b, various *E*-trisubstituted acrylates were also prepared stereospecifically using method A (**E-3ab–E-3ee**). Since these *E*-isomers are thermodynamically more stable, they could also be generated as a single isomer using method B in the absence of NHC ligand at heated conditions (**E-3ab–E-3ee**). The tolerance to sensitive functional groups of two coupling substrates under heated conditions is obviously a prominent advantage of our present protocol. Besides, by taking full advantage of isomerization, a single *E*-isomer could be also prepared facilely by using *Z*-tosyloxyacrylates and a mixture

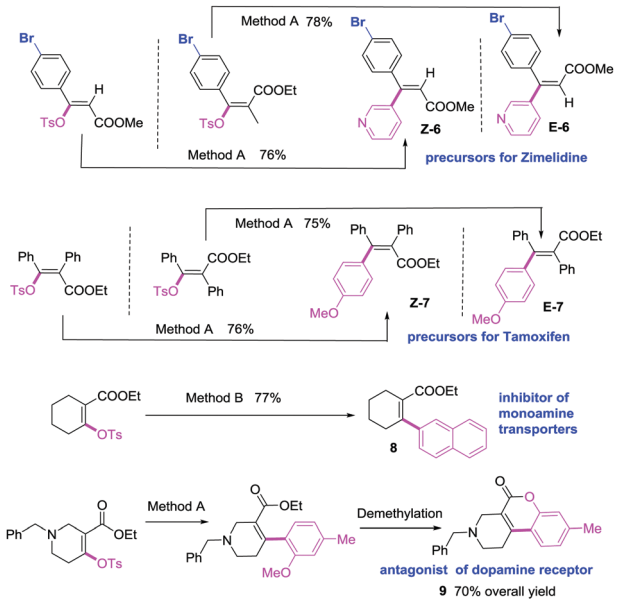
of *Z* and *E*-tosyloxyacrylates under the conditions of method B (**E-3ac–E-3af**). The use of a mixture of *Z* and *E*-tosyloxyacrylates as starting compounds also has obvious advantages because the preparations of these starting materials need no stereocontrol. This should be due to the inherent thermodynamic stability of these *E*-trisubstituted acrylates. Our preliminary experiments also indicated that *Z*-trisubstituted acrylates could be completely converted into their *E*-isomers under the conditions of method B.[12] Thus, it can be inferred that the reason for the high stereoselectivity and stereofidelity of method A lies in that the mild conditions avoid the isomerization of Fe intermediates (formed by oxidative addition in catalytic cycle) and the formed products.

Next, we explored the stereospecific arylations of fully substituted tosyloxyacrylates whose stereoselective preparations were also well reported by the Tanabe group.[11c] The results were outlined in Scheme 4. The present Fe-catalyzed arylation still proved to be facile for the tetrasubstituted substrates. Noteworthily, Fe-catalyzed arylations are often sensitive to steric hindrance;[13] and meanwhile even in the Pd-catalyzed stereoselective arylations of enol tosylates, the highly hindered aryl groups would prevent the reaction or lead to isomerization.[1d,14] Our experiments clearly showed that the present arylation of tetrasubstituted substrates could still proceed with stereospecificity only at 0 °C despite the high steric hindrance (**Z/E-4am** and **Z/E-4bn**). Once again, heteroaryl and Knochel-type functionalized Grignard reagents were also well suited to this reaction (**Z/E-4bo–Z/E-4cp**). The relative stability between *Z*- and *E*-tetrasubstituted acyclic olefins is not as easy to determine as that of trisubstituted olefins, and our preliminary experiments to convert **Z-4bn** into **E-4bn** under the heated conditions of method B were unsuccessful.[15] As a result, we did not use method B to implement the arylations of acyclic tetrasubstituted substrates.[15] Instead, 2-(tosyloxy)cyclohex-1-enecarboxylate was arylated using both method A and B, affording the tetrasubstituted products (**5a** and **5b**) in 66–79% yields.

To demonstrate the synthetic potential of this Fe-catalyzed stereospecific arylation reaction, we synthesized a range of



Scheme 4 *Z*- and *E*-tetrasubstituted acrylates by stereospecific arylations.[a,b]
[a] The reaction was carried out on 5 mmol scale under the same conditions as Scheme 3. [b] All reactions were conducted using method A unless indicated. [c] The reaction was carried out using method B.



Scheme 5 Stereospecific syntheses of precursors for pharmaceuticals and bioactive compounds. See the ESI.†

pharmaceutical precursors and bioactive compounds using the aforementioned two methods (Scheme 5). Both *Z*- and *E*-precursors to *Z*- and *E*-zimelidines (**Z-6** and **E-6**) were prepared using 3-pyridyl Grignard reagent where the selectivity between OTs and Br was well achieved. These precursors could be further transformed into zimelidines according to the reported procedures.[4d,16] Meanwhile, *Z*- and *E*-tetrasubstituted precursors to *Z*- and *E*-tamoxifens (**Z-7** and **E-7**)[14a,17] were also synthesized stereospecifically using method A. Besides, an inhibitor of monoamine transporters featuring a 2-naphthyl cyclohex-1-enecarboxylate skeleton (**8**)[18] and chromeno[3,4-*c*]pyridin-5-one (**9**), a selective human dopamine D4 receptor antagonist[19] were facilely synthesized using method A and B. To the best of our knowledge, although the stereospecific syntheses of all these compounds have already been achieved by Pd-catalyzed arylations, their syntheses *via* Fe-catalyzed arylations have been achieved for the first time. Obviously, these preparations proved to be straightforward and convenient with readily available Grignard reagents and enol tosylates. Furthermore, the use of two nontoxic metals (Fe and Ti) as catalysts is a distinct advantage of our syntheses.

In conclusion, while achieving both chemo- and stereoselectivity simultaneously is a highly challenging task in organic synthesis, our approaches presented here achieve this goal well unprecedentedly using sustainable transition metal catalysts (Fe/Ti) in constructing various *Z*/*E* tri- and tetrasubstituted acrylates.[20] The general protocol (method A) can implement stereospecific arylations under mild conditions to generate various *Z* and *E*-alkenes, showing high tolerance to sensitive functional groups and steric hindrance with complete stereofidelity. Meanwhile, method B could stereospecifically synthesize various thermodynamically more stable acrylates under heated conditions without NHC or phosphine ligands.

Using only a catalytic amount of $Ti(OEt)_4$, this mild Fe-catalyzed arylation with Grignard reagents is comparable to the corresponding Pd-catalyzed stereoslective Suzuki/Negishi arylations in terms of functional group tolerance and stereoselectivity. Thus, we expect that our Fe-catalyzed arylation combined with the previously reported Fe-catalyzed stereoselective alkylation will promote the replacement of noble and toxic transition metals in accessing stereodefined olefins.

We gratefully acknowledge the National Science Foundation of China (21372031 and 21572022).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For selected reviews: (*a*) A. B. Flynn and W. W. Ogilvie, *Chem. Rev.*, 2007, **107**, 4698; (*b*) E. Negishi, Z. Huang, G. Wang, S. Mohan, C. Wang and H. Hattori, *Acc. Chem. Res.*, 2008, **41**, 1474; (*c*) *Stereoselective Alkene Synthesis in Topics in Current Chemistry*, ed. J. Wang, Springer, Berlin/Heidelberg, 2012. For the applications of alkenes, see; (*d*) B. X. Li, D. N. Le, K. A. Mack, A. McClory, N.-K. Lim, T. Cravillion, S. Savage, C. Han, D. B. Collum, H. Zhang and F. Gosselin, *J. Am. Chem. Soc.*, 2017, **139**, 10777 and references cited therein.

2 (*a*) E. Negishi, Q. Hu, Z. Huang, M. Qian and G. Wang, *Aldrichimica Acta*, 2005, **38**, 71; (*b*) J. Li, A. S. Grillo and M. D. Burke, *Acc. Chem. Res.*, 2015, **48**, 2297; (*c*) V. Hornillos, M. Giannerini, C. Vila, M. Fananas-Mastral and B. L. Feringa, *Chem. Sci.*, 2015, **6**, 1394 and references cite therein.

3 For selected recent papers on the carbometalation of alkynes and alkene synthesis, see: (*a*) K. Murakami and H. Yorimitsu, *Beilstein J. Org. Chem.*, 2013, **9**, 278; (*b*) M. G. Suero, E. D. Bayle, B. S. L. Collins and M. J. Gaunt, *J. Am. Chem. Soc.*, 2013, **135**, 5332; (*c*) F. Xue, J. Zhao, T. S. A. Hor and T. Hayashi, *J. Am. Chem. Soc.*, 2015, **137**, 3189; (*d*) S. Wang and C. Xi, *Org. Lett.*, 2018, **20**, 4131.

4 Representive examples: (*a*) X. Zeng, M. Qian, Q. Hu and E. Negishi, *Angew. Chem., Int. Ed.*, 2004, **43**, 2259; (*b*) J. M. Baxter, D. Steinhuebel, M. Palucki and I. W. Davies, *Org. Lett.*, 2005, **7**, 215; (*c*) Y. Ashida, Y. Sato, T. Suzuki, K. Ueno, K.-I. Kai, H. Nakatsuji and Y. Tanabe, *Chem. – Eur. J.*, 2015, **21**, 5934; (*d*) S. Savage, A. McClory, H. Zhang, T. Cravillion, N.-K. Lim, C. Masui, S. J. Robinson, C. Han, C. Ochs, P. D. Rege and F. Gosselin, *J. Org. Chem.*, 2018, **83**, 11571; (*e*) G.-M. Ho, H. Sommer and I. Marek, *Org. Lett.*, 2019, **21**, 2913.

5 Selected reviews: (*a*) A. Guérinot and J. Cossy, *Top. Curr. Chem.*, 2016, **374**, 49; (*b*) E. Bisz and M. Szostak, *ChemSusChem*, 2017, **10**, 3964. Selected examples: (*c*) A. Fürstner, D. De Souza, L. Parra-Rapado and J. T. Jensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 5358; (*d*) B. Scheiper, M. Bonnekessel, H. Krause and A. Fürstner, *J. Org. Chem.*, 2004, **69**, 3943; (*e*) G. Cahiez, V. Habiak and O. Gager, *Org. Lett.*, 2008, **10**, 2389; (*f*) G. Cahiez, O. Gager and V. Habiak, *Synthesis*, 2008, 2636; (*g*) H. Nishikado, H. Nakatsuji, K. Ueno, R. Nagase and Y. Tanabe, *Synlett*, 2010, 2087; (*h*) A. C. P. Rivera, R. Still and D. E. Frantz, *Angew. Chem., Int. Ed.*, 2016, **55**, 6688; (*i*) T. Tsutsumi, Y. Ashida, H. Nishikado and Y. Tanabe, *Org. Synth.*, 2018, **95**, 403; (*j*) X.-L. Lu, M. Shannon, X.-S. Peng and H. N. C. Wong, *Org. Lett.*, 2019, **21**, 2546.

6 (*a*) W. Dohle, F. Kopp, G. Cahiez and P. Knochel, *Synlett*, 2001, 1901; (*b*) G. Dunet and P. Knochel, *Synlett*, 2006, 407; (*c*) W. M. Czaplik, M. Mayer and A. Jacobi von Wangelin, *ChemCatChem*, 2011, **3**, 135; (*d*) N. Tewari, N. Maheshwari, R. Medhane, H. Nizar and M. Prasad, *Org. Process Res. Dev.*, 2012, **16**, 1566.

7 Two selected reviews covering Fe-catalyzed biaryl cross couplings: (*a*) O. M. Kuzmina, A. K. Steib, A. Moyeux, G. Cahiez and P. Knochel, *Synthesis*, 2015, 1696; (*b*) A. Guérinot and J. Cossy, *Top. Curr. Chem.*, 2016, **374**, 265.

8 Even in the Pd-catalyzed steroselective arylations of enol tosylates, judicious optimizations of the catalysts, substrates and reaction conditions were required to prevent isomerization, see 1d. Besides, the isomerization to thermostatically stable *E*-isomers was observed in the Fe-catalyzed alkylation and arylation of enol phosphates and tosylates, see **5f** and **5g**.

9 A recently reported Co-catalyzed arylation showed that the reactions of acyclic *Z*-tosylates gave the *E*-configured products, see: J. Li and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 11436.

10 (*a*) R. Zhang, Y. Zhao, K. M. Liu and X. F. Duan, *Org. Lett.*, 2018, **20**, 7942; (*b*) L. Wang, Y. M. Wei, Y. Zhao and X. F. Duan, *J. Org. Chem.*, 2019, **84**, 5176; (*c*) L. C. Xu, K. M. Liu and X. F. Duan, *Adv. Synth. Catal.*, 2019, **361**, 5421.

11 (*a*) H. Nakatsuji, K. Ueno, T. Misaki and Y. Tanabe, *Org. Lett.*, 2008, **10**, 2131; (*b*) H. Nakatsuji, H. Nishikado, K. Ueno and Y. Tanabe, *Org. Lett.*, 2009, **11**, 4258; (*c*) Y. Ashida, Y. Sato, A. Honda, H. Nakatsuji and Y. Tanabe, *Synthesis*, 2016, 4072; (*d*) Y. Ashida, H. Nakatsuji and Y. Tanabe, *Org. Synth.*, 2017, **94**, 93.

12 Typically, after **Z-3ab** and **Z-3af** were heated for 8 hours in refluxed THF under the conditions of method B, **E-3ab** and **E-3af** were respectively obtained as a single isomer.

13 (*a*) T. Agrawal and S. P. Cook, *Org. Lett.*, 2014, **16**, 5080; (*b*) Y. M. Wei, M. F. Wang and X. F. Duan, *Org. Lett.*, 2019, **21**, 6471 and references cited therein.

14 Recently, this problematic isomerization in Pd-catalyzed arylations or alkylations was considerably overcome, see: (*a*) Y. Ashida, A. Honda, Y. Sato, H. Nakatsuji and Y. Tanabe, *ChemistryOpen*, 2017, **6**, 73; (*b*) Y. Sato, Y. Ashida, D. Yoshitake, M. Hoshino, T. Takemoto and Y. Tanabe, *Synthesis*, 2018, 4659.

15 After **Z-4bn** was heated for 8 hours in refluxed THF under the promotion of 15 mol% $FeCl_3$/30 mol% TMEDA/15 mol% SIPr/20 mol% PhOMgBr/20 mol% $Ti(OEt)_4$, a mixture of **Z-4bn** and **E-4bn** was generated with a ratio of about 85 : 15. Conversely, the same treatment of **E-4bn** results in only a slight isomerization (**E-4bn** : **Z-4bn** = 90 : 10). These facts indicate that under the conditions of method B, it is difficult to achieve the isomerization of tetrasubstituted acrylates.

16 (*a*) J.-E. Baeckvall, R. E. Nordberg, J.-E. Nystroem, T. Hoegberg and B. Ulff, *J. Org. Chem.*, 1981, **46**, 3479; (*b*) T. Hoegberg and B. Ulff, *J. Org. Chem.*, 1984, **49**, 4209.

17 For a review, see: (*a*) K. M. Kasiotis and S. A. Haroutounian, *Curr. Org. Chem.*, 2012, **16**, 335. For selected recent papers: (*b*) G. Cahiez, A. Moyeux and M. Poizat, *Chem. Commun.*, 2014, **50**, 8982; (*c*) H. Nakatsuji, Y. Ashida, H. Hori, Y. Sato, A. Honda, M. Taira and Y. Tanabe, *Org. Biomol. Chem.*, 2015, **13**, 8205; (*d*) D. Heijnen, M. van Zuijlen, F. Tosi and B. L. Feringa, *Org. Biomol. Chem.*, 2019, **17**, 2315.

18 (*a*) M. D. Petersen, S. V. Boye, E. H. Nielsen, J. Willumsen, S. Sinning, O. Wiborg and M. Bols, *Bioorg. Med. Chem.*, 2007, **15**, 4159; (*b*) I. Sasaki, H. Doi, T. Hashimoto, T. Kikuchi, H. Ito and T. Ishiyama, *Chem. Commun.*, 2013, **49**, 7546.

19 (*a*) P. C. Unangst, T. Capiris, D. T. Connor, T. G. Heffner, R. G. MacKenzie, S. R. Miller, T. A. Pugsley and L. D. Wise, *J. Med. Chem.*, 1997, **40**, 2688; (*b*) J. Xiao, Y. Chen, S. Zhu, L. Wang, L. Xu and H. Wei, *Adv. Synth. Catal.*, 2014, **356**, 1835.

20 The ester group in the trisubstituted or tetrasubstituted acrylates can act as a versatile handle for further transformations, see: (*a*) D. W. Jeffery, M. V. Perkins and J. M. White, *Org. Lett.*, 2005, **7**, 1581; (*b*) T. Zhang, N.-X. Wang and Y.-L. Xing, *J. Org. Chem.*, 2018, **83**, 7559, and references cited therein.

