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The Alkynyl Moiety as a Donor for Donor–Acceptor Cyclopropanes

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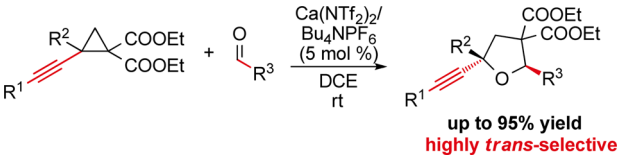
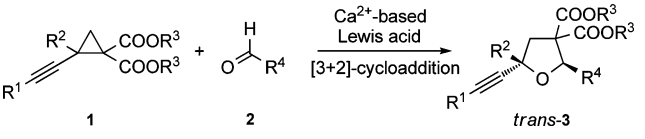
ABSTRACT



The first *trans*-selective [3 + 2]-cycloaddition of a new type of donor–acceptor cyclopropane with aldehydes is presented. 2,2-Disubstituted cyclopropanes, bearing an alkyne moiety as the sole donor entity, were transformed to highly substituted tetrahydrofurans in the presence of a catalytic amount of $Ca(NTf_2)_2/Bu_4NPF_6$. The protocol allows for an easy access to tetrahydrofurans bearing a versatile alkyne substituent at the quarternary 2-position under very mild reaction conditions.

The diastereoselective generation of complex heterocycles from donor–acceptor (DA) cyclopropanes[1] has emerged as an efficient strategy and a number of [3 + *n*]-cycloaddition reactions has been described over the past decade.[2] Despite the progress in the investigation of 2-substituted-cyclopropane-1,1-diesters, reactions involving the analogous 2,2-disubstituted species such as **1** (Scheme 1) remain scarce,[3] even though the thus generated heterocycles **3** contain a highly interesting quaternary stereocenter. Furthermore, with the exception of three examples,[3a,b] these inquiries are limited to cyclopropanes bearing a phenyl-moiety as the donor entity. The reactions were generally found to proceed with high diastereoselectivity, predictably yielding *cis*-configured heterocycles, orienting the substituent R^4 of the former dipolarophile on the same side of the newly formed ring as the former donor group.

Scheme 1. Proposed Cycloaddition with Quaternary Donor Sites[a]



[a] Alkynyl moiety as the sole donor moiety, R^2 = aliphatic.

We have recently developed a novel calcium catalyst as a sustainable alternative to traditionally used, expensive, rare, and oftentimes highly toxic transition metal catalysts for organic synthesis. Through the choice of appropriate counteranions, we were the first to successfully apply calcium salts as highly efficient Lewis acidic catalysts for the transformation of π-activated alcohols and olefins.[4] Having thus in hand a new Lewis acidic catalyst that provides

(1) For donor–acceptor cyclopropane reviews, see: (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196.

(2) (a) Zhu, W.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 2032–2037. (b) Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1758–1762. (c) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386–389. (d) Xing, S.; Li, Y.; Li, Z.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 12605–12609. (e) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848–1851. (f) Ivanova, O. A.; Budynina, E. M.; Chargarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Ya. *J. Org. Chem.* **2011**, *76*, 8852–8868. (g) Lebold, T. P.; Kerr, M. A. *Pure Appl. Chem.* **2010**, *82*, 1797–1812. (h) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317–6325. (i) Christie, S. D. R.; Cummins, J.; Elsegood, M. R. J.; Dawson, G. *Synlett* **2009**, 257–259. (j) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650. (k) Agrawal, D.; Yadav, V. K. *Chem. Commun.* **2008**, 6471–6488. (l) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1107–1110. (m) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541–2544. (n) Gupta, A.; Yadav, V. K. *Tetrahedron Lett.* **2006**, *47*, 8043–8047. (o) Christie, S. D. R.; Davoile, R. J.; Elsegood, M. R. J.; Fryatt, R.; Jones, R. C. F.; Pritchard, G. J. *Chem. Commun.* **2004**, 2474–2475.

(3) (a) Smith, A. G.; Slade, M. C.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 1996–1999. (b) Xing, S.; Pan, W.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3215–3218. (c) Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777–779. (d) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764–5765.

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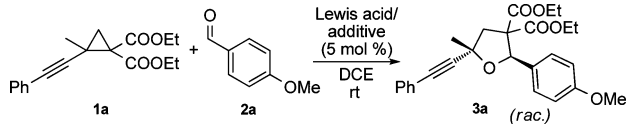
higher activity than most of the previously known ones, we envisioned a systematic investigation of the transformation of a new type of 2,2-disubstituted DA-cyclopropane **1**, bearing an alkyne as the sole donor entity, which might be highly beneficial in several ways. First, the alkyne moiety is developed into a versatile functional handle, also due to the tremendous success witnessed in the area of noble metal catalysis.[5] Hence, the obtained products represent highly interesting building blocks for further conversion into natural products. Second, the minor steric extension of this new donor moiety might account for a thus unprecedented *trans*-diastereoselectivity in the [3 + 2]-cycloaddition toward heterocycles **3**.

Our studies began with the optimization of the reaction conditions for the [3 + 2]-cycloaddition of cyclopropane **1a** with *p*-anisaldehyde **2a** (Table 1). In the presence of 5 mol % of $Ca(NTf_2)_2$ and 5 mol % of Bu_4NPF_6 the cycloaddition was completed after 5 min at room temperature affording tetrahydrofuran **3a** in 95% yield with a good stereoselectivity of 87:13 in favor of the *trans*-configured heterocycle. Other alkaline earth metal triflimides as well as $LiNTf_2$ showed very low or no reactivity (entries 1−4). Among other additives, the PF_6^- salt gave the best results (entries 5−7). As already mentioned in previous publications,[4f,g] the hexafluorophosphate salt is required to form the much more soluble $CaNTf_2PF_6$ species *via* an anion exchange reaction (entry 8). Only noncoordinating, polar solvents such as 1,2-dichloroethane (DCE) were found suitable. $Sn(OTf)_2$ promoted the reaction. However, the diastereoselectivity was poor in the presence of this catalyst that proved highly efficient regarding both conversion and selectivity, in previous studies with a phenyl-donor moiety (entries 12/13).[3a] Similar results were obtained in the presence of $Sc(OTf)_3$ that efficiently promotes this type of reaction, a single example also showcasing a 2,2-disubstituted cyclopropane.[3b] Here, in the presence of the additive the isolated yield was low due to oligomerization side reactions, or in the absence of the additive the diastereoselectivity was poor and, interestingly, in favor of the *cis*-configured tetrahydrofuran (entries 14/15). Formation of a hidden Brønsted acid[6] as a catalytic species was ruled out by NMR experiments (see Supporting Information (SI)).

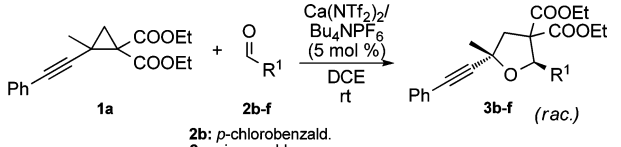
Table 1. Optimization of the Reaction Conditions



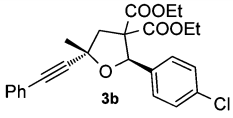
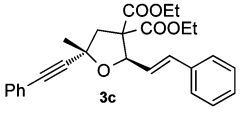
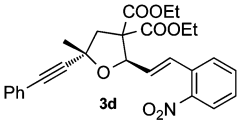
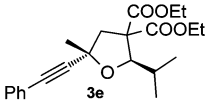
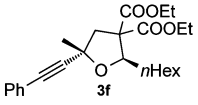
entry[a]	Lewis acid	additive	time	yield [%]	dr[e]
1	$Mg(NTf_2)_2$	Bu_4NPF_6	16 h	10	70:30
2	**$Ca(NTf_2)_2$**	**Bu_4NPF_6**	**5 min**	**95**	**87:13**
3	$Ba(NTf_2)_2$	Bu_4NPF_6	16 h	n.r.	–
4	$LiNTf_2$	Bu_4NPF_6	48 h	70	87:13
5	$Ca(NTf_2)_2$	Bu_4NSbF_6	30 min	89	88:12
6	$Ca(NTf_2)_2$	Bu_4NBF_4	30 min	84	87:13
7	$Ca(NTf_2)_2$	$PhMe_2HN^+$ $B(C_6F_5)_4^-$	16 h	n.r.	–
8	$Ca(NTf_2)_2$	–	16 h	n.r.	–
9[b]	$Ca(NTf_2)_2$	Bu_4NPF_6	16 h	n.r.	–
10[c]	$Ca(NTf_2)_2$	Bu_4NPF_6	4 h	79	82:18
11[d]	$Ca(NTf_2)_2$	Bu_4NPF_6	16 h	n.r.	–
12	$Sn(OTf)_2$	Bu_4NPF_6	45 min	72	57:43
13	$Sn(OTf)_2$	–	30 min	85	61:39
14	$Sc(OTf)_3$	Bu_4NPF_6	10 min	61	86:14
15	$Sc(OTf)_3$	–	15 min	92	45:55

[a] *p*-Anisaldehyde **2a** (0.2 mmol) and cyclopropane **1a** (0.1 mmol) were added to a Lewis acid (5 mol %) and an additive (5 mol %) in DCE (0.5 mL) at rt and stirred for the indicated time. [b] Reaction run in Et_2O. [c] Reaction run in toluene. [d] Reaction run in $MeNO_2$. [e] Determined by ^1H NMR spectroscopy.

Table 2. Reaction of Cyclopropane **1a** with Aldehydes



2b: *p*-chlorobenzald.
2c: cinnamald.
2d: *o*-nitrocinnamald.
2e: isobutyrald.
2f: hexanal

entry[a]	product	time	yield [%]	dr[c]
1	 **3b**	10 min	95	82:18
2	 **3c**	5 min	73	86:14
3[b]	 **3d**	10 min	66	89:11
4	 **3e**	15 min	45	89:11
5	 **3f**	1 h	56	89:11

[a] Aldehyde **2** (0.2 mmol) and cyclopropane **1a** (0.1 mmol) were added to $Ca(NTf_2)_2$ (5 mol %) and Bu_4NPF_6 (5 mol %) in DCE (0.5 mL) at rt and stirred for the indicated time. [b] Reaction run at 50 °C. [c] Determined by ^1H NMR spectroscopy.

(4) (a) Capitta, F.; Begouin, J.-M.; Wu, X.; Niggemann, M. *Org. Lett.* **2013**, *15*, 1370–1373. (b) Haven, T.; Kubik, G.; Haubenreisser, S.; Niggemann, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4016–4019. (c) Kena Diba, A.; Begouin, J.-M.; Niggemann, M. *Tetrahedron Lett.* **2012**, *53*, 6629–6632. (d) Meyer, V. J.; Niggemann, M. *Chem.—Eur. J.* **2012**, *18*, 4687–4691. (e) Meyer, V. J.; Niggemann, M. *Eur. J. Org. Chem.* **2011**, 3671–3674. (f) Haubenreisser, S.; Niggemann, M. *Adv. Synth. Catal.* **2011**, *353*, 469–474. (g) Niggemann, M.; Meel, M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3684–3687. (h) Niggemann, M.; Bisek, N. *Chem.—Eur. J.* **2010**, *16*, 11246–11249.

(5) (a) de Mendoza, P.; Echavarren, A. M. *Pure Appl. Chem.* **2010**, *82*, 801–820. (b) Yamamoto, Y.; Gridnev, I. D.; Patil, N.; Jin, T. *Chem. Commun.* **2009**, 5075–5087. (c) Abu Sohel, S. Md.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269–2281. (d) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111–1125.

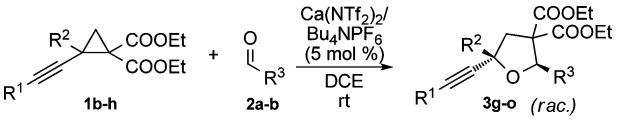
To investigate the scope of the cycloaddition, a series of different aldehydes were reacted with cyclopropane **1a** (Table 2). Aromatic aldehydes, bearing an electron-withdrawing group at the aryl moiety (**2b**), showed no difference in reactivity compared to *p*-anisaldehyde **2a**. Cinnamaldehyde **2c** proved equally suitable as a dipolarophile, providing high yields and good selectivity. The less reactive *o*-nitrocinnamaldehyde **2d** showed no reactivity at room temperature, but cycloaddition could be achieved at 50 °C within 10 min. Aliphatic aldehydes were suitable substrate; however, the tetrahydrofurans **3e/f** were obtained in moderate yields because of their fragility under the reaction conditions in combination with their considerably lower nucleophilicity.

We further explored the scope of the [3 + 2]-cycloaddition with regard to differently substituted cyclopropanes (Table 3). Special emphasis was given to both the second substituent at the quaternary donor site and the electronic properties of the alkyne. Cyclopropane **1b** afforded the desired tetrahydrofurans **3g** and **3h** in high yield. Once again, the *trans*-diastereomers, orienting the former donor moiety and the former aldehyde substituent on either side of the just formed tetrahydrofuran ring, were predominant. Due to the sterically more demanding *n*-propyl substituent, the diastereoselectivity is even higher in these cases. The electron-withdrawing benzyloxy substituent in **1c** reduced the reactivity to some degree, but the high reactivity of the calcium catalyst accounts for an acceptable conversion of these deactivated substrates to the highly interesting building blocks **3i** and **3j**. The diastereoselectivity was again excellent. The phenyl substituted cyclopropane **1d** afforded tetrahydrofuran **3k** in high yield and diastereoselectivity. Alteration of the electronic properties of the alkyne moiety revealed the suitability of a broad range of different substituents R^1 for the presented [3 + 2]-cycloaddition. Electron-withdrawing substituents in an aryl substituent such as in **1e** had no significant influence on the reaction outcome. Interestingly, an electron-rich aryl moiety was nonbeneficial for the reaction outcome. In this case the highly electron-rich alkyne moiety in **1f** seems to be entangled in side reactions, which could be suppressed to some extent at lower reaction temperatures. Much to our delight, the more electron-poor aliphatic alkyne donors in **1g** and **1h** also successfully promoted the reaction with high yield and good stereoselectivity although a slightly higher reaction temperature (50 °C) was required. All aldehydes, even the ones that showed only moderate reactivity in the reaction with cyclopropane **1a**, proved to be good dipolarophiles in the reaction with **1h** (see Table 4). In analogy to the previously proposed considerations for this reaction family,[2h,j] the mechanism of the reaction was outlined as depicted in Figure 1.

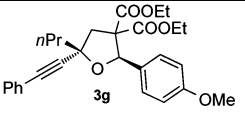
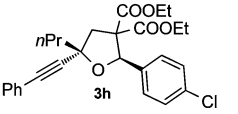
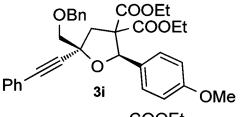
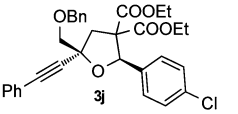
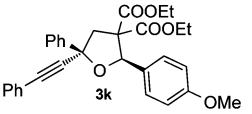
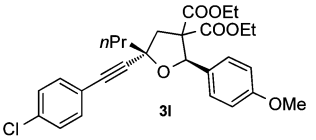
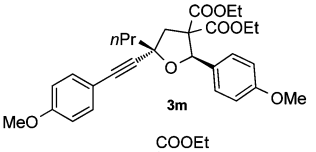
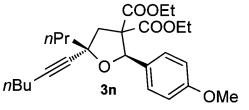
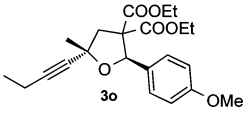
Coordination of the calcium Lewis acid induces the formation of the intimate contact ion pair **4**. The approach of the aldehyde occurs in such a way that the arising 1,3-diaxial steric clash is minimized, by orienting the slender alkyne moiety in **5** on the same side as the aldehyde hydrogen atom. A 120° bond rotation followed by ring closure via an envelope transition state then yields the *trans*-tetrahydrofuran **3**. Due to the already favorable pseudoaxial orientation of the two larger groups R^2 and R^4 the steric penalty in **6** is kept at a minimum and ring flip events therefore are unlikely.

As opposed to the observations made in previous studies,[2j] longer reaction times proved to be beneficial for

Table 3. Reaction of Cyclopropanes **1** with Aldehydes



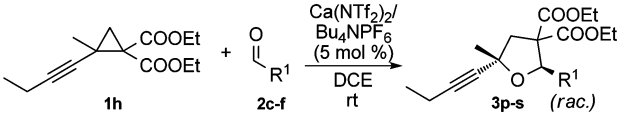
1b: R^1 = Ph, R^2 = *n*-propyl
1c: R^1 = Ph, R^2 = CH_2OBn
1d: R^1 = R^2 = Ph
1e: R^1 = 4-Cl-Ph, R^2 = *n*-propyl
1f: R^1 = 4-MeO-Ph, R^2 = *n*-propyl
1g: R^1 = *n*-butyl, R^2 = *n*-propyl
1h: R^1 = ethyl, R^2 = methyl

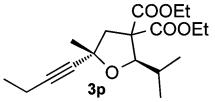
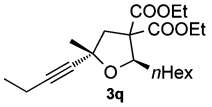
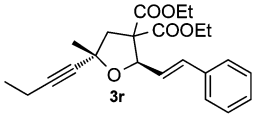
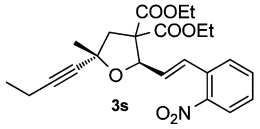
entry[a]	product	time	yield [%]	dr[d]
1	 **3g**	5 min	83	97:3
2	 **3h**	5 min	87	96:4
3	 **3i**	11 h	66	96:4
4	 **3j**	11 h	78	94:6
5	 **3k**	10 min	92	93:7
6	 **3l**	15 min	82	96:4
7[b]	 **3m**	10 min	61	96:4
8[c]	 **3n**	2 h	95	94:6
9[c]	 **3o**	2 h	91	92:8

[a] Aldehyde **2** (0.2 mmol) and cyclopropane **1** (0.1 mmol) were added to $Ca(NTf_2)_2$ (5 mol %) and Bu_4NPF_6 (5 mol %) in DCE (0.5 mL) and stirred for the time indicated. [b] Reaction run at 0 °C. [c] Reaction run at 50 °C. [d] Determined by ^1H NMR spectroscopy.

(6) Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* **2011**, *76*, 9353–9361.

Table 4. Reaction of Cyclopropane **1h** with Aldehydes



entry[a]	product	time	yield [%]	dr[b]
1	 **3p**	20 min	81	81:19
2	 **3q**	20 min	83	84:16
3	 **3r**	5 min	93	82:18
4	 **3s**	20 min	85	90:10

[a] Aldehyde **2** (0.2 mmol) and cyclopropane **1h** (0.1 mmol) were added to $Ca(NTf_2)_2$ (5 mol %) and Bu_4NPF_6 (5 mol %) in DCE (0.5 mL) and stirred for the time indicated. [b] Determined by ^1H NMR spectroscopy.

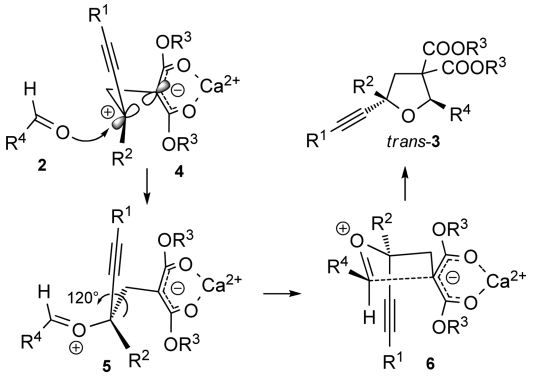
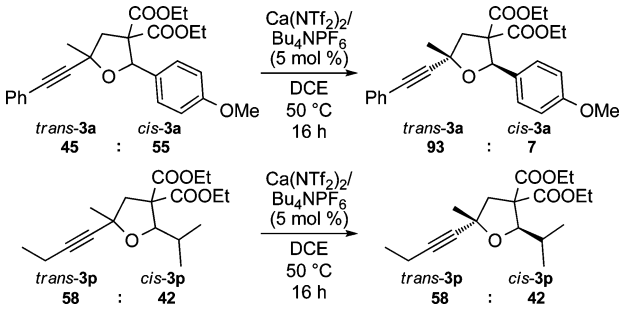


Figure 1. Mechanistic rationale.

the diastereoselectivity in our studies. Further investigations of this initial observation were conducted by exposing diastereomeric mixtures *trans*-/*cis*-**3a** and *trans*-/*cis*-**3p** to the reaction conditions (see Scheme 2). As confirmed by computational analysis on the B3LYP6-31G+(d,p) level of theory (see SI) tetrahydrofurans *trans*-**3a** and *trans*-**3p** are the more stable stereoisomers, due to the minimized 1,3-diaxial strain between the alkynyl substituent and the former aldehyde hydrogen atom. In the case of the tetrahydrofuran **3a** that bears an aryl and an arylalkynyl

Scheme 2. Prolonged Reaction Time and Diastereoselectivity[a]



[a] *Trans*/*cis*-mixtures of tetrahydrofurans **3a** or **3p** (0.1 mmol) were added to $Ca(NTf_2)_2$ (5 mol %) and Bu_4NPF_6 (5 mol %) in DCE (0.5 mL) and stirred for 16 h at 50 °C; dr determined by ^1H NMR spectroscopy.

substituent, both of them being electron-rich, equilibration to the thermodynamically more stable *trans*-product occurs, whereas no such event was observed in the case of **3p**. This process proceeds via a ring-opening reaction that is facilitated by the coordination of the calcium Lewis acid to the tetrahydrofuran oxygen atom (for a mechanistic rationale, see SI).[2j] Bond rotation in the ring opened species followed by reoccurring ring closure then accounts for the transformation of the unfavorable *cis*- to the more stable *trans*-product. The intermediary cationic ring opened species is highly stabilized by the two electron releasing substituents in the tetrahydrofuran **3a**, which are thus facilitating the overall process. Due to the much poorer stabilizing abilities of the substituents in the case of **3p**, either ring opening is prevented or the subsequent bond rotation is slow in comparison to the reoccurring ring closure. An equilibration of tetrahydrofuran **3p** seems therefore prohibited. These findings also explain the diminished diastereoselectivities in the cycloadditions of cyclopropane **1h** with sterically less demanding aldehydes.

In summary we have developed a calcium-catalyzed [3 + 2]-cycloaddition of aldehydes with a new type of quaternary donor site cyclopropanes, bearing an alkyne moiety as the sole donor entity. By taking advantage of the marginal steric extension of this new donor, the tetrahydrofurans could be obtained with excellent *trans*-diastereoselectivities for the first time. Thereby, an unprecedented general access has been granted to highly substituted tetrahydrofurans bearing an alkyne moiety as a versatile functional handle at the quarternary 2-position. Further exploration of the scope of other dipolarophiles for this type of reaction are currently underway in our laboratory.

Supporting Information Available. Experimental procedures, full characterization of products, NMR spectra, computational methods, additional information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.